CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761060Orig1s000
761060Orig2s000

SUMMARY REVIEW

DIVISION DIRECTOR SUMMARY REVIEW FOR REGULATORY ACTION AND CROSS-DISCIPLINE TEAM LEADER REVIEW

Application Number	**BLA 761060**
Application Type	Original-1 and Original-2
Applicant	Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Date of Submission	11/2/2016
PDUFA Goal Date	9/2/2017
Division/Office	DHP/OHOP
Division Director	Ann T. Farrell, MD
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD
Trade Name	Mylotarg
Proper Name	Gemtuzumab ozogamicin
Dosage form(s) / Strength(s)	Injection, lyophilized (4.5 mg)
Applicant's Proposed Indication(s)/Population(s)	• In combination with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia (AML) • For the treatment of patients with CD33-positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	• For the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults • For the treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older

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Material Reviewed/Consulted

	Names of Discipline Reviewers
Product Reviews	Antonina Aydanian, PhD; Charles Jewell, PhD; Thuy Nguyen, PhD; Maria Lopez-Barragan, PhD; Natalia Pripuzova, PhD; Benjamin Stevens, PhD, MPH; Reyes Candau-Chacon, PhD; Peter Qiu, PhD; Marjorie Shapiro, PhD
Clinical Reviews	Emily Jen, MD, PhD; Kelly Norsworthy, MD
Statistical Review	Chia-Wen Ko, PhD; Lei Nie, PhD
Pharmacology Toxicology Review	Pedro L. Del Valle, PhD; Christopher Sheth, PhD
Clinical Pharmacology Review	Jee Eun Lee, PhD, Jiang Liu, PhD, Christy John, PhD, Gene Williams, PhD, Yaning Wang, PhD
OPDP Review	Rachel Conklin; Nisha Patel
OSI Review	Min Lu, MD, MPH; Janice Pohlman, MD, MPH; Susan D. Thompson, MD; Kassa Ayalew, MD
OSE/DMEPA Reviews	Nicole Garrison, PharmD, BCPS; Leeza Rahimi, PharmD; Hina Mehta, PharmD
OSE/DPV Review	Connie Cheng, PharmD, BCOP; Afrouz Nayernama, PharmD
OSE/DRISK Review	Mei-Yean Chen, PharmD; Elizabeth Everhart, MSN, RN, ACNP

OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPV= Division of Pharmacovigilance
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

The Cross-Discipline Team Leader recommends regular approval of gemtuzumab ozogamicin (GO) under 21 CFR 601 for the following indications:

- For the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults
- For the treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older

Approval for these indications is supported by the results of ALFA-0701 showing an event-free survival (EFS) advantage when GO was added to standard chemotherapy for adults with newly-diagnosed de novo acute myeloid leukemia (AML), by the results of AML 19 showing a survival (OS) advantage for GO in comparison to best supportive care for patients with newly-diagnosed AML being treated without curative intent, and by the results of MyloFrance-1 showing durable complete remissions (CR) in patients with AML in first relapse, supported by extensive clinical trial and published data on GO for treatment of relapsed or refractory (R/R) AML. Additional studies to further characterize safety, assess for effects on QT and better characterize immunogenicity are also recommended.

Benefit-Risk Framework

	Evidence and Uncertainties	**Conclusions and Reasons**
Analysis of Condition	• The median survival of patients with AML is 2 mos.	AML is a fatal disease.
Current Treatment Options	• The current standard of care is combination chemotherapy for newly diagnosed AML and for R/R AML. • HSCT is used postremission to improve survival. • Using standard therapy, long-term survival is 20-60% for those treated intensively for newly-diagnosed AML, and <10% for patients with R/R AML and those treated with nonintensive therapies without curative intent.	There is a need for an effective agent for treatment of AML.
Benefit	• ALFA-0701 was an open-label randomized trial of GO 3 mg/m^2 days 1, 4 and 7 plus daunorubicin/cytarabine (DA) for patients between 50-70 years old with newly-diagnosed AML (n=271). - Median EFS with GO was 13.6 months compared with 8.8 mos in the DA arm (HR 0.68 (95% CI 0.51, 0.91). • AML 19 was a randomized, open-label trial of GO 6 mg/m^2 day 1 and 3 mg/m^2 day 8 versus BSC for patients with newly diagnosed AML treated without curative intent (n=237) - Median OS was 4.9 months with GO versus 3.6 months on BSC (HR 0.69, 95% CI 0.53-0.90). • MyloFrance-1 was an open-label single-arm trial of GO 3 mg/m^2 days 1, 4 and 7 for patients with first relapse of AML. (n=57) - CR rate was 26% (95% CI, 16%-40%). - Median RFS was 11.6 months. • Numerous publications report a meaningful CR rate using GO at various doses for treatment of R/R AML in adults and children.	There is substantial evidence of effectiveness for lower dose fractionated GO in addition to DA as treatment of newly-diagnosed AML with curative intent and as a single agent for treatment of newly-diagnosed or R/R AML without curative intent. The benefit for patients with adverse cytogenetics is unclear.

Benefit-Risk Framework

	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most common adverse reactions (>15%) were hemorrhage, infection, fever, nausea, vomiting, constipation, headache, rash, and mucositis. • Cytopenias and elevated liver tests are the most common laboratory abnormalities. Thrombocytopenia can be prolonged. • Veno-occlusive disease (VOD) is a potential fatal adverse reaction. • Infusions reactions and hemorrhage are additional potentially fatal or life-threatening adverse reactions. • A increase in infections and treatment-related mortality was reported when GO was added to chemotherapy for pediatric patients. • QT prolongation is a potential class effect that has not been studied with GO. • The assays used to test for ADA were not considered up to date. • There are no data for the lower-dose fractionated regimen to confirm the exposure-response analysis that showed a reduction in VOD without an impact on CR.	Although there are some substantial risks associated with GO, they are acceptable for the intended populations. Further characterizations of safety, PK, ADA and effects on QT are needed.
Risk Management	• Serious toxicities were mitigated in the clinical trials by use of premedications, frequent monitoring for known toxicities, and dose modifications.	Labeling should include a boxed warning VOD; warnings for infusion reactions, hemorrhage, QT prolongation, embryofetal toxicity and lack of efficacy in certain subgroups; instructions for premedication and dose modifications for toxicity.

GO was granted accelerated approval on May 17, 2000, as a single agent at 9 mg/m^2 for the treatment of patients with CD33-positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy. GO was withdrawn from marketing in 2010 when Study S0106, the confirmatory trial using GO 6 mg/m^2 in combination with DA failed to confirm clinical benefit and showed a higher rate of fatal induction toxicities in the GO arm (5.8% vs 1.3%). VOD, myelosuppression and infusion-related reactions were identified as the major safety concerns. Although AML, and especially R/R AML, is undoubtedly a fatal disease, GO has serious side effects that need to be balanced by clear and substantial clinical benefit. The trials in this new application are based on a lower-dose fractionated schedule of GO.

ALFA-0701 was the trial used to support the first indication. The primary endpoint of this study was EFS. Because FDA usually uses OS as the endpoint to confirm clinical benefit for treatment of AML, the applicant performed analyses to determine if EFS was a surrogate of OS. These included a trial-level analysis of 33 randomized AML studies and a subgroup of 5 randomized GO studies for which patient-level data were available. Since the analyses showed that the correlation was modest at best (R^2 0.45 with a copula model), surrogacy could not be established. The use of additional salvage therapies that prolonged OS in patients with treatment failure was

identified as a major confounding factor. ODAC agreed with the conclusions of the statistician, but also voiced the opinion that in the current era with multiple treatment options that might prolong survival of patients with AML, EFS could be used not as a surrogate endpoint but rather as a direct measure of clinical benefit itself. Based on the assessment of the EFS-OS relationship provided by the statistician, I agree that EFS may be a measure of clinical benefit for patients with newly-diagnosed AML.

In ALFA-0701, using the preferred definition of EFS, the HR was 0.68 (95% CI: 0.51-0.91) with only a 5-month improvement in median EFS. However, there was a clear and persistent separation of the EFS curves, and although OS was not significantly improved, the trend was positive (HR 0.81). Taken together, this demonstrates effectiveness. There were more bleeding events, prolonged thrombocytopenias, infections and VOD with GO, but early mortality was not considerably different between the study arms. Although there is substantial toxicity with GO, for the appropriate population, this may be outweighed by the benefit of treatment. The lingering concern is that no treatment benefit was demonstrated in the subgroup of patients with adverse cytogenetics. Although the firmness of a conclusion from a subgroup analysis is limited, this information should be highlighted in the Prescribing Information to allow patients and healthcare providers to make informed decisions about use of GO. Moreover, the subgroup that had the greatest benefit, those with favorable or intermediate risk cytogenetics, are represented more in the adult population younger than those in the study cohort. On the basis of the biology of the disease, the age range for the indication should therefore extend to all adults.

In AML 19, there was a 1.3-month median OS advantage for GO over best supportive care (HR 0.69; 95% CI: 0.53 0.90), and the CR rate was 15% (95% CI: 9%, 23%) with GO. Since the adverse event rates did not differ substantially between treatment arms, it can be concluded that the potential benefit of GO outweighs the risks. Although GO monotherapy is clearly not curative, the monotherapy regimen would be of particular importance for the subgroup of patients who desire even a short survival benefit but are not willing to accept the risks of intensive chemotherapy. Such a decision is in the purview of the practice of medicine and cannot be limited by age alone. Taken together, the results of ALFA-0701 and AML 19 provide the treatment options for all adults with newly-diagnosed CD33-positive AML and serve as the basis for the intended population in the first indication.

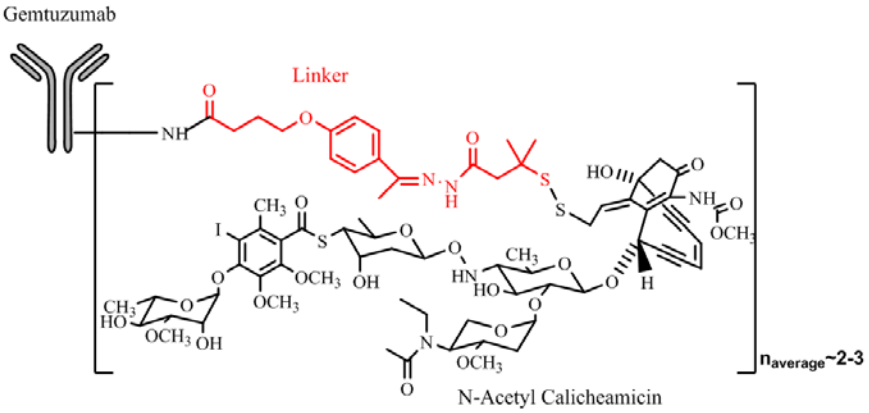
In MyloFrance-1, the CR rate was 26% (95% CI: 16%, 40%) with GO, and the median RFS was 11.6 months. The durable CRs are considered favorably in light of the safety profile in this population, and the results in the broad portfolio of single-arm trials of GO for treatment of adults and children with R/R AML are supportive. However, at the present time, the available data support safety and efficacy of BSA-based dosing of GO in children with R/R AML only down to the age of 2 years.

The totality of the evidence supports regular approval of GO for the indications described above. Safety issues can be addressed by labeling, although additional studies will be needed to further characterize safety of combination therapy in children, PK and exposure-response relationships for the new dose-schedule, immunogenicity and effects on QT.

2. Background

2.1 Product Information

Proper Name:	Gemtuzumab ozogamicin
Prior Names:	CMA-676, PF-0520874, CL-555201
Trade Name:	Mylotarg
Dosage Forms:	Injection, lyophilized (4.5 mg)
Chemical Class:	Recombinant antibody-drug conjugate
Molecular Mass:	152-153 KDa
Description:	Gemtuzumab ozogamicin is composed of gemtuzumab (a CD33-directed monoclonal antibody (hP67.6; recombinant humanized IgG4) covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. The drug product includes conjugated and unconjugated gemtuzumab. Product structure:



Therapeutic Class:	Antineoplastic
Pharmacologic Class:	CD33-directed antibody-drug conjugate
Mechanism of Action:	Binding of the ADC to CD33 expressing tumor cells, followed by internalization of the ADC-CD33 complex, and the intracellular release of N-acetyl gamma calicheamicin dimethyl hydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl gamma calicheamicin dimethyl hydrazide induces double-strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

2.2 Therapeutic Context

The applicant proposed 2 indications, one for adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia, and the other for treatment of patients with CD33-

positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

The current standard of care for treatment of patients with newly-diagnosed AML with curative intent is up to 2 cycles of induction chemotherapy using a combination of an anthracycline and cytarabine ("7+3" or DA) followed by consolidation using high-dose cytarabine. Age and genetic risk group are important baseline predictors of survival. Survival is prolonged by postremission allogeneic HSCT in patients with intermediate or adverse prognostic factors. Even with risk-stratified approaches to therapy, persistent disease and relapse remain the most common causes of death for patients with newly-diagnosed AML with overall survivals of 20-60%. For patients with newly-diagnosed AML treated with less-intensive therapies, overall survival is less than 10%.

There are numerous drugs approved for treatment of relapsed or refractory AML. None has substantial activity as a single-agent, so combinations of drug are the mainstay for treatment of relapsed or refractory AML. Patients treated in first relapse after a long remission have CR rates of 40-60%. For patients treated for relapse after a short first remission and those with later relapses, the CR rates are less than 40%, median survival 3-12 months, and 5-year survival less than 10%.

2.3 Regulatory Background

GO was developed under IND 046635 which was received by FDA on November 10, 1994. The first marketing application for GO (NDA 021174) was received on October 29, 1999. Orphan designation was granted on November 24, 1999. The marketing application was discussed by ODAC on March 20, 2000. GO (Mylotarg) received accelerated approval on May 17, 2000, contingent on fulfilling the post-marketing requirement of a randomized trial to confirm clinical benefit. GO was also discussed at ODAC meetings on March 13, 2003, and November 8, 2005; the subject of these meetings was delays in PMR fulfillment for products which had received accelerated approval.

Wyeth identified SWOG study S0106 as the study to fulfill the PMR. S0106 was a randomized trial comparing DA with or without GO 6 mg/m^2 for treatment of patients <60 years old with newly-diagnosed AML. The primary endpoint was CR rate post induction and disease-free survival (DFS) post consolidation. There were 637 patients randomized. The study showed no improvement in CR, DFS or OS with the addition of GO. There was a higher rate of fatal induction toxicities in the GO arm (5.8% vs 1.3%). FDA concluded that clinical benefit was not confirmed and that there was a potential safety issue due to the increase in early deaths. On May 21, 2010, FDA requested that Wyeth withdraw GO from marketing and establish an expanded access protocol. Wyeth voluntarily withdrew GO from marketing, and the NDA was formally withdrawn on October 25, 2010. An expanded access protocol was submitted April 10, 2013.

On multiple occasions between 2012 and 2016, FDA and Wyeth discussed or corresponded about additional emerging data on the efficacy of GO and the information that would be required

for submission of a new marketing application. Key advice provided by FDA to Wyeth included:

- A meta-analysis of GO trials for EFS or OS would not be sufficient as the sole basis for approval. Clinical benefit should be demonstrated in adequate and well-controlled trials.

- OS is the accepted endpoint to demonstrate clinical benefit for patients with newly-diagnosed AML. ALFA-0701 showed only an EFS benefit. A meta-analysis of all randomized trials for treatment of newly-diagnosed AML may be submitted to support use of EFS as a valid surrogate for OS.

- The BLA submission should include a prespecified statistical analysis plan for ALFA-0701 that takes into account all interim analyses.

- The retrospective collection of limited safety data for ALFA-0701 might be sufficient if the safety profile can be developed from a large body of other evidence. All available safety data should be submitted.

- All available data from adequate and well-controlled pediatric trials should be submitted.

- The integrated summary of efficacy should include an assessment of outcomes by CD33 expression, GO dose and schedule, and use of product with the (b) (4)

- The integrated summary of safety should include an assessment of the effect of GO on QTc. Given the nature of the biologic and the intended population, an alternative to a thorough QT study may be proposed.

- It is expected is that validated immunogenicity screening, confirmatory and neutralizing assays will be submitted in the initial BLA submission.

On January 22, 2015, FDA determined that GO is a biologic-drug combination product and will be reviewed under Section 351 of the PHS Act. BLA 761060 was received November 2, 2016. The data proposed to support the indication for treatment of patients with newly-diagnosed de novo CD33-positive AML was discussed at an ODAC meeting on July 11, 2017.

GO (Mylotarg) was approved in Japan in 2005 for treatment of patients with relapsed or refractory CD33-positive AML. It has not been approved or marketed in any other countries.

3. Product Quality

GO is an antibody-drug conjugate (ADC) composed of a CD33-directed monoclonal antibody (hP67.6; recombinant humanized immunoglobulin [Ig] G4, kappa antibody produced by mammalian cell culture in NS0 cells) covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. (b) (4)

(b) (4). GO consists of conjugated and unconjugated gemtuzumab. The conjugated molecules differ in the number of activated calicheamicin derivative moieties attached to gemtuzumab. The number of conjugated calicheamicin derivatives per gemtuzumab molecule ranges from predominantly zero to 6, with an average of 2 to 3 moles of calicheamicin derivative per mole of gemtuzumab. Potency is based on a cytotoxicity assay using CD33-expressing HL60 cells.

Mylotarg drug product for injection is presented as a single-dose vial white to off white lyophilized cake or powder. It is intended for intravenous use. Inactive ingredients include dextran 40 (41.0 mg), sodium chloride (26.1 mg), sodium phosphate dibasic anhydrous (2.7 mg), sodium phosphate monobasic monohydrate (0.45 mg), and sucrose (69.8 mg). All impurities are expected to be within the maximal acceptable limits for the intended population. The drug product has an expiry of up to 60 months when stored at 2-8°C.

When drug product is reconstituted in 5 mL of Sterile Water for Injection US , the vial can consistently deliver 4.5 mg. The reconstituted solution is stable for up to 1 hour when stored at 2-8°C. The reconstituted solution can be diluted further in 0.9% Sodium Chloride Injection. The diluted solution is stable for up to 6 hours at 15-25°C or for up to 12 hours at 2-8°C.

There were several manufacturing changes over time. In addition, an (b) (4) was detected with trace levels as early as 1999, a shift to higher levels in 2005, and consistent levels since 2006. The ATL confirmed that all forms used were considered comparable products, and thus, the reviewed clinical data are applicable to to-be-marketed drug product.

The immunogenicity assays were not updated since the original methods were validated in 1998. The immunogenicity data from the original GO trials were evaluated in the review of the original NDA, but since the assays would not meet the current FDA recommendations, the results from the older trials were not reviewed again. Since the original review revealed no immunogenicity issue and the current clinical review revealed no new safety issue pertaining to immunogenicity, updated assays and testing of clinical samples with contemporary assays as confirmation was determined as acceptable as a post-marketing requirement.

There were no outstanding safety issues identified for the manufacturing process The facilities inspected were considered acceptable. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(b).

Approval of the BLA was recommended by the product quality review team.

4. Nonclinical Pharmacology/Toxicology

4.1 Mechanism of Action

Nonclinical data suggest that the anticancer activity of GO results binding of the ADC to CD33-expressing tumor cells, followed by internalization of the ADC-CD33 complex, and the

intracellular release of toxic N-acetyl gamma calicheamicin dimethyl hydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl gamma calicheamicin dimethyl hydrazide induces double-strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death. The nonclinical reviewer reported that in the primary nonclinical pharmacology studies, "CMA-676 was 1000-fold more cytotoxic to HL-60 cells than a comparable conjugate made with a non-targeting control antibody, and the unconjugated hP67.6 antibody showed no cytotoxicity in this assay. CMA-676 also showed an in vivo dose-response effect with >80% inhibition of tumor growth at doses between 0.8 and 2.4 mg/m2 NAc-gamma calicheamicin DMH equivalents."

4.2 Nonclinical Toxicology

The nonclinical development program included only all study reports previously submitted to the NDA that was granted approval in 2000. On the basis of review of this material, the nonclinical reviewer indicated that GO was hepatotoxic, nephrotoxic, and myelotoxic in rats and monkeys at doses of ≥7.2 mg/m^2, it was clastogenic and N-Ac-ɣ-calicheamicin DMH was mutagenic and clastogenic in in vitro tests, and it was embryotoxic and reprotoxic at approximately similar human clinical exposure after repeat doses of 3 mg/m^2. In safety pharmacology studies, GO was associated with reductions in mean arterial blood pressure, increases in heart rate and increases in P- and T-wave amplitude at ≥ 13 mg/m^2. N-Ac-ɣ-calicheamicin DMH did not inhibit the hERG current amplitude (IC50 > 6.77 mcM). Pharmacokinetic studies in rats and monkeys with the drug substance showed little dissociation of calicheamicin from the ADC in vivo.

The nonclinical reviewer identified no outstanding issues that would prevent the approval of this BLA.

5. Clinical Pharmacology

5.1 Pharmacokinetics

In the review of pharmacokinetics (PK) for the prior marketing application for Mylotarg (Kieffer, et al. Clinical Pharmacology and Biopharmaceutics NDA Review of NDA 21-174 dated April 21, 2000), the clinical pharmacology reviewer confirmed the Applicant's findings that for hP67.6 (the anti-CD33 antibody), total and unconjugated calicheamicin, a) exposure increased more than dose-proportional, b) there was accumulation with multiple doses of GO; increases in Cmax and AUC were observed in Dose Period 2 compared to Dose Period 1 when multiple doses were administered 14 days apart, and c) corresponding decreases in clearance and volume of distribution were observed between dosing periods. The clinical pharmacology reviewer for the current BLA submission indicated that PK was not assessed in the new pivotal trials, so PK and PD were inferred using available data from the early single agent trials using doses of 0.25 mg/m^2 to 9 mg/m^2. The findings included:

Distribution: N-acetyl gamma calicheamicin dimethyl hydrazide is approximately 97% bound to human plasma proteins in vitro. Population PK analyses found the total volume of distribution of hP67.6 antibody (sum of V1 [6.31 L] and V2 [15.1 L]) to be approximately 21.4 L in patients.

Elimination: The clearance (CL) value of hP67.6 from plasma was 0.35 L/h after the first dose and 0.15 L/h after the second dose, a decrease of roughly 60%. The terminal plasma half-life ($t_{½}$) for hP67.6 was 62 hours after the first dose and 90 hours after the second dose.

Metabolism: In vitro studies demonstrated that N-acetyl gamma calicheamicin dimethyl hydrazide is extensively metabolized, primarily via nonenzymatic reduction of the disulfide moiety.

Specific Populations: Age, race, sex, mild or moderate renal impairment (creatinine clearance [CLcr] 30-89 mL/min calculated by the Cockcroft-Gault equation) or mild hepatic impairment had no clinically significant effect on the pharmacokinetics of gemtuzumab ozogamicin. The pharmacokinetics of gemtuzumab ozogamicin in patients with severe renal impairment (CLcr 15-29 mL/min) or moderate (total bilirubin greater than >1.5x to 3.0x ULN) and severe hepatic impairment (total bilirubin >greater than 3x ULN) is unknown.

Drug Interaction Studies: No clinical drug interaction studies have been performed. In vitro studies showed:

At clinically relevant concentrations, gemtuzumab ozogamicin had a low potential to:

- *Inhibit CYP450 Enzymes*: CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

At clinically relevant concentrations, N-acetyl gamma calicheamicin dimethyl hydrazide had a low potential to:

- *Inhibit CYP450 Enzymes*: CYP1A2, CYP2B6 , CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.
- *Induce CYP450 Enzymes*: CYP1A2, CYP2B6, and CYP3A4.
- *Inhibit UGT Enzymes*: UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7.
- *Inhibit Drug Transporters*: P-gp (P-glycoprotein), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1 and OATP1B3.

5.2 Pharmacodynamics

The assessment of pharmacodynamics from the original dose-escalation studies showed that CD33 is saturated at GO doses of 2 mg/m^2 and higher.

The sponsor collected no information on ECG intervals for the patients treated with GO, and there was no thorough QT study for this product.

5.3 Dose Considerations

The results of the pharmacometric analyses using data from the 9 mg/m^2 dose reported by the clinical pharmacology reviewer indicated that "the effect of exposure on VOD was significant with any exposure measures and Cmax after first dose showed the most significant effect on VOD. Based on covariate analyses using baseline risk factors, prior stem cell transplantation was a significant predictor for the risk of VOD. Nonetheless, the effect of exposure on the risk of VOD was notable in both groups of patients regardless of stem cell transplantation status. After adjusting for the prior stem cell transplantation effect, Cmax of hP67.6 after first dose of GO was still a significant effect on the risk of VOD." "Exposure-efficacy relationship, however, was relatively flat. Among baseline risk factors associated with baseline disease condition, baseline platelet counts, baseline bone marrow blasts, and baseline P-glycoprotein (P-gp) levels were significant predictors for complete remission." The reviewer concluded that GO doses lower than 9 mg/m^2 should result in less VOD due to the lower Cmax, but a substantial loss of therapeutic effect is not expected by reducing dose of GO. The clinical pharmacology team leader indicated that the proposed (b) (4) dosing would be acceptable for patients over the age of 2 years. However, since PK and PD were not evaluated using the proposed 3 mg/m^2 fractionated schedule, the clinical pharmacology reviewer recommended further study for confirmation as a postmarketing requirement.

The Office of Clinical Pharmacology found the BLA to be approvable from a clinical pharmacology perspective.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

7.1 Sources of Data

The key materials used in the reviews of efficacy and safety included:

- All information submitted in BLA 761006
- Information in the cross-reference files NDA 021174 and IND 046635
- The MyloFrance-1 analysis data set provided by Dr. Sylvie Castaigne on June 30, 2017.
- The AML 19 efficacy analysis data set provided by Dr. Stefan Suciu on August 28, 2017.
- Published literature
- Relevant information in the public domain

Since the original approval of GO in 2000, there has been a substantial body of literature generated that describes the safety and activity of GO for treatment of newly-diagnosed or

R/R AML in various populations. Since there is no known biosimilar of gemtuzumab ozogamicin, any literature citing use of GO or Mylotarg was considered relevant for this review.

The body of literature on GO also informed medical practice while GO was marketed. Among this literature, Dr. Norsworthy identified Study AML 19 and Study MyloFrance-1 as studies of interest for this review. She determined that both of these studies fulfilled the regulatory criteria for adequate and well-controlled trials (Clinical Review Original-2 Table 5) and that they used Mylotarg as the test article. The applicant did not submit the data sets for these trials in the BLA, but in the interest of promoting the public health, FDA contacted the sponsors of Study AML 19 and Study MyloFrance-1directly to request the data for review.

Table 1 shows an overview of the 3 clinical trials that provided pivotal efficacy data.

Table 1: Clinical Trials Cited in the Prescribing Information

Trials / Status	Design	Population	Primary Endpoint
ALFA-0701 ***(Completed)***	Randomized, open-label Phase 3 trial • GO: 3 mg/m^2/dose (max dose 5mg) D1, 4, 7 plus Chemotherapy: 1) DNR: 60 mg/m^2/d D1-3 2) AraC: 200 mg/m^2/d D1-7 *vs* • DNR/AraC without GO	Adults 50-70 years old with previously untreated de novo AML - 271 patients randomized	EFS
AML 19 – EORTC/ GIMEMA 06031 ***(Completed)***	Randomized open-label Phase 2-3 trial • GO 6 mg/m^2 d1 and 3 mg/m^2 d8 (n=118) *vs* • BSC (n=119)	Newly-diagnosed AML age >75, 61-75 with PS>2, or unwilling to receive intensive therapy - 237 total patients randomized	OS
MyloFrance-1 - WS1591694 ***(Completed)***	Single-arm, open-label Phase 2 trial Induction: GO 3 mg/m^2 d 1, 4, and 7 Consolidation: AraC 3 g/m^2 q12h d1-3 (1 g/m^2 for patients >55 y or CrCl >50 mL/min)	Adults with CD33+ AML in first relapse after CR ≥3, ≤18 months - 57 patients	CR+CRp

7.2 Information Relevant to Dose

A major safety concern that the applicant sought to address was the toxicities, including early mortality, reported in the clinical trials using GO 9 mg/m^2 as monotherapy or GO 6 mg/m^2 in combination with chemotherapy. As indicated in Section 5.3, the pharmacology reviewer reported that the exposure response curve was flat for GO 9 mg/m^2 as monotherapy. The pharmacometric analysis was limited by the lack of data from a range of doses. Dr. Norsworthy provided a meta-analysis of efficacy in 19 trials of GO as treatment for relapsed or refractory AML (Clinical Review Original-2 Figure 6). She reported that the CR rate was 13.7% (10.7, 17.1) for patients treated on trials using GO 9 mg/m^2, 1.2% (0.0, 5.7) using GO 6 mg/m^2, and

25.3% (15.5, 36.7) using GO 3 mg/m^2 d1, 4, 7. Although there are many caveats for cross-study comparison, the data do not suggest that lowering the dose of GO would reduce the CR rate for monotherapy.

The NCRI AML17 trial was a randomized study comparing GO 3 mg/m^2 vs 6 mg/m^2 on day 1 in combination with intensive induction chemotherapy for first-line treatment of patients with AML or high-risk MDS. The accrued population included 788 patients of median age 50 years (range, 0-81 years), and 95% of the patients had AML rather than MDS. Interpretation of the study is somewhat confounded by the inclusion of multiple chemotherapy regimens and multiple additional rerandomizations for consolidation, but the investigators reported that in comparison to GO 6 mg/m^2, the patients treated with GO 3 mg/m^2 had a higher numerically-higher CR rate (82% vs 76%), and there was no significant difference between the study arms for the endpoints of overall survival or relapse-free survival.

Both clinical reviewers concluded that the fractionated schedule with the lower GO dose was reasonable to study.

7.3 Indication #1: Treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults

ALFA-0701

ALFA-0701 (NCT00927498) was a multicenter, randomized, open-label Phase 3 study of 271 patients with newly-diagnosed de novo AML age 50 to 70 years. Patients were randomized 1:1 to receive induction therapy consisting of daunorubicin (60 mg/m^2 on Days 1 to 3) and cytarabine (200 mg/m^2 on Days 1 to 7) (DA) with (n=135) or without (n=136) GO 3 mg/m^2 on Days 1, 4, and 7. Patients who did not achieve a response after first induction could receive a second induction with daunorubicin and cytarabine alone. Patients with response received consolidation therapy with 2 courses of treatment including daunorubicin (60 mg/m^2 on Day 1 of consolidation course 1; 60 mg/m^2 on Days 1 and 2 of consolidation course 2) and cytarabine (1 g/m^2 every 12 hours on Days 1 to 4) with or without GO 3 mg/m^2 on Day 1 according to their initial randomization. Patients who experienced remission were also eligible for allogeneic transplantation. An interval of at least 2 months between the last dose of MYLOTARG and transplantation was recommended.

The median age of the patients was 62 years (range,50-70), 137 were female and 134 were male, and 88% had an ECOG PS of 0 to 1. Baseline characteristics were balanced between treatment arms with the exception of gender as a higher percentage of males were enrolled in the GO arm (55%) than in the DA alone arm (44%). Overall, 59%, 65% and 70% of patients had documented favorable/intermediate risk and 33%, 27% and 21% had poor/adverse disease by the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) and cytogenetic risk classifications, respectively. CD33 expression on AML blasts by flow cytometry was determined in 194/271 (72%) patients overall. Few patients (14%) had low CD33 expression (less than 30% of blasts), and none had no expression of CD33.

Efficacy was established on the basis of event-free survival (EFS), measured from the date of randomization until induction failure, relapse, or death by any cause. Per protocol, induction failure was defined as failure to achieve CR or CRp in induction, and date of induction failure was defined as date of marrow evaluation after the last course of induction. Median EFS was 17.3 months in the GO arm versus 9.5 months in the control arm; hazard ratio (HR) 0.56 (95% CI: 0.42-0.76); 2-sided p less than 0.001 by log-rank test. In an exploratory analysis of EFS using the preferred definition (failure to achieve CR in induction, relapse, or death from any cause and using the date of randomization as the date of induction failure), median EFS was 13.6 months for GO + DA and 8.8 months for DA with HR 0.68 (95% CI: 0.51-0.91). There was no statistically significant difference between treatment arms in overall survival (HR 0.81 (0.60, 1.09).

The subgroup analyses for EFS and OS were consistent with the main analysis except for patients with unfavorable cytogenetics, for whom there was a distinct disadvantage for the GO arm for both EFS (HR 1.11 [0.63, 1.95]) and OS (HR 1.55 [0.88, 2.75]).

The applicant also provided meta-analyses of EFS and OS across 5 randomized trials using combination chemotherapy with or without various doses of GO. Since meta-analyses are not use as the basis for approval of drugs for first-line treatment of AML, these are not considered further in this review.

Because FDA usually uses OS as the endpoint to confirm clinical benefit for treatment of AML, the applicant performed analyses to determine if EFS was a surrogate of OS. In a trial-level analysis of 33 randomized studies in untreated patients with de novo AML, the trial-level weighted R^2 was only 0.46 (95% CI 0.23, 0.70). (Note that an R2 close to 1 indicate a strong trial-level surrogacy.) In the subgroup of 5 randomized GO studies for which patient-level data were available, the weighted R^2 through a copula model was 0.45 (95% CI 0.00, 1.00) and was 0.61 (95% CI 0.20, 1.00) without application of a copula model. Dr. Ko provided additional analyses for correlations between EFS and OS using the patient-level data and various definitions of EFS (Statistical Review Table 11). She observed that "none of the EFS definitions that consider failure to attain CR as an event are able to demonstrate both a strong correlation between individual EFS and OS times and a strong correlation between hazard ratios for treatment effects on EFS and OS." She also identified salvage therapies for induction failures and relapse was major factors that affect the correlation between EFS and OS.

Despite the lack of correlation between EFS and OS, Dr. Ko noted that ALFA-0701 did demonstrate an improvement in EFS, and EFS was considered a clinical benefit by ODAC. She recommended approval for the proposed indication but also suggested additional investigation for patients with adverse cytogenetics.

Dr. Jen concurred that a benefit for GO was not observed for EFS or OS in patients with adverse cytogenetics, and she also observed that "The risks involved with GO treatment may outweigh the lack of benefit in patients with adverse cytogenetics. But, while the oncology field may be moving towards precision medicine, from a real-world perspective, cytogenetic data may not be available at the time of treatment initiation. Additionally, the safety data for GO+DA do not

support an increased risk of harm in these patients. Restricting the indication by cytogenetic risk category would require that all patients delay treatment until that information is obtainable. This may be an unacceptable risk for many patients. Therefore, the label should be clear with regards to the lack of evidence in this subset; however, the decision regarding the use of GO in these patients should be left to the discretion of the treating physician to be assessed on an individual patient basis."

Dr. Jen also provided additional exploratory analyses of EFS and OS by CD33 expression. She noted "Although some smaller early studies failed to find a predictive role for CD33 expression, the majority of recent large randomized trials demonstrate a correlation between CD33 expression and response to GO. However, the cut-offs used for these determinations vary widely between trials. All patients in ALFA-0701 who had a CD33 level in the dataset had a level greater than 0. FDA's analysis showed that, although patients with >70% CD33 expression had the most significant improvement in EFS, all groups appeared to derive some degree of benefit... while data clearly show that only patients who are CD33-positive derive benefit from GO, there are no data to support a specific cut-off value, and we will define CD33-positivity as any level >0." She therefore recommended approval of the proposed indication without qualifiers.

AML 19

AML 19 (NCT00091234) was a multicenter, randomized, open-label Phase 3 study comparing GO to best supportive care (BSC) for patients with newly-diagnosed AML who were a) greater than 75 years of age or b) 61 to 75 years of age with a World Health Organization performance status (WHO PS) greater than 2 or were unwilling to receive intensive chemotherapy. Patients were randomized 1:1 and stratified by age (61-75 vs 76-80 years vs ≥ 81 years), CD33 positivity of bone marrow blasts (less than 20 % vs 20-80% vs greater than 80% vs unknown), initial white blood cell count (less than 30 vs greater than or equal to 30 x 10^9/L), WHO PS (0-1 vs 2 vs 3-4), and institution. During induction, GO 6 mg/m^2 was given on day 1 and GO 3 mg/m^2 was given on day 8. Patients with no evidence of disease progression or significant toxicities after GO induction received continuation therapy as outpatients with up to 8 courses of treatment including GO 2 mg/m^2 on day 1 every 4 weeks. Patients continued therapy if they did not experience significant toxicities, relapse, or disease progression. BSC included standard supportive care measures and hydroxyurea or other anti-metabolites for palliative purposes.

In total, 118 patients were randomized to treatment with GO and 119 patients to BSC. Overall, the median age of patients was 77 years (range, 62-88 years), and most patients (65%) had a WHO PS of 0 to 1 at baseline. Baseline characteristics were balanced between treatment arms with the exception of gender and cytogenetics. Compared to the BSC arm, the GO arm had a higher percentage of females (52% vs 39%) and patients with favorable/intermediate risk cytogenetics (50% vs 38%). The proportion with adverse cytogenetics was similar between arms (28% vs 27%). Fewer patients on the GO arm had missing cytogenetics data (22% vs 35%). CD33 expression on AML blasts by flow cytometry at a centralized location was determined in 235/237 (99%) patients; 10% had CD33 expression less than 20%.

The efficacy of GO was established on the basis of improvement in overall survival (OS). The hazard ratio (HR) for OS was 0.69 (95% CI: 0.53 0.90) (2 sided p=0.005 by log-rank test). Median OS was 4.9 months in the GO arm versus 3.6 months in the control arm.

Dr. Norsworthy reviewed the results of AML 19 in terms of clinical benefit and recommended approval of the monotherapy regimen as described.

AAML0531

AAML0531 randomized 1022 pediatric patients with AML to GO + standard chemotherapy vs chemotherapy alone. The primary endpoints were EFS and OS, with induction failure defined as failure to achieve CR and IF date being the date of study entry. EFS was 53.1% with GO compared to 46.9% without GO at 3 years (HR 0.83, 95% CI, 0.70-0.99, p=0.04). Similarly to the adult trials, there was no corresponding OS benefit. A reduction in relapse risk (3 years: 32.8% vs 41.3%; HR 0.73; 95% CI 0.58-0.91, p=0 .006) was reported. Dr. Jen reviewed the published report, protocol and study report. She determined that the study fulfilled the requirements of an adequate and well-controlled trial, and she recommended extension of the indication for treatment of newly-diagnosed AML to the pediatric population.

7.4 Indication #2 : Treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older

MyloFrance-1

MyloFrance-1 was a phase 2, single-arm, open-label study of GO monotherapy in adults with CD33-positive AML in first relapse. Patients with secondary leukemia or a prior autologous or allogeneic stem cell transplantation were excluded. Study treatment included a single course of GO 3 mg/m^2 on Days 1, 4, and 7. Consolidation therapy consisted of cytarabine intravenously administered every 12 hours for 3 days. The cytarabine dose was 3 g/m^2 for patients less than 55 years old and 1 g/m^2 for patients 55 years or older and/or patients with a creatinine clearance below 50 mL/minute. Hematopoietic stem cell transplantation (HSCT) was allowed after treatment with GO, but it was recommended to delay HSCT by at least 90 days following GO.

There were 57 patients treated with GO. The median age of patients was 64 years (range 22-80 years). The median duration of first remission was 10 months. Forty-four (78%) patients had intermediate-risk and 12 (22%) poor-risk cytogenetics.

The efficacy of GO was established on the basis of complete remission (CR) rate and duration of remission. Fifteen (26%; 95% CI 16% - 40%) patients achieved CR following a single course of GO. Median relapse-free survival, measured from the first documentation of CR to the date of relapse or death, was 11.6 months.

Dr. Norsworthy reviewed the results of MyloFrance-1 as well as CR rates from all available studies of GO monotherapy in adults and children with relapsed or refractory CD33-positive AML. She indicated that “Approval in the relapsed/refractory (R/R) setting is supported by the

results of MyloFrance 1... Efficacy in the setting of refractory or subsequently relapsed AML was determined based on supporting studies and the literature showing meaningful, albeit lower, remission rates in different relapse populations. (b) (4)

7.5 Conclusions on the Substantial Evidence of Effectiveness

I agree with Dr. Ko's conclusion that EFS is not a valid surrogate for OS for treatments of newly-diagnosed AML, but I also agree with the opinion of the ODAC that EFS itself can be considered a clinical benefit if defined in a way that accurately reflects achievement of CR and meaningful durability of CR.

Therefore, the results of ALFA-0701 which showed an EFS benefit when GO is used in combination with DA, and the results of AML 19 which showed an OS benefit for GO as a single agent in comparison to best supportive care, demonstrate effectiveness of GO for treatment of newly-diagnosed CD33-positive AML. Although GO monotherapy is clearly not curative, the monotherapy regimen would be of particular importance for the subgroup of patients who desire even a short survival benefit but are not willing to accept the risks of intensive chemotherapy. Such a decision is in the purview of the practice of medicine and cannot be limited by age alone.

I disagree with Dr. Jen's recommendation to extend the first indication to pediatric patients based on the results of AAML0531. Although this study was an adequate and well-controlled trial, the study report raises a concern regarding a potential safety issue. Since the applicant did not provide the data set that would allow FDA to conduct an adequate risk-benefit assessment for children in this intended population, the data are not sufficient to support the recommendation. The safety concern, however, warrants a PMR to assess and submit the data from this trial in order to determine if any other action is needed.

There remains concern about the observed lack of effect of GO in ALFA-0701 in the subgroup of patients with adverse cytogenetics. Dr. Jen rightly noted that limiting the indication to exclude this subgroup might not be feasible, since treatment of AML may start before the results of cytogenetics are available. Dr. Jen's recommendation to include a warning to consider whether treatment with GO should continue once the cytogenetics results are available provides a reasonable approach to managing the risk. Since adults younger than 50 years of age are more likely to have favorable or intermediate risk cytogenetics, extending the age range to all adult on the basis of the mechanism of action and biology of the disease would seem reasonable.

I also agree with Dr. Norsworthy's conclusion that MyloFrance-1 demonstrates effectiveness of the 3 mg/m^2 fractionated regimen for treatment of relapsed CD33-positive AML, and that the totality of the evidence including all monotherapy trials allows extrapolation to adults and children with later relapse or with refractory disease.

8. Clinical Safety

8.1 Safety Database

The applicant provided safety data for 2747 subjects treated with GO on applicant-sponsored studies (n=1088) or investigator-initiated studies (n=1659). These included 953 subjects with AML treated with GO monotherapy and 1730 subjects with AML treated with GO in combination with other chemotherapy. The major limitation of the safety database was that the data collection was incomplete for the recommended dose-schedules specifically.

8.2 Information Relevant to Dose

As indicated in Section 5.3, the clinical pharmacology reviewer reported that there was a significant exposure-toxicity relationship for Cmax (but not AUC) and VOD. Dr. Norsworthy provided a meta-analysis of safety in 20 trials of GO as treatment for relapsed or refractory AML (Clinical Review Original-2 Figure 8). She reported that the incidence of VOD was 5.6% (3.5, 8.1) for patients treated on trials using GO 9 mg/m^2, 15.0% (6.4, 26.4) using GO 6 mg/m^2, and 0% (0.0, 1.1) using GO 3 mg/m^2 d1, 4, 7. The results suggested that the low-dose fractionated regimen of GO would have a lower risk of VOD rate for monotherapy.

8.3 Safety of GO in Combination with DA

From Dr. Jen's review:

"The safety dataset included 131 patients treated with fractionated GO + DA and 137 patients treated with DA alone. The demographics of the group was representative of the intended population; although ALFA-0701 enrolled patients between 50-70 years old, trials included in the supportive IPD Meta-Analysis allowed for safety analyses across a broader age range (including patients between the ages of 15 and 90 years old). However, it is important to note that the safety analysis was limited by the retrospective nature of the collection of adverse events. The study population was examined for early mortality, treatment-related deaths, serious adverse events, adverse events of special interest, common adverse events, and common laboratory tests. There were no QT data available, and only baseline ECGs were collected.

The key results from the review of safety showed:

- 30-day mortality was not significantly different between the GO + DA arm vs the DA arm (4% vs 2%). Importantly, the disparity in early mortality between treatment arms was lower in ALFA-0701 than in SWOG S0106 with odds ratios of 1.99 and 3.58, respectively. This suggests that the 3 mg/m^2 fractionated GO schedule is safer with regards to early mortality.

- Overall, incidence of treatment-related mortality was low, but remained higher in the GO arm (6% vs 2%). In the GO arm, these deaths were predominantly due to hemorrhage and VOD. In the control arm, all TRM was related to sepsis.

- Treatment discontinuation due to adverse event was higher in the GO arm (31% vs 7%). The adverse events that primarily accounted for this difference were thrombocytopenia (15% vs 0%) and hepatobiliary disorders (6% vs <1%).

- The most common adverse events occurring more frequently with GO + DA vs DA were due to bleeding or infection, and differences in rates occurred during each phase of treatment.

- There remains a risk for VOD which occurred in 5% of patients randomized to GO+DA vs 0% in patients who did not receive GO. There were 3 fatal cases of VOD. 7 of 8 patients developed VOD without prior transplantation.

- Hemorrhage events occurred more frequently with GO + DA than with DA during all phases of treatment. ALFA-0701 had a higher overall risk difference for Grade 3 and higher hemorrhage (in any phase) than other protocols in the meta-analysis or literature review, with a risk difference of 13.4% with GO+DA over DA alone.

- Platelet recovery appeared to be delayed in patients treated with GO + DA vs DA alone.

- The laboratory shifts to Grade≥3 that were higher in the GO arm were AST and bilirubin elevations, hypophosphatemia, hypokalemia, and hyponatremia.

- The results of the IPD meta-analysis were consistent with the expectation that the lower GO dose and fractionated schedule had less toxicity than GO 6 mg/m^2 used in S0106 previously."

8.4 Safety of GO Monotherapy

From Dr. Norsworthy's review:

"Of the 57 patients in MyloFrance 1, there were 40 (70%) deaths observed. There were 4 early deaths (7%) before day 43 of therapy. There was one death before the day 15 bone marrow evaluation, one at day 27 during treatment-induced bone marrow hypoplasia with no persistent leukemia, and two on days 23 and 30 with persistent leukemia. Other key safety results showed the following:

- No infectious deaths occurred
- Grade 3 TEAEs in > 1% patients included sepsis (32%), fever (16%), rash (11%), pneumonia (7%), bleeding (7%), mucositis (4%), diarrhea (2%), headaches (2%), and edema (2%)
- No grade 4 toxicity was observed
- Grade 1 or 2 hyperbilirubinemia was reported in 4 (7%) patients
- Grade 1 or 2 elevations in AST or ALT were observed in 23 (40%) and 9 (16%) patients, respectively
- No episodes of VOD occurred
- CR and CRp patients had median time to ANC >500/µL 23 days from the first dose of GO
- CR and CRp patients had median time to platelets >50,000/µL of 20 days

Comparison of fractionated dosing (3 mg/m^2 days 1, 4, and 7) with unfractionated dosing of GO (at doses of 6 or 9 mg/m^2 every 14 days), using all available data in relapsed AML patients revealed the following observations:

- Early mortality lower across studies with lower doses of GO (9% overall using 3 mg/m^2 fractionated dosing, 10% using 6 mg/m^2 unfractionated, and 16% using 9 mg/m^2 unfractionated dosing)
- Treatment-related causes of death appeared to be reduced in patients treated with the 3 mg/m^2 fractionated regimen
- Grade 3-4 hemorrhage 7% on MyloFrance 1 versus 8-48% across studies using 6 and 9 mg/m^2 unfractionated doses of GO (28% on Studies 201-203)
- Grade 3-4 hepatotoxicity was not seen on Study MyloFrance 1 using the fractionated dose regimen, compared to rates up to 29% on studies 201-203
- No cases of VOD reported across all fractionated dose trials to date compared to 6% and 15% incidence across trials using 9 mg/m^2 and 6 mg/m^2 unfractionated dose regimens, respectively
    - Fatal VOD 4% on Studies 201-203 and 5% on the post-transplant Study 100374
    - Incidence of VOD with unfractionated dosing higher when administered pre- or post-HSCT
    - No cases of VOD out of 19 patients reported to date receiving fractionated doses of GO pre- or post-HSCT

- Time to neutrophil and platelet recovery on MyloFrance 1 substantially shorter than studies 201-203

Regarding a broader subset of R/R AML patients, the safety profile was similar in the R/R AML subgroup, although with a slightly higher incidence of VOD of 8% (only 2% fatal). Retrospective studies by Thomas *et al* (Thomas, Le et al. 2005) and Brethon *et al* (Brethon, Auvrignon et al. 2006) indicate a comparable safety profile in R/R patients with AML treated with fractionated doses of GO (i.e. not limited to the first relapse setting) without any cases of VOD.

Regarding pediatric use, the safety profile of unfractionated doses of GO in pediatric patients with relapsed or refractory AML was comparable to that seen in adults, with the exception that VOD was much more common on study 102, with an incidence of 31% overall. However, fatal VOD was only 3%. The retrospective pediatric trial by Brethon *et al* (Brethon, Auvrignon et al. 2006) indicated that fractionated doses of GO may be better tolerated in children, with none of the 6 patients treated with this dosing regimen developing VOD.

Lastly, regarding patients with AML who are post-HSCT, the safety of unfractionated doses of GO in these patients has not been established. DLTs occurred at all dose levels for the allogeneic HSCT group in Study 100374 and VOD incidence was 14% overall. There is little data on safety pre- or post- HSCT with the fractionated dosing regimen, but there are no safety signals to date.

Out of 19 documented patients with a prior or subsequent HSCT with respect to treatment with fractionated dose GO, there were no cases of VOD.

Of 118 patients randomized to GO on AML-19, there were 113 (96%) deaths observed versus 115/119 (97%) on the BSC arm. The all-cause 30-day mortality was 11% in the GO arm versus 13.5% in the BSC arm. 60-day mortality was 18% in the GO arm versus 30% in the BSC arm. Of 111 patients who were treated with GO, 8 (7%) experienced early deaths that were deemed treatment-related (infection, n=5; hemorrhage, n=1; renal failure, n=1; and cardiac failure, n=1). Deaths due to any AE over the course of the trial were 17% on the GO arm versus 20% on the BSC arm. Other key safety results showed the following:

- Grade ≥ 3 TEAEs in > 5% patients were comparable between the GO and BSC arms, including infection (GO 35% vs BSC 34%), febrile neutropenia (18% vs 24%), bleeding (13% vs 12%), fatigue (12% vs 21%), liver toxicity (7% vs 6%), cardiac toxicity (6% vs 14%), metabolic toxicities (4% vs 6%), and renal toxicity (4% vs 4%)

- No episodes of VOD occurred."

8.5 Safety Summary

The most common adverse reactions (>15%) were hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, and mucositis. Cytopenias and elevated liver tests are the most common laboratory abnormalities.

The most serious adverse reaction is VOD, which warrants a boxed warning. Infusions reactions, hemorrhage and QT prolongation are additional adverse reactions that are potentially fatal or life-threatening and need to be highlighted for mitigation greater than usual for the intended population.

Infusions reactions (including anaphylaxis) may occur, and the instructions for use should specify the premedications to mitigate infusion reactions.

Myelosuppression is common, but thrombocytopenia can be prolonged. Dose modifications should be specified to mitigate severe or life-threatening complications of cytopenias. The observation that hemorrhages occurred even without severely depressed platelet counts suggests that the drug may be having an effect on platelet function as well. This warrants further study.

No data are available to evaluate the effect of GO on QT. Inotuzumab ozogamicin, a related ADC, carries a warning due to a demonstrated risk of QTc prolongation. This will be considered a class risk and applied to GO until there are data to demonstrate otherwise.

The assessment of GO 3 mg/m2 days 1, 4 and 7 alone or in combination with DA suggest that the lower dose fractionated schedule was associated with less early mortality and a lower risk of VOD. However, since safety data collection was incomplete, the safety profile remains to be confirmed in an additional study postmarketing.

9. Advisory Committee Meeting

The indication for treatment of patients with newly-diagnosed de novo CD33-positive AML was discussed at an Advisory Committee Meeting on July 11, 2017. Dr. Jen summarized the meeting as "Acknowledging the lack of surrogacy of EFS for OS, FDA requested a discussion of the utility of EFS as a stand-alone endpoint in newly-diagnosed AML. The voting question for the committee was "Do the results of ALFA-0701 demonstrate a favorable risk:benefit for gemtuzumab ozogamicin 3 mg/m2 days 1, 4 and 7 added to DA for patients with newly-diagnosed CD33-positive AML?"

The committee unanimously voiced agreement on the use of EFS as an endpoint in newly-diagnosed AML. The final vote regarding the positive risk:benefit in ALFA-0701 was 6 votes Yes, 1 vote No. The committee member voting No voiced concerns regarding the inclusion of patients with adverse risk cytogenetics in the indication given the risks of the treatment and the lack of data supporting benefit in this subset of patients; however, he agreed that for patients with favorable/ intermediate risk the evidence was sufficient to support a favorable risk:benefit."

10. Pediatrics

GO received orphan designation for treatment of acute myeloid leukemia on November 24, 1999. As such, this application is exempt from the requirement for a pediatric assessment for both indications.

However, the application did include safety and efficacy data for children. Specifically, the safety and efficacy of GO as a single agent in the pediatric patients with relapsed or refractory AML was supported by a single-arm trial in 29 patients in the following age groups: 1 patient 1 month to less than 2 years old, 13 patients 2 years to less than 12 years old, and 15 patients 12 years to 18 years old. A literature review included an additional 96 patients with ages ranging from 0.2 to 21 years. No differences in efficacy and safety were observed by age.

11. Other Relevant Regulatory Issues

Clinical Site Inspections

Four clinical sites and the sponsor sites (Wyeth and Versailles Hospital Center) were selected for inspection for Study ALFA-0701. The final classification for inspections of three clinical sites, Wyeth and Versailles Hospital Center is No Action Indicated (NAI). The preliminary classification for inspection of one clinical site is Voluntary Action Indicated (VAI) for failure to retain investigational records for a period of two years following approval of a drug's marketing application. The Office of Scientific Investigations concluded that the study data derived from these clinical sites are considered acceptable in support of the requested indication. Since one of the missing records was the consent form for one study subject, the clinical reviewer chose to remove that subject from the analysis. There were no clinical site inspections for AML 19 or MyloFrance-1.

Financial Disclosures

Financial disclosure forms could not be obtained from several of the investigators for ALFA-0701, and one investigator had a reportable financial conflict of interest due to consulting revenues. The clinical reviewer concluded that these deficiencies affect study outcome, since the results reported were adjudicated by a blinded Independent Review Committee. Data for AML 19 and MyloFrance-1 were not submitted by the applicant, so no financial disclosures were obtained for these trials.

12. Labeling

The Prescribing Information was revised substantially. See the final agreed-upon labeling for the changes incorporated.

13. Postmarketing Recommendations

Risk Evaluation and Mitigation Strategies (REMS)

The DRISK reviewer indicated that "Based on the available data, a REMS is not necessary for Mylotarg to ensure the benefits outweigh the risks. The safety concerns associated with Mylotarg use are well-documented. Healthcare providers who treat AML should be familiar with the risks and the importance of patient monitoring."

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMR-1

Further characterize the safety and pharmacokinetics of the 3 mg/m^2 day 1, 4, and 7 dose-schedule of Mylotarg as a single agent for treatment of patients with relapsed or refractory CD33-positive acute myelogenous leukemia. Submit a study report and datasets, including an analysis of hemorrhage, complete blood counts, PT, aPTT, and fibrinogen, hepatotoxicity, hepatic veno-occlusive disease (VOD), and the impact of hematopoietic stem cell transplantation pre- or post-Mylotarg on the incidence of VOD. Enroll at least 50 patients.

PMR -2

Conduct a study to determine the effect of Mylotarg on the QT interval in humans.

PMR -3

Provide data to confirm the safety of gemtuzumab ozogamicin in pediatric patients. Submit an abbreviated study report, including data sets, for Study AAML0531, a randomized trial of approximately 1000 pediatric patients with acute myeloid leukemia evaluating Mylotarg in approximately 500 pediatric patients.

PMR -4

Submit a validation report for a validated, sensitive, and accurate assay(s) for the detection of binding antibodies to gemtuzumab ozogamicin, including procedures for the accurate detection of binding antibodies to gemtuzumab ozogamicin in the presence of gemtuzumab ozogamicin levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay(s) should be able to detect and confirm binding antibodies directed against both gemtuzumab and the calicheamicin/linker moiety.

PMR -5

Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to gemtuzumab ozogamicin, including procedures for the accurate detection of neutralizing antibodies to gemtuzumab ozogamicin in the presence of gemtuzumab ozogamicin levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMR -6

Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to gemtuzumab ozogamicin with the validated assay developed under PMRs #4 and #5.

PMC -1

To conduct the bioburden and endotoxin drug substance release method qualifications using two additional batches of drug substance.

PMC-2

To conduct the sterility and endotoxin drug product release method qualification using two additional batches of drug product.

PMC -3

Determine the effect of a broad range of concentrations of Mylotarg on the potential to inhibit platelet function by conducting in vitro studies on platelets and megakaryocytes. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).

PMC -4

Re-evaluate gemtuzumab ozogamicin drug substance and drug product lot release acceptance criteria for appearance, iCE, CGE and cytotoxicity assays based on ≥25 unique combinations of

gemtuzumab [redacted] (b) (4) lots used to manufacture gemtuzumab ozogamicin drug substance and drug product using the commercial manufacturing process and tested using the commercial specification methods. Pfizer will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

14. Recommended Comments to the Applicant

There are no recommended comments to the Applicant.

15. Division Director Comments

I concur with the discipline review teams' recommendations and ODAC's recommendation that Mylotarg (gemtuzumab ozogamicin) should receive approval: for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults and for the treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older. Wyeth has provided substantial evidence of effectiveness with adequate safety to label the product. In this review, Dr. Przepiorka has very nicely summed up Mylotarg's marketing history, the withdrawal, reasons why Mylotarg's approval is prudent at this time including the clinical and statistical issues. A few issues arose during the review such as whether EFS is a surrogate for OS or represents clinical benefit, concern about potential lack of benefit for those patients with AML and adverse cytogenetics, and the recommendation to extend the newly diagnosed indication to pediatric patients. The clinical and statistical teams did outstanding analyses which contributed greatly to our understanding of relationship of EFS and OS with respect to Mylotarg therapy. I concur with ODAC's recommendation for Mylotarg that EFS itself can be considered a clinical benefit if defined in a way that accurately reflects achievement of CR and meaningful durability of CR. I also agree with not limiting Mylotarg's use to those patients with AML that has favorable or intermediate risk cytogenetics as cytogenetic data may not be available at the time of treatment initiation and including a warning in the Prescribing Information. Third I agree with Dr. Przepiorka's recommendation to not extend the newly diagnosed indication at this time to pediatric patients without review of clinical data. Mylotarg was relabeled more than once for safety concerns shortly after its original approval in 1999, and a better understanding of the safety concerns associated with use with combination therapies in pediatric patients is warranted. I agree that this issue warrants a PMR. A REMS will not be required for this approval. I concur with the proposed PMRS and PMCs.

Ann T. Farrell, MD
Director, Division of Hematology Products

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/s/

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08/31/2017

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