

**Mylotarg<sup>®</sup> (gemtuzumab ozogamicin for Injection)**  
**NDA No. 21-174**  
**Briefing Document**  
**Prepared for the**  
**Oncologic Drugs Advisory Committee (ODAC) Meeting**  
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**Summary**

On November 26, 2002, the Division of Oncology Drug Products sent notice to pharmaceutical companies with drugs approved under 21 CFR Part 314.500 (Subpart H, accelerated approval regulations), inviting participation in an open session at the March 12-13, 2003 meeting of the Oncologic Drugs Advisory Committee (ODAC). Wyeth was asked to provide an update on the status of Subpart H phase IV commitments for Mylotarg.

In the following sections, Wyeth provides background information on the Subpart H accelerated approval of Mylotarg and on its labeled use and safety. This document also provides information on acute myeloid leukemia (AML) and its treatment options as this is relevant to the conditions of Mylotarg use. A review of Wyeth's post-marketing clinical commitments and their status is included.

**Background**

On October 29, 1999, Wyeth submitted a new drug application (NDA) for Mylotarg® (gemtuzumab ozogamicin for Injection). The Food and Drug Administration (FDA) completed the review of the application according to the regulations for accelerated approval, and concluded that adequate information was presented to approve Mylotarg 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. This application was approved on May 17, 2000 under 21 CFR Subpart H, a program described in the regulations as intending to make promising products for life threatening diseases available on the market on the basis of preliminary evidence of safety and efficacy.<sup>1</sup>

In order to qualify for accelerated approval under Subpart H, FDA indicated that the response rate demonstrated with gemtuzumab ozogamicin should be comparable to that obtained with current standard therapies, assuming a safety advantage. If there was no safety advantage with gemtuzumab ozogamicin, the response rate would need to be better than that with standard chemotherapy. The FDA stated that determining historic complete remission (CR) and morphological remission (MR) rates associated with conventional chemotherapy would be considered helpful.

Mylotarg was approved on the basis that the product has an effect on a surrogate endpoint reasonably likely to predict a clinical benefit (in this case an effect on CR and CR<sub>p</sub> [remission with incomplete platelet recovery]). Mylotarg was evaluated in preclinical studies, two phase I studies, and three phase II studies of patients with relapsed AML. The effectiveness of Mylotarg is based on overall response (OR) rates. There are no controlled trials demonstrating a clinical

benefit, such as improvement in disease-related symptoms or increased survival, compared to any other treatment. The safety and efficacy of Mylotarg in patients with poor performance status and organ dysfunction have not been established.

### **Acute Myeloid Leukemia (AML)**

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults. The American Cancer Society estimated that 10,500 new cases of AML and 7,800 deaths from AML would occur in the United States in 2002.<sup>2</sup> Among the new cases it is estimated that Mylotarg can potentially treat approximately 2,600 patients within its indicated use. Slightly more than one half of all patients with AML are 60 years of age or older.

Untreated AML is a rapidly fatal disease, with a median survival time of less than 3 months. With standard treatments for patients with de novo AML a high rate of first remission is achieved, but approximately 75% of patients with first remission ultimately relapse. The majority of relapses occur within 2 years after remission is attained. The American Cancer Society reported 5-year survival rates of 18.7% for patients with AML.<sup>2</sup> Patients 60 years of age and older have a lower remission rate, a reduced probability of remaining in remission, and have a lower cure rate than younger patients.

Patients with relapsed AML have a particularly poor prognosis (approximately 5% to 10% long-term disease-free survival). Significant morbidity and mortality are associated with current therapies for patients with relapsed AML, particularly for patients 60 years of age and older and for patients with co-morbid conditions. While numerous therapies and dosage regimens have been investigated in an attempt to improve remission and survival rates in patients with relapsed AML, none have emerged as a standard of care. Prior to the Subpart H approval of Mylotarg, there were no agents specifically approved for the treatment of patients with relapsed AML.

### **Therapeutic Options**

Most patients diagnosed with AML receive induction therapy to attain remission and postremission therapy to maintain remission.<sup>3</sup> Approximately 50% to 70% of adults with AML attain complete remission (CR) following treatment.<sup>4,5</sup> About 25% of these patients survive 3 or more years.<sup>6</sup> Unfortunately, about 75% of patients relapse.

Induction chemotherapy with cytarabine and an anthracycline has been a standard treatment of newly diagnosed AML for the past 20 years. Complete remission can be achieved in 50% to 80% of adult patients less than 60 years old with de novo AML when treated with continuous infusion (CI) cytarabine and an anthracycline, depending on the prognostic factors in the population treated. However, only 20% to 40% of patients who achieve a remission have prolonged leukemia-free survival. The induction CR rates for patients over the age of 60 are generally lower due to a higher incidence of poor prognostic cytogenetic abnormalities and from greater mortality from intensive therapy. Several non-transplant strategies have been employed

to intensify the induction regimen with the hope of improving the remission rate, duration of remission, and survival. While these strategies have produced promising leads, none has emerged as providing a clear advantage to therapy with cytarabine and an anthracycline followed by post-remission therapy for patients with de novo AML. In addition, many of these approaches have resulted in additional safety concerns.

Induction therapy typically consists of 7 days of cytarabine (ara-C) plus 3 days of an anthracycline such as idarubicin or daunorubicin and/or an anthracenedione such as mitoxantrone.<sup>3</sup> Reported remission rates are variable. In large randomized clinical trials, these regimens have been shown to achieve CR in 52% to 72% of patients.<sup>4</sup> In a report by Bennett and colleagues (1997), 62% of patients experienced CR, and the median 5-year disease-free survival rate was 22%.<sup>7</sup>

The most common toxicity associated with induction regimens is myelosuppression. Thrombocytopenia frequently occurs and, if severe, can lead to hemorrhage. Neutropenia coupled with mucositis makes severe infections, fever, and sepsis common as well. Nausea, vomiting, mucositis, and alopecia also frequently accompany treatment. Cardiotoxicity is a common effect of the anthracyclines, especially when used at high doses.<sup>8,9,10,11,12,13,14</sup>

Patients must be closely monitored and must receive hematologic supportive care and broad-spectrum antimicrobial therapy to combat hemorrhage and infection, major causes of death in AML patients.<sup>4</sup> Platelet transfusions may be necessary to maintain platelet counts (>20,000/uL). Red blood cell transfusions are indicated when hemoglobin is below 8.5 g/dL and can help manage symptoms of fatigue.<sup>15</sup>

Disease-free survival and 5-year survival rates have been shown to increase following postremission therapy and intensification therapy.<sup>7,16</sup> Postremission strategies include low-dose maintenance therapy and intensive consolidation therapy. High-dose, marrowablative therapy with allogeneic hematologic stem-cell transplantation (HSCT) and high-dose chemotherapy or chemoradiotherapy with autologous HSCT have been used as postremission therapy for patients with AML.<sup>17,18,19,20,21</sup>

Relapsed AML is associated with poor probability of attaining second remission or substantial disease-free and overall survival.<sup>3</sup> Usually, the outcome is better the younger and healthier the patient is, the longer the initial remission, and the longer the duration since chemotherapy exposure. For patients 15 to 60 years of age, the probability of inducing a second remission is approximately 50%, whereas for patients 60 years of age and older, the probability is only 25%.<sup>3</sup>

There is no standard treatment for patients with relapsed AML. If relapse occurs  $\geq 6$  months after first remission, re-administration of the original remission-induction regimen may be effective.<sup>3</sup> Regimens consisting of high-dose cytosine arabinoside alone or in combination with agents such as mitoxantrone have been investigated. Other agents that have been used to treat AML in first relapse include etoposide, and 4<sup>1</sup>-(9-acridinyl-amino) methane-sulfon-*m*-anisidine (AMSA).<sup>22,23,24,25,26</sup> Reported remission rates are about 40% with durations ranging from 3 to 6 months, although remission rates are considerably lower in patients over 60 years old.<sup>3,27</sup>

Furthermore, adverse effects such as cardiac, central nervous system, gastrointestinal, and hematologic toxicity limit the use of these regimens, particularly in patients who have already been exposed to chemotherapeutic agents. Some patients with relapsed AML respond to allogeneic bone marrow transplant (BMT) and autologous BMT with or without purging.<sup>6,18,28,29</sup>

Monoclonal antibodies (MoAbs) that target specific antigens can be used to deliver cytotoxic agents to specific cells within the body. Despite the simplicity of this concept, the actual development of therapeutic agents has been complicated by a number of technical difficulties, including the selection of an appropriate target antigen.<sup>30</sup>

CD33 is expressed on normal myeloid precursor cells and on leukemic blasts of > 80% of patients with AML but not on nonmyeloid cells or nonhematopoietic tissues.<sup>31,32</sup> Antibody-targeted chemotherapy consists of a MoAb conjugated to a cytotoxin or a chemotherapeutic agent. To exert their effects, MoAbs conjugated to potent cytotoxic agents must be internalized by the cell to disrupt critical intracellular processes and induce cell death.<sup>30</sup> The “linker” between the MoAb and the toxic agent is a key element of this type of therapy. The toxic agent must remain bound to the linker in the serum and be efficiently released within the target cell without significant alteration in its activity.<sup>33</sup> Mylotarg is one example of this type of conjugate and is discussed in more detail in the following section. Mylotarg contains a humanized anti-CD33 antibody linked to a derivative of calicheamicin, a novel and potent cytotoxic antitumor antibiotic.<sup>31</sup> Calicheamicins are antibiotics originally isolated from soil microorganisms. In preclinical studies, calicheamicins were shown to be up to 1,000-fold more potent than other chemotherapy agents.<sup>34</sup>

### **Mylotarg (gemtuzumab ozogamicin)**

Mylotarg provides a new method of drug delivery by utilizing an antibody to target the cytotoxic agent to leukemic cells. It is the first antibody targeted chemotherapy agent approved by the FDA, and is composed of a humanized anti-CD33 antibody [hp67.6] linked to a potent antitumor antibiotic, calicheamicin. It is indicated 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 candidates for other cytotoxic chemotherapy.

Mylotarg as a single agent demonstrated efficacy comparable to that reported in the literature for conventional AML treatment in similar patient populations as measured by remission rate, relapse-free survival, overall survival, and post-hematopoietic stem cell transplant survival. Mylotarg demonstrated an improved safety profile in comparison with conventional combination therapy. There was no alopecia. Rates of myelosuppression, severe bleeding, and liver enzyme abnormalities were similar to the rates reported for current combination therapies. However, patients treated with Mylotarg experienced a reduced rate of severe mucositis occurring during the time of severe neutropenia. As a result there was a low rate of infections, and subsequently a lower total duration of hospitalization for Mylotarg-treated patients. Our data demonstrating that 4.8% of Mylotarg-treated patients were not hospitalized during the treatment period and 21% of these patients were hospitalized for  $\leq 7$  days represents an improvement over results reported in

the literature for conventional chemotherapy. When those patients who died during the treatment phase are excluded, these numbers become 5.6% and 22%, respectively. Hospitalization is generally regarded as universal in this population of seriously ill patients. These data indicate an improved tolerability for Mylotarg compared with conventional chemotherapy treatments in this seriously ill patient population.

Patients 60 years of age and older with AML are a distinct subset of AML patients; they have lower response rates to conventional antileukemic therapies, which are associated with decreased survival rates. In the Mylotarg studies, the median age was 60 years. The OR rate in all patients was 31%, in patients < 60 years old the OR rate was 34%, and in patients ≥ 60 years old the OR rate was 28%. The observation of only a modest decrease in remission rate in older patients is clinically important in that it suggests that Mylotarg is an effective and safe treatment for the older patient population.

With conventional therapy, remission consists almost entirely of CR, and the response that was defined by Wyeth as CR<sub>p</sub> (remission with incomplete platelet recovery) is seldom observed. A review of the literature and external databases showed that the incidence of CR<sub>p</sub> was ≤ 5% with conventional therapy. Patients treated with Mylotarg have a higher incidence of CR<sub>p</sub>. This may be because of the effects of Mylotarg on CD33 positive platelet precursors or because of decreased bone marrow reserves. However, the clinical outcome for CR and CR<sub>p</sub> patients after Mylotarg therapy is comparable, including a comparable incidence of clinically serious bleeding incidents.

In phase II clinical studies, a 26% overall response was observed in patients ≥ 60 years of age with AML in first relapse. A 30% overall response rate was observed in all patients studied, regardless of age.<sup>31</sup>

Similar to other antibody-based therapies, a mild infusion-related symptom complex of fever, chills and, less frequently, hypotension and dyspnea, associated with Mylotarg administration was observed in most patients. These events were usually brief in duration and without clinical sequelae. Transient and generally reversible liver function test abnormalities occurred with moderate incidence, and were comparable to those reported in the literature for conventional combination chemotherapy.

As with all antibody-containing compounds, there is a potential for production of antibodies against the antibody or chemotherapy component of the agent. No patients developed an immune response to Mylotarg in the phase II studies.

The major toxicity associated with Mylotarg was severe myelosuppression. An acute infusion-related symptom complex occurred within 24 hours after administration of Mylotarg.<sup>31</sup>

Hepatotoxicity, including severe hepatic veno-occlusive disease (VOD), has been reported in association with the use of Mylotarg as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or HSCT. Patients who receive Mylotarg either before or after HSCT, patients with underlying hepatic disease or abnormal liver

function, and patients receiving Mylotarg in combinations with other chemotherapy may be at increased risk for developing severe VOD. Death from liver failure and from VOD has been reported in patients who received Mylotarg.

The overall benefit/risk of gemtuzumab ozogamicin for treatment of relapsed AML is positive. The efficacy of gemtuzumab ozogamicin, when administered in 2 doses of 9 mg/m<sup>2</sup> IV with a 14-day interval between doses, was comparable to that seen with conventional AML therapy in similar patient populations. The risks of treatment with Mylotarg should be compared with those of treatment with conventional chemotherapy presently used for relapsed AML patients, which include alopecia, mucositis, severe myelosuppression, bleeding, neutropenic fever, infection, and abnormal liver function tests.

### **Post-Marketing Clinical Commitment**

The following post-marketing clinical study commitments were specified in the approval of Mylotarg:

"A randomized controlled trial of gemtuzumab ozogamicin, daunorubicin and cytarabine versus daunorubicin and cytarabine as induction therapy in patients with de novo CD 33 positive acute myeloid leukemia. This trial should be designed to demonstrate superior survival in the three-drug (gemtuzumab ozogamicin containing) group. Response rate results can be used as supportive evidence; responses should be defined as CRs or CRps of at least 4 weeks duration. If the three-drug regimen cannot be designed with acceptable toxicity, a randomized controlled trial designed to show that survival in patients treated with gemtuzumab ozogamicin and cytarabine is not inferior to survival in patients given daunorubicin and cytarabine should be initiated following discussion with the division. Again, the definition of the supportive secondary end point, response (CR and CRp), should include a pre-specified minimum duration of response of 4 weeks. For either trial it will be necessary to:

- Clarify the purpose and the number of interim analyses planned, adjusting type I error as necessary. An independent, expert data monitoring committee will review bone marrow results, conduct the interim analyses, and make recommendations regarding continuation of the study. Responses should be determined by an independent pathologist blinded to the treatment arm.
- Pre-specify subgroups and covariates that are likely to be used in the analyses. The relationship of CD33 quantitative expression to response should be examined.
- Perform a thorough evaluation of toxicity, both hematologic and non-hematologic, in patients undergoing subsequent postremission therapy such as hematopoietic stem cell transplantation or high dose cytarabine, as well as in patients who receive no further therapy.
- Perform long-term follow-up for relapse and survival in patients following postremission therapy, as well as for patients who receive no further therapy.

- Perform the appropriate phase I trials to ensure that the toxicities observed with the dose combinations in the above trials are acceptable; and to identify any potentially significant pharmacokinetic drug-drug interactions."

### **Preliminary Work for the Clinical Commitment**

Phase I/phase II dose-ranging studies were needed prior to the initiation of the aforementioned commitment study to determine dosing of Mylotarg with other standard of care chemotherapy agents. Since Mylotarg was approved as a single agent treatment, new assessments regarding the use of Mylotarg with other chemotherapy agents were required. Many variables needed to be evaluated including (but not limited to) multiple-ascending dose studies to determine the safe use of combination regimens and determining single dose versus two dose regimen of Mylotarg concomitantly with each chemotherapy cycle.

The following overviews the status of the dose-ranging studies to date.

#### **A Dose-Ranging Study of the Safety and Efficacy of Gemtuzumab Ozogamicin (GO) Given in Combination with Cytarabine and Daunorubicin in Relapsed or Refractory Patients and in Younger de novo Patients with Acute Myeloid Leukemia (Study 206)**

This pilot study is evaluating the safety and efficacy of administering gemtuzumab ozogamicin concurrently with an anthracycline and cytarabine in AML patients. The goal of the study is to define a combination treatment arm utilizing gemtuzumab ozogamicin, an anthracycline, and cytarabine which will be compared to an anthracycline and cytarabine arm in a randomized phase III trial of de novo AML.

Wyeth has recently completed the first segment of Protocol 206-US, which had 22 patients enrolled, and has conducted an ad hoc analysis of the data from this segment, enabling development of a Phase III protocol in collaboration with Southwest Oncology Group (SWOG). A brief summary of the ad hoc analysis was provided to the Agency on December 23, 2002. An abstract from that data is attached as Appendix 2.

#### **A Dose Ranging Study of the Safety and Efficacy of Gemtuzumab Ozogamicin (GO) given in Combination with Cytarabine in Relapsed or Refractory Patients and Older de novo Patients with Acute Myeloid Leukemia (Study 205)**

In an attempt to improve the survival of older patients with AML, this trial is designed to substitute gemtuzumab ozogamicin for standard anthracycline dosing in remission induction therapy for de novo AML. As toxicity of therapy is a major barrier to treating older AML patients, the proposed study is a pilot trial to evaluate the safety and efficacy of administering gemtuzumab ozogamicin with continuous infusion cytarabine in AML patients. The eventual goal of the study is to define a combination treatment arm which will be compared to cytarabine/anthracycline therapy in a randomized trial of AML in older patients.

This study is ongoing. A total of 21 patients have enrolled in phase I of study 205. Complete data on these patients are not yet available. An abstract from that data is attached as Appendix 3.

### **Status of the Commitment**

Based on the findings from studies 205 and 206 referenced above, Wyeth, in collaboration with the Southwest Oncology Group (SWOG), designed the following study:

#### **Southwest Oncology Group (SWOG): A Phase III Study of the Addition of Gemtuzumab Ozogamicin (Mylotarg) During Induction Therapy and Post-Consolidation Therapy Versus Standard Induction and Consolidation Therapy with Daunomycin and Cytosine Arabinoside for Patients Under Age 56 with Previously untreated de novo Acute Myeloid Leukemia (AML)**

Wyeth, in cooperation with Southwest Oncology Group (SWOG), has submitted the above-referenced study protocol to the FDA for review and approval. Study initiation is anticipated for Second Quarter 2003. The anticipated accrual is 640 patients over a four year period with an 18 month follow-up period from the time of the last enrolled patient. The estimated completion timeline is 2008 with study results anticipated for submission to the FDA in 2009.

This study will determine if patients without acute promyelocytic leukemia (non-M3) AML, and who have not been previously treated, will achieve a higher complete response rate when gemtuzumab ozogamicin is added to standard induction therapy. The study will also determine if patients who receive induction therapy with gemtuzumab ozogamicin plus standard induction followed by post-consolidation therapy with gemtuzumab ozogamicin will have improved disease-free and overall survival. Patients will be randomized to receive either standard induction therapy utilizing 7 days of cytosine arabinoside and 3 days of an anthracycline, such as daunomycin or idarubicin (7+3), or the experimental arm with 7+3+gemtuzumab ozogamicin. All patients with acute myeloid leukemia express CD33 at varying levels and thus all patients with acute myeloid leukemia will be eligible for randomization. Complete responders will receive 3 cycles of alternate day high dose cytosine arabinoside as consolidation. After completion of consolidation, patients who received gemtuzumab ozogamicin during induction will receive 3 additional doses of gemtuzumab ozogamicin at monthly intervals. Patients on the standard therapy arm will receive no additional therapy.

The objectives of this study are as follows:

- To compare the overall survival (OS) and disease-free survival (DFS) of patients under age 56 with previously untreated, non-M3, AML who receive gemtuzumab ozogamicin versus patients who receive chemotherapy alone.
- To compare the complete remission rate achieved by the addition of gemtuzumab ozogamicin to standard induction chemotherapy to that achieved with standard induction

chemotherapy in patients under the age of 56 with previously untreated, de novo, non-M3 AML.

- To estimate the frequency and severity of toxicities of the gemtuzumab ozogamicin regimen.
- To evaluate the prognostic significance of FLT3 mutation prior to therapy, and of minimal residual disease in remission specimens collected before and after consolidation therapy and after post-consolidation therapy with gemtuzumab ozogamicin.
- To evaluate the prognostic significance of the flow cytometric detection of minimal residual disease in specimens collected before and after consolidation therapy and after post-consolidation therapy with gemtuzumab ozogamicin.

### **Prospective Observational Study**

Mylotarg has a boxed warning on the label (see attached prescribing information) addressing hypersensitivity reactions including anaphylaxis, infusion reaction, pulmonary events, and hepatotoxicity including veno-occlusive disease (VOD). It is important to note that this boxed warning only addresses the safety of Mylotarg for use as a single agent, and not in combination with other therapies.

On April 12, 2001, Wyeth, in conjunction with FDA, agreed to develop a Voluntary Patient Safety Registry and to provide quarterly reports to the FDA providing incremental and cumulative analysis after the observational study commenced.

All centers that agree to participate in the observational study are required to seek permission from every patient at their institution who is going to be given Mylotarg, regardless of whether it is given on- or off-label or if the patient is in another study or not. The study design is that of a prospective observational registry conducted under conditions of routine clinical practice by oncologists/hematologists administering Mylotarg. The primary objectives of this registry are to estimate the incidence rate of hepatic veno-occlusive disease (VOD) among patients treated with Mylotarg and to identify risk factors associated with the development of VOD after Mylotarg treatment. Secondary objectives of the registry are to collect and report all serious adverse events, and nonserious adverse events of special interest comprised of hepatic, hypersensitivity, infusion-related, pulmonary, and renal events, and to collect information on Mylotarg use in various practice settings.

To date, this observational study has enrolled approximately 92 patients, and there are more than 50 sites participating. Wyeth anticipates enrollment of approximately 500 patients in this prospective observational trial. Quarterly “Prospective Observational Study in Usual Care” reports have been subsequently submitted to the FDA. These observations indicate that there has not been a significant change in the safety profile of Mylotarg.

## **Conclusion**

Wyeth has been diligent in meeting all of our obligations for Mylotarg and has done so in a timely fashion. Mylotarg is approved as a single agent treatment. However, the post-marketing clinical commitment required Wyeth to conduct studies using Mylotarg in combination with other chemotherapy agents. Before this clinical commitment study could be conducted, Wyeth had to conduct phase I/II dose-ranging studies to determine a safe dose of Mylotarg when used in combination with other agents. Now that the dose-ranging studies have established this safe dose, Wyeth has developed a study protocol for our post-marketing clinical commitment in cooperation with SWOG.

Wyeth continues to meticulously monitor any safety issues that may be associated with Mylotarg as demonstrated through the Prospective Observational Study, clinical study analysis, and routine post-marketing surveillance. Any safety concerns are provided to the Agency for review and discussion.

The Subpart H program has allowed Mylotarg to be available as a treatment option to doctors with patients who are  $\geq 60$  years of age and have AML in first relapse. Prior to the approval of Mylotarg, there were no approved options. Mylotarg has demonstrated a clinically important positive benefit in its target population. The Subpart H approval program has provided great value to the medical community.

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