Mylotarg®
(gemtuzumab ozogamicin for Injection)
for intravenous use only

Rx only

WARNINGS
Mylotarg should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.

Controlled trials have failed to demonstrate efficacy and safety using Mylotarg in combination with other chemotherapeutic agents (see **CLINICAL STUDIES** section). Therefore, Mylotarg should only be used as single agent chemotherapy and not in combination chemotherapy regimens outside clinical trials.

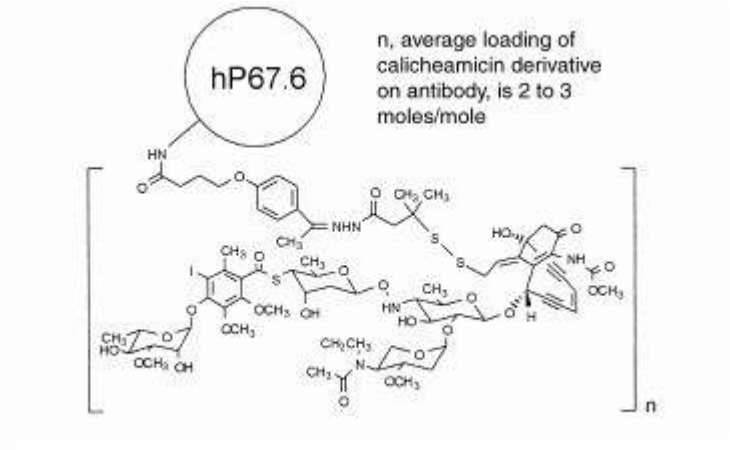
Severe myelosuppression occurs when Mylotarg is used at recommended doses.

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS, INFUSION REACTIONS, PULMONARY EVENTS
Mylotarg administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal. In most cases, infusion-related symptoms occurred during the infusion or within 24 hours of administration of Mylotarg and resolved. Mylotarg infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Mylotarg treatment should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Since patients with high peripheral blast counts may be at greater risk for pulmonary events and tumor lysis syndrome, physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000/μL prior to administration of Mylotarg. (See **WARNINGS**.)

HEPATOTOXICITY:
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 hematopoietic stem cell transplant (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 are at increased risk for developing VOD, including severe VOD. Death from liver failure and from VOD has been reported in patients who received Mylotarg. Physicians should monitor their patients carefully for symptoms of hepatotoxicity, particularly VOD. These symptoms can include: rapid weight gain, right upper quadrant pain, hepatomegaly, ascites, elevations in bilirubin and/or liver enzymes. However, careful monitoring may not identify all patients at risk or prevent the complications of hepatotoxicity. (See **WARNINGS** and **ADVERSE REACTIONS** sections.)

DESCRIPTION

Mylotarg® (gemtuzumab ozogamicin for Injection) is a chemotherapy agent composed of a recombinant humanized IgG4, kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin, isolated from fermentation of a bacterium, *Micromonospora echinospora* subsp. *calichensis.* The antibody portion of Mylotarg binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells.



The anti-CD33 hP67.6 antibody is produced by mammalian cell suspension culture using a myeloma NS0 cell line and is purified under conditions which remove or inactivate viruses. Three separate and independent steps in the hP67.6 antibody purification process achieves retrovirus inactivation and removal. These include low pH treatment, DEAE-Sepharose chromatography, and viral filtration. Mylotarg contains amino acid sequences of which approximately 98.3% are of human origin. The constant region and framework regions contain human sequences while the complementarity-determining regions are derived from a murine antibody (p67.6) that binds CD33. This antibody is linked to N-acetyl-gamma calicheamicin via a bifunctional linker. Gemtuzumab ozogamicin has approximately 50% of the antibody loaded with 4-6 moles calicheamicin per mole of antibody. The remaining 50% of the antibody is not linked to the calicheamicin derivative. Gemtuzumab ozogamicin has a molecular weight of 151 to 153 kDa.

Mylotarg is a sterile, white, preservative-free lyophilized powder containing 5 mg of drug conjugate (protein equivalent) in an amber vial. The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. The inactive ingredients are: dextran 40; sucrose; sodium chloride; monobasic and dibasic sodium phosphate.

CLINICAL PHARMACOLOGY

General

Gemtuzumab ozogamicin binds to the CD33 antigen. This antigen is expressed on the surface of leukemic blasts in more than 80% of patients with acute myeloid leukemia (AML). CD33 is also expressed on normal and leukemic myeloid colony-forming cells, including leukemic clonogenic precursors, but it is not expressed on pluripotent hematopoietic stem cells or on nonhematopoietic cells.

Mechanism of Action: Mylotarg is directed against the CD33 antigen expressed by hematopoietic cells. Binding of the anti-CD33 antibody portion of Mylotarg with the CD33 antigen results in the formation of a complex that is internalized. Upon internalization, the calicheamicin derivative is released inside the lysosomes of the myeloid cell. The released calicheamicin derivative binds to DNA in the minor groove resulting in DNA double strand breaks and cell death.

Gemtuzumab ozogamicin is cytotoxic to the CD33 positive HL-60 human leukemia cell line. Gemtuzumab ozogamicin produces significant inhibition of colony formation in cultures of adult leukemic bone marrow cells. The cytotoxic effect on normal myeloid precursors leads to substantial myelosuppression, but this is reversible because pluripotent hematopoietic stem cells are spared. In preclinical animal studies, gemtuzumab ozogamicin demonstrates antitumor effects in the HL-60 human promyelocytic leukemia xenograft tumor in athymic mice.

Human Pharmacokinetics

After administration of the first recommended 9 mg/m^2 dose of gemtuzumab ozogamicin, given as a 2 hour infusion, the elimination half lives of total and unconjugated calicheamicin were about 41 and 143 hours, respectively. After the second 9 mg/m^2 dose, the half life of total calicheamicin was increased to about 64 hours and the area under the concentration-time curve (AUC) was about twice that in the first dose period. The AUC for the unconjugated calicheamicin increased 30% after the second dose. Age, gender, body surface area (BSA), and weight did not affect the pharmacokinetics of Mylotarg.

Patients, especially patients previously treated with HSCT, have an underlying risk of VOD. The AUC of total calicheamicin was correlated with additional risk of hepatomegaly and the risk of veno-occlusive disease (VOD). There is no evidence that reducing Mylotarg dose will reduce the underlying risk of VOD. Metabolic studies indicate hydrolytic release of the calicheamicin derivative from gemtuzumab ozogamicin. Many metabolites of this derivative were found after *in vitro* incubation of gemtuzumab ozogamicin in human liver microsomes and cytosol, and in HL-60 promyelocytic leukemia cells. Metabolic studies characterizing the possible isozymes involved in the metabolic pathway of Mylotarg have not been performed.

CLINICAL STUDIES

The efficacy and safety of Mylotarg as a single agent have been evaluated in 277 patients in three single arm open-label studies in patients with CD33 positive AML in first relapse. The studies included 84, 95, and 98 patients. In studies 1 and 2 patients were ≥ 18 years of age with a first remission duration of at least 6 months. In study 3, only patients ≥ 60 were enrolled and their first remission had to have lasted for at least 3 months. Patients with secondary leukemia or white blood cell (WBC) counts ≥ 30,000/μL were excluded. Some patients were

leukoreduced with hydroxyurea or leukapheresis to lower WBC counts below 30,000/μL in order to minimize the risk of tumor lysis syndrome. The treatment course included two 9 mg/m^2 doses separated by 14 days and a 28-day follow-up after the last dose. Although smaller doses had elicited responses in earlier studies, the 9 mg/m^2 was chosen because it would be expected to saturate all CD33 sites regardless of leukemic burden. A total of 157 patients were ≥ 60 years of age and older. The primary endpoint of the three clinical studies was the rate of complete remission (CR), which was defined as

a. leukemic blasts absent from the peripheral blood;
b. ≤ 5% blasts in the bone marrow, as measured by morphology studies;
c. hemoglobin (Hgb) ≥ 9 g/dL, platelets ≥ 100,000/μL, absolute neutrophil count (ANC) ≥ 1500/μL; and
d. red cell and platelet-transfusion independence (no red cell transfusions for 2 weeks; no platelet transfusions for 1 week).

In addition to CR, a second response category, CRp, was defined as patients satisfying the definition of CR, including platelet transfusion independence, with the exception of platelet recovery ≥100,000/μL. Remission status was determined at approximately 28 days after the last dose of Mylotarg. This category was added because Mylotarg appears to delay platelet recovery in some patients. Clinical equivalence between CR and CRp responses has not been established. Median time to recovery of platelet counts in patients who achieved a CR or a CRp is summarized in TABLE 4 (see **ADVERSE REACTIONS** section).

All patients were pre-medicated with acetaminophen 650-1000 mg and diphenhydramine 50 mg to decrease acute infusion-related symptoms. Growth factors and cytokines were not permitted. Use of prophylactic antibiotics was not specified.

Response Rate
The overall response (OR) rate for the three pooled monotherapy studies was 26% (71/277) consisting of 13% (35/277) of patients with CR and 13% (36/277) of patients with CRp. The median time to blast clearance in both CR and CRp patients was 28 days from the first dose of Mylotarg. The median time to remission was 60 days for both CR and CRp. Remission rates are shown in Table 1. Of the 157 patients who were ≥ 60 years old, the overall remission rate (OR = CR + CRp) was 24%. For the patients < 60 years old and all 277 patients the OR rates were 28% and 26%, respectively. Two of the most important determinants of response following relapse are age and duration of first remission. Remission rates by prognostic category are outlined in Table 1.

TABLE 1: PERCENTAGE OF PATIENTS BY REMISSION CATEGORY AND PROGNOSTIC GROUP

	Age < 60 years	Age ≥ 60 years	First Remission < 6 months	First Remission 6 – 12 months	First Remission ≥ 12 months
Type of Remission	n = 120	n = 157	n = 37	n = 124	n = 116
CR (95% CI)	13 8, 21	12 7, 18	5 1, 18	10 5, 16	18 12, 26
CRp (95% CI)	14 8, 22	12 7, 18	5 1, 18	12 7, 19	16 10, 24
OR (CR + CRp) (95% CI)	28 20, 36	24 18, 32	11 3, 25	22 15, 30	35 26, 44

The overall response rates were similar for females and males: 27% of females and 25% of males achieved remission.

In the studies, 95% of the patients were white and 5% of the patients were non-white.

Survival

Overall survival was measured from date of first dose of gemtuzumab ozogamicin to date of death or data cut-off date (Table 2). Relapse-free survival (duration of remission) for patients in remission was defined as the time period from date of first documentation of maximum response (CR or CRp) to the first date of documentation of relapse (pathology report or complete blood count showing leukemic blast recurrence in peripheral blood or bone marrow), or death, or data cut-off date.

TABLE 2: SUMMARY OF RELAPSE FREE[a] and OVERALL SURVIVAL FOR PATIENTS WITH CR AND CRp

Remission Group	N	Relapse-Free Median months	Overall Survival Median months[c]
CR	35	6.4	12.0
CRp	36	4.5	12.7
OR[b]	71	5.2	12.4
Patients who responded to Mylotarg and received no further therapy			
CR	17	3.7	11.5
CRp	18	2.4	10.7
OR	35	2.4	11.1

a: Number of months after achieving CR or CRp.
b: Sixteen OR patients (6 CR and 10 CRp; 16/277; 5.7%) had a relapse-free survival at 12 months. 14/16 had stem cell transplants. 1/14 had a stem cell transplant prior to Mylotarg. The remaining 13 patients had stem cell transplants after Mylotarg. Six OR patients (3 CR and 3 CRp) had a relapse-free survival > 36 months. All 6 of these patients had subsequent stem cell transplants, representing 2.2% (6/277) of all patients.
c: The median overall survival was 3.3 months for NR patients; in all 277 patients it was 4.9 months.

Rates of Remission by Cytogenetic Risk
Patients in all three cytogenetic risk classification groups (poor, intermediate, favorable) responded to gemtuzumab ozogamicin.

Post-Remission Therapy
Twenty-five (25/71, 35%) OR patients (11 CR and 14 CRp patients) went on to hematopoietic stem cell transplantation (HSCT). Fourteen (14) received allogeneic HSCT and 11 received autologous HSCT.

Thirty-five (35/71, 49%) OR patients (17 CR and 18 CRp patients) who responded to treatment with Mylotarg received no additional therapy.

Repeat Courses
Twenty (20) patients have received more than 1 course of Mylotarg in clinical trials. These patients were initially treated with Mylotarg, achieved remission, then subsequently relapsed and then received additional doses of Mylotarg.

Overview of Clinical Data
Available single arm trial data do not provide valid comparisons with various cytotoxic regimens that have been used in relapsed acute myeloid leukemia. Response rates are in the range of rates reported with such regimens only if the CRp responses are included. Nevertheless, treatment with Mylotarg can provide responses, including some of reasonable

duration. The data support its use in patients for whom aggressive cytotoxic regimens would be considered unsuitable, such as many patients 60 years of age or older.

Acute Myeloid Leukemia (AML) First-line Treatment in Combination with Chemotherapy

One, large, open-label, randomized phase III trial was conducted to evaluate the benefit and safety of adding Mylotarg to standard induction therapy, followed by a post-consolidation randomization to receive either 3 additional doses of Mylotarg or no additional therapy (OBS). Eligible patients were adults (age 18-60) with previously untreated *de novo* non-M3 AML. A total of 637 patients were randomized to receive induction therapy with daunorubicin and cytarabine and Mylotarg versus standard induction therapy with daunorubicin and cytarabine. Patients in either arm who did not achieve aplasia were re-treated with daunorubicin and cytarabine. Patients achieving complete remission (CR) received consolidation therapy with 3 courses of high-dose cytarabine every 28 days. Patients remaining in CR after consolidation were eligible for a second randomization (stratified by cytogenetic risk category at diagnosis and use of Mylotarg during induction) between 3 doses of Mylotarg (5 mg/m^2 every 28 days) or OBS. Among all patients evaluable for induction toxicity, the rate of fatal adverse events (AEs), at least possibly attributable to treatment (most commonly hemorrhage, infection and/or ARDS) was significantly higher in the daunorubicin cytosine arabinoside (DA) + Mylotarg arm (16/283 = 5.7% vs. 4/281 = 1.4%, P = 0.01).

In this study, the addition of Mylotarg to induction therapy did not improve response rate or relapse-free survival, and as post-consolidation therapy did not improve relapse-free survival (RFS), post-consolidation disease-free survival (DFS), or overall survival, but was associated with a significantly higher risk of fatal-induction adverse events.

INDICATIONS AND USAGE

Mylotarg 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 considered candidates for other cytotoxic chemotherapy. The safety and efficacy of Mylotarg in patients with poor performance status and organ dysfunction has not been established.

The effectiveness of Mylotarg is based on OR rates (see **CLINICAL STUDIES** section). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival, compared to any other treatment.

A phase III, open-label, randomized study in *de novo* acute myeloid leukemia (AML) patients ages 18-60, with Mylotarg added to standard induction therapy followed by post-consolidation randomization, did not confirm clinical benefit (see **CLINICAL STUDIES** section).

Based upon the above study findings, Mylotarg should only be used as single agent chemotherapy and not in combination chemotherapy regimens outside clinical trials.

Results from this single, open-label, randomized phase III study showed no benefits from adding Mylotarg to daunorubicin and cytarabine.

CONTRAINDICATIONS

Mylotarg is contraindicated in patients with a known hypersensitivity to gemtuzumab ozogamicin or any of its components: anti-CD33 antibody (hP67.6), calicheamicin derivatives, or inactive ingredients.

WARNINGS

Mylotarg should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.

There are no controlled trials demonstrating efficacy and safety using Mylotarg in combination with other chemotherapeutic agents. Therefore, Mylotarg should only be used as single agent chemotherapy and not in combination chemotherapy regimens outside clinical trials.

Myelosuppression: Severe myelosuppression will occur in all patients given the recommended dose of this agent. Careful hematologic monitoring is required. Systemic infections should be treated.

Hypersensitivity Reactions Including Anaphylaxis, Infusion Reactions, Pulmonary Events: Mylotarg administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal. In most cases, infusion-related symptoms occurred during the infusion or within 24 hours of administration of Mylotarg and resolved.

Mylotarg infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of further Mylotarg treatment should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Since patients with high peripheral blast counts may be at greater risk for such reactions, physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000/μL prior to administration of Mylotarg.

Infusion Reactions: Mylotarg can produce a post-infusion symptom complex of fever and chills, and less commonly hypotension and dyspnea that may occur during the first 24 hours after administration. Grade 3 or 4 non-hematologic infusion-related adverse events included chills, fever, hypotension, hypertension, hyperglycemia, hypoxia, and dyspnea. Most patients received the following prophylactic medications before administration: diphenhydramine 50 mg po and acetaminophen 650-1000 mg po; thereafter, two additional doses of acetaminophen 650-1000 mg po, one every 4 hours as needed. Vital signs should be monitored during infusion and for the four hours following infusion.

In clinical studies, these symptoms generally occurred after the end of the 2-hour intravenous infusion and resolved after 2 to 4 hours with a supportive therapy of acetaminophen, diphenhydramine, and IV fluids. Fewer infusion-related events were observed after the second dose.

Pulmonary Events: Severe pulmonary events leading to death have been reported infrequently with the use of Mylotarg in the postmarketing setting. Signs, symptoms and clinical findings include dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, and acute respiratory distress syndrome. These events occur as sequelae of infusion reactions; patients with WBC counts ≥ 30,000/µL may be at increased risk. (See **Infusion Reactions** section of **WARNINGS**.) Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000/µL prior to administration of Mylotarg. Patients with symptomatic intrinsic lung disease may also be at greater risk of severe pulmonary reactions.

Hepatotoxicity: Hepatotoxicity, including severe 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 VOD, including severe VOD. Patients who had received HSCT before Mylotarg were at a higher risk of VOD (22%) than patients who had not been transplanted (1%). Patients who had received HSCT following Mylotarg were at a higher risk of VOD (15%) than patients who had not been transplanted (1%). Death from liver failure and from VOD has been reported in patients who received Mylotarg. Physicians should monitor their patients carefully for symptoms of hepatotoxicity, particularly VOD. These symptoms can include: rapid weight gain, right upper quadrant pain, hepatomegaly, ascites, elevations in bilirubin and/or liver enzymes. However, careful monitoring may not identify all patients at risk or prevent the complications of hepatotoxicity. (See **ADVERSE REACTIONS** section.)

Use in Patients with Hepatic Impairment: Mylotarg has not been studied in patients with bilirubin > 2 mg/dL. Extra caution should be exercised when administering Mylotarg in patients with hepatic impairment (see **ADVERSE REACTIONS** section).

Tumor Lysis Syndrome (TLS): TLS may be a consequence of leukemia treatment with any chemotherapeutic agent including Mylotarg. Renal failure secondary to TLS has been reported in association with the use of Mylotarg. Appropriate measures, (e.g. hydration and allopurinol), must be taken to prevent hyperuricemia. Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white blood count to < 30,000/µL prior to administration of Mylotarg (see **CLINICAL STUDIES** section).

Pregnancy: Mylotarg may cause fetal harm when administered to a pregnant woman. Daily treatment of pregnant rats with gemtuzumab ozogamicin during organogenesis caused dose-related decreases in fetal weight in association with dose-related decreases in fetal skeletal ossification beginning at 0.025 mg/kg/day. Doses of 0.060 mg/kg/day (approximately 0.04 times the recommended human single dose on a mg/m^2 basis) produced increased embryo-fetal mortality (increased numbers of resorptions and decreased numbers of live fetuses per litter). Gross external, visceral, and skeletal alterations at the 0.060 mg/kg/day dose level included digital malformations (ectrodactyly, brachydactyly) in one or both hind feet, absence of the aortic arch, wavy ribs, anomalies of the long bones in the forelimb(s) (short/thick humerus, misshapen radius and ulna, and short/thick ulna), misshapen scapula, absence of vertebral centrum, and fused sternebrae. This dose was also associated with maternal toxicity (decreased

weight gain, decreased food consumption). There are no adequate and well-controlled studies in pregnant women. If Mylotarg is used in pregnancy, or if the patient becomes pregnant while taking it, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Mylotarg.

PRECAUTIONS
DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS

General
Treatment by Experienced Physicians: Mylotarg should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.

Laboratory Monitoring: Electrolytes, tests of hepatic function, complete blood counts (CBCs) and platelet counts should be monitored during Mylotarg therapy.

Drug Interactions: There have been no formal drug-interaction studies performed with Mylotarg. The potential for drug-drug interaction with drugs affected by cytochrome P450 enzymes may not be ruled out.

Laboratory Test Interactions: Mylotarg is not known to interfere with any routine diagnostic tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of Mylotarg. Gemtuzumab ozogamicin was clastogenic in the mouse *in vivo* micronucleus test. This positive result is consistent with the known ability of calicheamicin to cause double-stranded breaks in DNA. Gemtuzumab ozogamicin adversely affected male, but not female, fertility in rats. Following daily administration of gemtuzumab ozogamicin to male rats for 28 days at doses of 0.02 to 0.16 mg/kg/day (approximately 0.01 to 0.11 times the human dose on a mg/m^2 basis) gemtuzumab ozogamicin caused: decreased fertility rates, epididymal sperm counts, and sperm motility; increased incidence of sperm abnormalities; and microscopic evidence of decreased spermatogonia and spermatocyte count. These findings did not resolve following a 9-week recovery period.

Pregnancy Category D: See **WARNINGS** section.

Nursing Mothers: It is not known if Mylotarg is excreted in human milk. Because many drugs, including immunoglobulins, are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Mylotarg, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Mylotarg in pediatric patients have not been established.

Use in Patients with Renal Impairment: Patients with renal impairment were not studied.

ADVERSE REACTIONS

Mylotarg has been administered to 277 patients with relapsed AML at 9 mg/m^2. Mylotarg was generally given as two intravenous infusions separated by 14 days.

Acute Infusion-Related Events (Table 3)

TABLE 3: NUMBER AND PERCENTAGE OF PATIENTS REPORTED TO HAVE ACUTE INFUSION-RELATED ADVERSE EVENTS (N = 277)

Adverse Event	Any Severity (%)	Grade 3 or 4 (%)
Fever	227 (82)	17 (6)
Nausea	188 (68)	8 (3)
Chills	183 (66)	21 (8)
Vomiting	162 (58)	3 (1)
Headache	102 (37)	2 (< 1)
Dyspnea	73 (26)	4 (1)
Hypotension	55 (20)	12 (4)
Hypertension	43 (16)	5 (2)
Hyperglycemia	29 (10)	3 (1)
Hypoxia	15 (5)	4 (1)

Fever and chills were commonly reported despite prophylactic treatment with acetaminophen and antihistamines (see **WARNINGS** section). Generally, these symptoms occurred at the end of the 2 hour infusion and resolved after 2 to 4 hours with supportive therapy including acetaminophen, diphenhydramine, and intravenous fluids. These events all occurred on the same day as gemtuzumab ozogamicin infusion. Fewer infusion-related events were observed after the second dose. Methylprednisolone given prior to Mylotarg infusion may ameliorate infusion-related symptoms.

Antibody Formation: Antibodies to gemtuzumab ozogamicin were not detected in any of the 277 patients, including the 20 patients who received more than 1 course of study drug, in the Phase 2 clinical studies. Two patients in a Phase 1 study developed antibody titers against the calicheamicin/calicheamicin-linker portion of gemtuzumab ozogamicin after three doses. One patient experienced transient fever, hypotension and dyspnea; the other patient had no clinical symptoms. No patient developed antibody responses to the hP67.6 antibody portion of Mylotarg.

Myelosuppression: Severe myelosuppression is the major toxicity associated with Mylotarg.

Neutropenia: During the treatment phase, 267/272 (98%) patients experienced Grade 3 or Grade 4 neutropenia. For all patients, the median times to ANC recovery at 500/µL for the CR and CRp patients were 40.0 and 43.0 days, respectively.

Anemia, Thrombocytopenia: During the treatment phase, 143/276 (52%) patients experienced Grade 3 or Grade 4 anemia and 272/276 (99%) patients experienced Grade 3 or Grade 4 thrombocytopenia. A summary of the platelet recovery for responding patients is provided in Table 4.

TABLE 4: MEDIAN TIME TO RECOVERY OF PLATELET COUNTS FOR ALL CR AND CRp PATIENTS (DAYS)

	CR		CRp	
Platelet levels	< 60 years of age	≥ 60 years of age	< 60 years of age	≥ 60 years of age
> 25,000/µL	35	38	39	75
50,000/µL	42	40	56	100
75,000/µL	48	42	122	NA
100,000/µL	56	50	NA	NA

Abbreviation: NA = Not Available

Infection: During the treatment phase, 84/277 (30%) patients experienced Grade 3 or Grade 4 infections, including opportunistic infections. The most frequent Grade 3 or Grade 4 infection-related treatment-emergent adverse events (TEAEs) were sepsis (17%), pneumonia (8%), shock (4%), infection (3%), stomatitis (2%), and herpes simplex (2%).

Bleeding: During the treatment phase, 36/277 (13%) patients experienced Grade 3 or Grade 4 bleeding. The most common bleeding events for all patients were epistaxis (3%), cerebral hemorrhage (2%), intracranial hemorrhage (1%), melena (1%), petechiae (1%), hematuria (1%), and disseminated intravascular coagulation (1%).

A greater proportion of NR patients (15%) experienced NCI grade 3 or 4 bleeding events compared with OR patients (7%). Among CR patients, 1 grade 3 bleeding event, epistaxis, was experienced. Bleeding events occurred in 1/35 CR patients and 4/36 CRp patients.

Transfusions: During the treatment phase, more transfusions were required in the NR and CRp patients compared with the CRs (Table 5):

TABLE 5: NUMBER OF TRANSFUSIONS BY RESPONSE GROUP

Transfusions	All Patients	CR	CRp	NR
	N = 277	N = 35	N = 36	N = 206
Platelet transfusions				
Mean (SD)	NA	6.8 (7)	23.7 (67)	15.7 (20)
(95% CI)*	NA	(5.6, 8.0)	(12.5, 34.9)	(14.3, 17.1)
RBC transfusions				
Mean (SD)	NA	2.9 (3)	5.4 (4)	8.1 (22)
(95% CI)	NA	(2.4, 3.4)	(4.7, 10.1)	(8.0, 8.2)

* calculated - mean ± se where se = sd/sqr(n)

Mucositis: A total of 69/277 (25%) patients were reported to have a TEAE consistent with oral mucositis or stomatitis. During the treatment phase, 9/277 (3%) patients experienced Grade 3 or 4 stomatitis/mucositis after the first dose.

Hepatotoxicity: In clinical studies, 80/274 (29%) patients experienced Grade 3 or Grade 4 hyperbilirubinemia. 26/274 (9%) of patients experienced Grade 3 or Grade 4 abnormalities in levels of ALT, and 49/274 (18%) patients experienced Grade 3 or Grade 4 abnormalities in levels of AST. One patient died with liver failure in the setting of tumor lysis syndrome and multisystem organ failure 22 days after treatment. Another patient died after an episode of persistent jaundice and hepatosplenomegaly 156 days after treatment. Ascites, an event that can be associated with liver damage, was observed in 8 patients. Abnormalities of liver function were often transient and reversible.

VOD: A total of 299 courses of Mylotarg were administered in 277 relapsed patients and 16 episodes of VOD (in 15 patients) were identified (16/299, 5%). The incidence of VOD in patients treated with Mylotarg who had no prior or subsequent HSCT was 1.0%. The risk of developing VOD was 20% for patients with a history of HSCT prior to Mylotarg administration. In patients who received HSCT after Mylotarg administration, the risk of developing VOD was 15%. (See Table 6). In the 15 patients that developed VOD, 9 patients had fatal VOD or ongoing VOD at the time of death:

TABLE 6: INCIDENCE OF VOD REPORTED BY TREATMENT GROUPS

	Number Courses of Mylotarg	Number Episodes of VOD	Incidence of VOD (episodes per courses)	Number Patients in Classification	Number Patients with VOD	Incidence of VOD (in patients)
Mylotarg Total	299	16	5%	277	15	5%
Mylotarg Only	215	2	1%	200	2	1%
HSCT with Mylotarg (total)[a]	84	14	17%	77	13	17%
HSCT prior to Mylotarg[b,c]	30	6	20%	27	6	22%
HSCT following Mylotarg[b,c]	54	8	15%	52	8	15%

a: 3 patients are included in more than one HSCT category.
b: 2 patients with a pre-trial history of HSCT each received HSCT after Mylotarg.
c: 1 patient received Mylotarg followed by HSCT and then received a second course of Mylotarg. This patient developed VOD after HSCT and again after the second course of Mylotarg.

Skin: Pruritus was reported in 18/277 (6%) patients, while rash occurred in 51/277 (18%) patients. Cutaneous herpes simplex was reported in 59/277 (21%) patients. No patient experienced alopecia.

Early Mortality in Clinical Studies
The overall mortality rate within 28 days of last dose was 16% (44/277). The mortality rate was 14% (17/120) for patients who were < 60 years old, and 17% (27/157) for patients who were ≥ 60 years old.

Retreatment Events: Twenty (20) patients received additional courses of Mylotarg in the studies. One (1) patient received a total of 4 courses of treatment.

Dose Relationship for Adverse Events: Dose-relationship data were generated from a small dose-escalation study. The most common clinical adverse event observed in this study was an infusion-related symptom complex of fever and chills. In general, the severity of fever, but not chills, increased as the dose level increased. Only one dose level of Mylotarg was studied in the Phase 2 clinical trials in relapsed AML.

Treatment-Emergent Adverse Events (TEAE): TEAEs (Grades 1-4) that occurred in ≥ 10% of the patients regardless of causality are listed in Table 7.

TABLE 7: COMMONLY REPORTED (≥ 10%) TREATMENT-EMERGENT ADVERSE EVENTS BY AGE GROUP: NUMBER (%) OF PATIENTS

	----------Patient Age in Years----------		
Body System Adverse Event	Age ≥ 60 (n = 157)	Age < 60 (n = 120)	Any Age (n = 277)
Any adverse event	157 (100)	119 (99)	276 (100)
Body as a whole			
Abdominal pain	41 (26)	47 (39)	88 (32)
Asthenia	56 (36)	44 (37)	100 (36)
Back pain	19 (12)	19 (16)	38 (14)
Chills	101 (64)	82 (68)	183 (66)
Fever	122 (78)	105 (88)	227 (82)
Headache	42 (27)	60 (50)	102 (37)
Infection	16 (10)	10 (8)	26 (9)
Neutropenic fever	30 (19)	18 (15)	48 (17)
Pain	28 (18)	21 (18)	49 (18)
Sepsis	40 (25)	33 (28)	73 (26)
Cardiovascular system			
Hemorrhage	14 (9)	16 (13)	30 (11)
Hypertension	27 (17)	16 (13)	43 (16)
Hypotension	28 (18)	27 (23)	55 (20)
Tachycardia	17 (11)	11 (9)	28 (10)
Digestive system			
Anorexia	43 (27)	26 (22)	69 (25)
Constipation	36 (23)	27 (23)	63 (23)
Diarrhea	47 (30)	43 (36)	90 (32)
Dyspepsia	13 (8)	15 (13)	28 (10)
Gum hemorrhage	8 (5)	17 (14)	25 (9)
Liver function tests abnormal	31 (20)	35 (29)	66 (24)
Nausea	99 (63)	89 (74)	188 (68)
Stomatitis	34 (22)	35 (29)	69 (25)
Vomiting	83 (53)	79 (66)	162 (58)

TABLE 7: COMMONLY REPORTED (≥ 10%) TREATMENT-EMERGENT ADVERSE EVENTS BY AGE GROUP: NUMBER (%) OF PATIENTS

	----------Patient Age in Years----------		
Body System Adverse Event	Age ≥ 60 (n = 157)	Age < 60 (n = 120)	Any Age (n = 277)
Hemic and lymphatic system			
Anemia	34 (22)	26 (22)	60 (22)
Ecchymosis	17 (11)	11 (9)	28 (10)
Leukopenia	67 (43)	62 (52)	129 (47)
Petechiae	30 (19)	24 (20)	54 (19)
Thrombocytopenia	77 (49)	62 (52)	139 (50)
Metabolic and nutritional			
Alkaline phosphatase increased	15 (10)	6 (5)	21 (8)
Bilirubinemia	18 (11)	15 (13)	33 (12)
Hyperglycemia	17 (11)	12 (10)	29 (10)
Hypocalcemia	15 (10)	14 (12)	29 (10)
Hypokalemia	38 (24)	35 (29)	73 (26)
Hypomagnesemia	4 (3)	12 (10)	16 (6)
Hypophosphatemia	9 (6)	12 (10)	21 (8)
Lactic dehydrogenase increased	28 (18)	17 (14)	45 (16)
Peripheral edema	30 (19)	10 (8)	40 (14)
Musculoskeletal system			
Myalgia	5 (3)	13 (11)	18 (6)
Nervous system			
Anxiety	15 (10)	8 (7)	23 (8)
Depression	15 (10)	9 (8)	24 (9)
Dizziness	15 (10)	18 (15)	33 (12)
Insomnia	17 (11)	16 (13)	33 (12)
Respiratory system			
Cough increased	28 (18)	19 (16)	47 (17)
Dyspnea	41 (26)	32 (27)	73 (26)
Epistaxis	37 (24)	41 (34)	78 (28)
Pharyngitis	16 (10)	17 (14)	33 (12)
Pneumonia	20 (13)	15 (13)	35 (13)
Pulmonary physical finding	13 (8)	12 (10)	25 (9)
Rhinitis	11 (7)	12 (10)	23 (8)

TABLE 7: COMMONLY REPORTED (≥ 10%) TREATMENT-EMERGENT ADVERSE EVENTS BY AGE GROUP: NUMBER (%) OF PATIENTS

	----------Patient Age in Years----------		
Body System Adverse Event	Age ≥ 60 (n = 157)	Age < 60 (n = 120)	Any Age (n = 277)
Skin and appendages			
Herpes simplex	29 (18)	30 (25)	59 (21)
Pruritus	6 (4)	12 (10)	18 (6)
Rash	29 (18)	22 (18)	51 (18)
Urogenital system			
Metrorrhagia	1 (2)	6 (10)	7 (3)
Vaginal hemorrhage	3 (5)	9 (15)	12 (4)
Adverse event associated with miscellaneous factors			
Local reaction to procedure	27 (17)	33 (28)	60 (22)

TEAEs of NCI grade 3 or 4 severity that occurred in part I of studies with an incidence of ≥ 10% in at least 1 age subgroup, are presented in Table 8.

TABLE 8: NUMBER (%) OF PATIENTS REPORTING NCI GRADE 3 OR 4 TREATMENT-EMERGENT ADVERSE EVENTS DURING PART I BY AGE GROUP: EVENTS WITH INCIDENCE ≥ 10%

	----------Patient Age in Years----------		
Body System Adverse Event	Age ≥ 60 (n = 157)	Age < 60 (n = 120)	Any Age (n = 277)
Any adverse event	138 (88)	112 (93)	250 (90)
Body as a whole			
Chills	17 (11)	9 (8)	26 (9)
Fever	20 (13)	16 (13)	36 (13)
Sepsis	23 (15)	24 (20)	47 (17)
Digestive system			
Liver function tests abnormal	11 (7)	12 (10)	23 (8)

TABLE 8: NUMBER (%) OF PATIENTS REPORTING NCI GRADE 3 OR 4 TREATMENT-EMERGENT ADVERSE EVENTS DURING PART I BY AGE GROUP: EVENTS WITH INCIDENCE ≥ 10%

	----------Patient Age in Years----------		
Body System Adverse Event	Age ≥ 60 (n = 157)	Age < 60 (n = 120)	Any Age (n = 277)
Hemic and lymphatic system			
Anemia	19 (12)	19 (16)	38 (14)
Leukopenia	67 (43)	60 (50)	127 (46)
Thrombocytopenia	75 (48)	61 (51)	136 (49)
Respiratory system			
Dyspnea	15 (10)	8 (7)	23 (8)

Abbreviation: NCI = National Cancer Institute.

Clinically important laboratory abnormalities with a Grade 3 or 4 severity are listed in Table 9.

TABLE 9: NUMBER (%[a]) OF PATIENTS WITH LABORATORY TEST RESULTS OF GRADE 3 OR 4 SEVERITY[b]

	Efficacy and Safety Studies Grades 3 – 4		
Test	Age ≥ 60 (n = 157)	Age < 60 (n = 120)	All Patients (n = 277)
Hematologic			
Hemoglobin	79/157 (50)	64/119 (54)	143/276 (52)
WBC	149/157 (95)	117/119 (98)	266/276 (96)
Total neutrophils, absolute	152/155 (98)	115/117 (98)	267/272 (98)
Lymphocytes	144/155 (93)	111/117 (95)	255/272 (94)
Platelet count	155/157 (99)	117/119 (98)	272/276 (99)
Prothrombin time	2/35 (6)	4/34 (12)	6/69 (9)
Partial thromboplastin time	1/66 (2)	1/61 (2)	2/127 (2)
Non-hematologic			
Glucose (hypo/hyper)	19/155 (12)	13/119 (11)	32/274 (12)
Creatinine	1/157 (<1)	4/119 (3)	5/276 (2)
Total bilirubin	45/156 (29)	35/118 (30)	80/274 (29)
AST	25/156 (16)	24/118 (20)	49/274 (18)
ALT	12/156 (8)	14/118 (12)	26/274 (9)
Alkaline phosphatase	4/156 (3)	7/118 (6)	11/274 (4)
Calcium (hypo/hyper)	14/157 (9)	21/119 (18)	35/276 (13)

a: Percentage is based on the number of patients receiving a particular laboratory test during the study as is indicated for each test.
b: Severity as defined by NCI common toxicity scale version 1.

There were considered to be no clinically important differences in TEAEs between patients < 60 years of age and those patients ≥ 60.

There were considered to be no clinically important differences in TEAEs between female and male patients.

Other Clinical Experience:
In postmarketing experience and other clinical trials, additional cases of VOD have been reported, some in association with the use of other chemotherapeutic agents, underlying hepatic disease/abnormal liver function, or a history of prior or subsequent HSCT. Renal failure, renal failure secondary to TLS, renal impairment, hypersensitivity reactions (including bradycardia), anaphylaxis, pulmonary events, pulmonary hemorrhage, gastrointestinal hemorrhage, Budd Chiari Syndrome, portal vein thrombosis, and neutropenic sepsis have also been reported in association with the use of Mylotarg. (See **WARNINGS** section).

Observational Study: A prospective postmarketing registry study is being conducted to assess the safety of Mylotarg under conditions of routine clinical practice. The primary objectives is to estimate the incidence of hepatic veno-occlusive disease (VOD) among patients treated with Mylotarg. In an interim analysis of 225 patients, SAEs are presented according to an "events of special interest" (ESI) classification comprised of hepatic (including VOD), renal, infusion-related, pulmonary, and hypersensitivity events (Table 10).

There were 816 SAEs reported in 197/225 patients (87.6% of all patients). Of the SAEs, 159 were also ESIs reported in 64 (28.4%) patients. The percentage of patients experiencing a serious ESI was 9.8% (hepatic), 6.7% (renal), 8.0% (infusion-related), and 12.9% (pulmonary). Among the 816 SAEs, 225 (27.6%) were fatal events (multiple concurrent fatal events could be reported for a patient) reported in 134 (59.6%) patients. Using the ESI classification, there were 30 fatal ESIs reported in 19 (8.4%) patients.

In this registry, the incidence of VOD based on an independent review is 10.2% (23/225). Among patients with HSCT before or after Mylotarg infusion the incidence of VOD was 14.9% (10/67 patients). For patients without HSCT the VOD incidence was 8.2% (12/146 patients). HSCT status was not reported in 8.3% (19/225) of patients.

TABLE 10: SERIOUS ADVERSE EVENTS REPORTED IN THE MYLOTARG PROSPECTIVE OBSERVATIONAL STUDY (N=225)[a]

	All events			Fatal events		
Reported events	Number events	Number patients	Percent patients (n=225)	Number events	Number patients	Percent patients (n=225)
TOTAL	816	197	87.6	225	134	59.6
Hepatic	51	22	9.8	6	4	1.8
Renal	21	15	6.7	5	5	2.2
Infusion-related	35	18	8.0	4	1	0.4
Pulmonary	52	29	12.9	15	13	5.8
Hypersensitivity	0	0	-	0	0	-
Other	657	188	83.6	195	130	57.8

[a]Based on interim data, the denominator represents all patients in the registry, including 11 patients for whom no adverse events were reported at the time of database lock for the interim analysis.

OVERDOSAGE

No cases of overdose with Mylotarg were reported in clinical experience. Single doses higher than 9 mg/m^2 in adults were not tested. When a single dose of Mylotarg was administered to animals, mortality was observed in rats at the dose of 2 mg/kg (approximately 1.3-times the recommended human dose on a mg/m^2 basis), and in male monkeys at the dose of 4.5 mg/kg (approximately 6-times the recommended human dose on a mg/m^2 basis).

Signs and Symptoms: Signs of overdose with Mylotarg are unknown.

Recommended Treatment: General supportive measures should be followed in case of overdose. Blood pressure and blood counts should be carefully monitored. Gemtuzumab ozogamicin is not dialyzable.

DOSAGE AND ADMINISTRATION

The recommended dose of Mylotarg is 9 mg/m^2, infused over a 2-hour period. Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white blood count to below 30,000/μL prior to administration of Mylotarg. Appropriate measures (e.g. hydration and allopurinol) must be taken to prevent hyperuricemia. Patients should receive the following prophylactic medications one hour before Mylotarg administration: diphenhydramine 50 mg po and acetaminophen 650-1000 mg po; thereafter, two additional doses of acetaminophen 650-1000 mg po, one every 4 hours as needed. Vital signs should be monitored during infusion and for four hours following infusion. The recommended treatment course with Mylotarg is a total of 2 doses with 14 days between the doses. Full recovery from hematologic toxicities is not a requirement for administration of the second dose.

Methylprednisolone given prior to Mylotarg infusion may ameliorate infusion-related symptoms.

Hepatic Insufficiency: Patients with hepatic impairment were not included in the clinical studies. (See **WARNINGS** section).

Renal Insufficiency: Patients with renal impairment were not included in the clinical studies.

Instructions for Reconstitution
The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. **All preparation should take place in a biologic safety hood with shielded fluorescent light.** Reconstitute the contents of each vial with 5 mL Sterile Water for Injection, USP, using sterile syringes. Gently swirl each vial. Each vial should be inspected for complete dissolution of the drug. The final concentration of the reconstituted drug solution is 1 mg/mL. See Table 11 for storage conditions for reconstituted product.

Instructions for Dilution
Prepare an admixture corresponding to 9 mg/m^2 dose of Mylotarg by injecting the reconstituted solution into a 100 mL 0.9% sodium chloride injection solution in either a polyvinyl chloride (PVC) or ethylene/polypropylene copolymer (non-PVC) IV bag covered by an ultraviolet (UV) light protector. Mylotarg should only be diluted with 0.9% sodium chloride solution. DO NOT DILUTE WITH ANY OTHER ELECTROLYTE SOLUTIONS or 5% DEXTROSE or MIX WITH OTHER DRUGS. See Table 11 for storage conditions for diluted product.

The drug solution in the vial, transfer syringe, or the IV bag may appear hazy due to normal light scattering from the protein.

Administration
DO NOT ADMINISTER AS AN INTRAVENOUS (IV) PUSH OR BOLUS

Once the reconstituted Mylotarg is diluted into the IV bag containing normal saline, the resulting solution should be infused over a 2-hour period. See Table 11 for infusion times. Mylotarg may be given peripherally or through a central line. During the infusion, only the IV bag needs to be protected from light. An in-line, low protein binding filter must be used for the infusion of Mylotarg. The following filter membranes are qualified: 0.22 µm or 1.2 µm polyether sulfone (PES) (Supor®); 1.2 µm acrylic copolymer hydrophilic filter (Versapor®); 0.8 µm cellulose mixed ester (acetate and nitrate) membrane; 0.2 µm cellulose acetate membrane. DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE. Premedication, consisting of acetaminophen and diphenhydramine, should be given before each infusion to reduce the incidence of a post-infusion symptom complex (see **ADVERSE REACTIONS, Acute Infusion-Related Events**).

Stability and Storage:
Prior to Reconstitution: Mylotarg should be stored refrigerated 2° to 8° C (36° to 46° F) and protected from light.

After Reconstitution: Follow the instructions for reconstitution, dilution, and administration in the section above. See Table 11 below for reconstitution, dilution, and administration storage conditions and time intervals.

TABLE 11: STORAGE CONDITION AND TIME FOR RECONSTITUTION, DILUTION, AND ADMINISTRATION

The following time intervals for reconstitution, dilution, and administration should be followed for storage of the reconstituted solution.			
Time Intervals			**Total Maximum Hours[a]**
Reconstitution	**Dilution**	**Administration**	
≤ 2 hours at room temperature or refrigeration	≤ 16 hours at room temperature	2 hour infusion	20

a: Total maximum time allowed for the storage of the reconstituted and diluted solutions and completion of infusion.

Instructions for Use, Handling and for Disposal: Individuals who have contact with anti-cancer drugs or work in areas where these drugs are used may be exposed to these agents through direct contact with contaminated objects.[1] Potential health effects may be reduced by adherence to institutional procedures, published guidelines and local regulations for preparation, administration, transportation and disposal of hazardous drugs. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.[2,3,4]

Mylotarg should be inspected visually for particulate matter and discoloration, once in the transfer syringe. Additionally, the diluted admixture solution should be inspected visually for particulate matter and discoloration. Mylotarg is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion (using an ultraviolet [UV] protective bag over the IV bag during infusion). All preparation should take place in a biologic safety hood with shielded fluorescent light. Vials are for single use. Aseptic technique must be strictly observed throughout the handling of Mylotarg since no bacteriostatic agent or preservative is present.

HOW SUPPLIED

Mylotarg® (gemtuzumab ozogamicin for Injection) is supplied as a single-vial package with an amber glass vial containing 5 mg of Mylotarg lyophilized powder. Single-unit 5 mg package: each vial contains 5 mg of Mylotarg. NDC 0008-4510-01.

United States Patent Numbers: 5,606,040; 5,712,374; 5,714,586; 5,739,116; 5,767,285; 5,770,710; 5,773,001; 5,877,296.

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