3.1 Proposed Text of Labeling for the Drug - Annotated

Mylotarg™ (gemtuzumab ozogamicin for Injection**)**

FOR INTRAVENOUS USE ONLY

WARNINGS

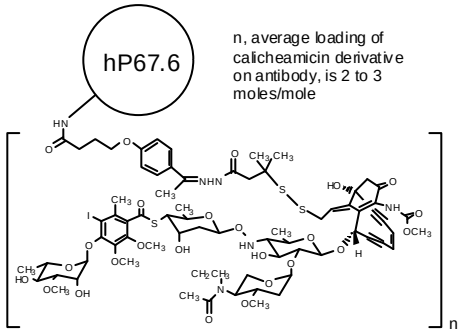
Mylotarg should be administered under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

Severe myelosuppression occurs when Mylotarg is used at recommended doses.

DESCRIPTION

Mylotarg™ (gemtuzumab ozogamicin for Injection) is a chemotherapy agent composed of a recombinant humanized IgG_4, kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin, isolated from fermentation of a bacterium, *Micromonospora echinospora* sp. *calichensis.* The antibody portion of Mylotarg binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of leukemic myeloblasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoetic 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 achieve 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 a 20-mL 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 45 and 100 hours, respectively. After the second 9 mg/m² dose, the half life of total calicheamicin was increased to about 60 hours and the area under the concentration-time curve (AUC) was about twice that in the first dose period. The pharmacokinetics of unconjugated calicheamicin did not appear to change from period one to two. 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 142 patients in three single arm open-label studies in patients with CD33 positive AML in first relapse. The studies included 65, 40, and 37 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 were excluded. The treatment course included two 9mg/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/m² was chosen because it would be expected to saturate all CD33 sites regardless of leukemic burden. A total of 80 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. This category was added because Mylotarg appears to delay platelet

recovery in some patients. Most of these patients (18/19) achieved platelet counts of at least 25,000/µL and about two-thirds (13/19) achieved platelet counts of at least 50,000/µL, before any additional therapy was administered. It is not yet clear whether CR and CRp responses are clinically equivalent; but survival in the two groups appeared similar.

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

Response Rate

The OR rate for the three pooled monotherapy studies was 30% (42/142) consisting of 16% (23/142) of patients with CR and 13% (19/142) of patients with CRp. The median time to remission was 60 days for both CR and CRp. Remission rates in the individual studies are shown in Table 1.

TABLE 1: PERCENTAGE OF PATIENTS BY REMISSION CATEGORY

	Study 1	Study 2	Study 3[a]	All Studies
Type of Remission	n = 65	n = 40	n = 37	n = 142
CR (95% CI)	17 (9, 28)	20 (9, 36)	11 (3, 25)	16 (11, 23)
CRp (95% CI)	15 (8,26)	13 (4, 27)	11 (3, 25)	13 (8, 20)
OR (CR + CRp) (95% CI)	32 (21,45)	33 (19, 49)	22 (10, 38)	30 (22, 38)
a: Patients 60 years of age or greater				

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 2; the impact of age and duration of first remission in these patients was minimal:

TABLE 2: PERCENTAGE OF PATIENTS BY REMISSION CATEGORY AND PROGNOSTIC GROUP

	Age < 60 years	Age ≥ 60 years	First Remission ≥ 1 yr	First Remission < 1 yr
Type of Remission	n = 62	n = 80	n = 62	n = 80
CR (95% CI)	18 (9, 30)	15 (8, 25)	21 (12, 33)	13 (6, 22)
CRp (95% CI)	16 (8, 28)	11 (5, 20)	11 (5, 22)	15 (8, 25)
OR (CR + CRp) (95% CI)	34 (22, 47)	26 (17, 37)	32 (21, 45)	28 (18, 39)

Among patients < 60 years of age the overall response rate was 34%; among patients ≥ 60 years of age the overall response rate was 26%. The overall response rates were similar for females and males: 31% of females and 29% of males achieved remission.

The majority of patients (94%) in the Phase 2 clinical trials were white, only 6% were non-white. All 42 of the responding patients were white.

Relapse-free Survival

Relapse-free survival was calculated from the date of initial therapy (Table 3).

TABLE 3: SUMMARY OF RELAPSE-FREE SURVIVAL[a] FOR PATIENTS WITH CR AND CRp

Remission Group	n	No. Relapsed	Median months	Min-Max months[b]
CR	23	14	7.2	0.5 - 24.8
CRp	19	9	4.4	0.33[b] - 21.5
OR[c]	42	23	6.8	0.33[b] - 24.8

a: Number of months after achieving CR or CRp.
b: Data are limited by data cut-off date; First event occurred in 0.83 months for CRp and in 0.5 months for OR.
c: Six OR patients (1 CR and 5 CRp) had a relapse-free survival of >12 months.

Overall Survival

Median duration of overall survival for the 142 patients was 5.9 months, and 56/142 patients were alive as of the data cutoff date.

Post-Remission Therapy

Fifteen (15/42, 36%) OR patients (8 CRs and 7 CRps) received hematopoietic stem cell transplantations. The survival of these 15 patients ranged from 3.5 to 26.9 months as of the data cut-off date. Nine OR patients (4 CR and 5 CRp) had an overall survival of >12 months as of the data cut-off date.

Repeat Courses

Five patients have received a second treatment course of Mylotarg in clinical trials. These patients were initially treated with Mylotarg, achieved remission, then subsequently relapsed. One of these patients (≥ 60 years of age) achieved a second CR after receiving the second course of Mylotarg. Prolonged severe myelosuppression was observed in four patients receiving a third dose.

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.

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 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). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival, compared to any other treatment.

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 is intended for administration under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

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.

Use in Patients With Hepatic Impairment: Mylotarg has not been studied in patients with bilirubin > 2 mg/dL. Caution should be exercised when administering Mylotarg in patients with hepatic impairment [see ADVERSE REACTIONS section.]

Allergic 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.

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, absense 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: Treatment should be initiated by and remain under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

Tumor lysis syndrome: Tumor lysis syndrome may be a consequence of leukemia treatment. Appropriate measures, (e.g. hydration and allopurinol), must be taken to prevent hyperuricemia.

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.

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. Formal fertility studies were not conducted in animals. When given weekly for 6 doses to rats, gemtuzumab ozogamicin caused atrophy of the seminiferous tubules, oligospermia, desquamated cells in the epididymis, and hyperplasia of the interstitial cells at the dose of 1.2 mg/kg/week (approximately 0.9 times the human dose on a mg/m^2 basis). These findings did not resolve following a 5-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 studied.

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

ADVERSE REACTIONS

Mylotarg has been administered to 142 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 4**)**

TABLE 4: PERCENTAGE OF PATIENTS REPORTED TO HAVE ACUTE INFUSION-RELATED ADVERSE EVENTS

Adverse Event	(%) Any Severity	(%) Grade 3 or 4
Chills	62	11
Fever	61	7
Nausea	38	<1
Vomiting	32	<1
Headache	12	<1
Hypotension	11	4
Hypertension	6	3
Hypoxia	6	2
Dyspnea	4	1
Hyperglycemia	2	2

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. (see WARNINGS section) Fewer infusion-related events were observed after the second dose.

Antibody formation: Antibodies to gemtuzumab ozogamicin were not detected in a total of 142 patients 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. During the treatment phase, 137/140 (98%) patients experienced Grade 3 or Grade 4 neutropenia. Responding patients recovered ANCs to500/µL by a median of 40.5 days after the first dose of Mylotarg.

Anemia, Thrombocytopenia: During the treatment phase, 139/141 (99%) patients experienced Grade 3 or Grade 4 thrombocytopenia. Responding patients recovered platelet counts to 25,000/µL by a median of 39 days after the first dose of Mylotarg. 66/141 (47%) patients experienced Grade 3 or Grade 4 anemia.

Infection: During the treatment phase, 40/142 (28%) 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 (16%) and pneumonia (7%). Herpes simplex infection was reported in 22% of the patients.

Bleeding: During the treatment phase, 21/142 (15%) patients experienced Grade 3 or Grade 4 bleeding. The most frequent severe TEAE was epistaxis (3%). There were also reports of cerebral hemorrhage (2%), disseminated intravascular coagulation (2%), intracranial hemorrhage (2%), and hematuria (1%).

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 = 142	n = 23	n = 19	n = 100
Platelet transfusions				
Mean (SD)	14 (23)	5.4 (6)	14.8 (12)	15.8 (27)
(95% CI)	(10.2, 17.8)	(3, 7.8)	(9.3, 20.4)	(10.6, 21.1)
RBC transfusions				
Mean	8.2 (26)	2.6 (2)	6.2 (5)	9.9 (31)
(95% CI)	(3.9, 12.6)	(1.7, 3.5)	(4, 8.4)	(3.7, 16)

Mucositis: A total of 50/142 (35%) patients were reported to have a TEAE consistent with oral mucositis or stomatitis. During the treatment phase, 5/142 (4%) patients experienced Grade 3 or 4 stomatitis/mucositis after the first dose. The mucositis events for the remaining 45/142 (32%) patients were categorized as Grade 1 or 2.

Hepatotoxicity: Abnormalities of liver function were transient and generally reversible. In clinical studies, 33/141 (23%) patients experienced Grade 3 or Grade 4 hyperbilirubinemia. Nine percent (12/141) of patients experienced Grade 3 or Grade 4 abnormalities in levels of ALT, and 24/141 (17%) patients experienced Grade 3 or Grade 4 abnormalities in levels of AST. Thirteen patients had concurrent elevations of transaminases (grade 3 to 4) and bilirubin. 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. Among 27 patients who received hematopoietic stem cell transplantations following Mylotarg, four (3 NRs and 1 CR) died of hepatic veno-occlusive disease (VOD) 22 to 392 days following transplantation.

Skin: No patients experienced alopecia. A nonspecific rash was reported in 22%.

Retreatment Events: Five (5) patients have received more than one course of Mylotarg, 4 of these patients at 9 mg/m^2. The adverse event profile for retreated patients was similar to that following their initial treatment. One of the repeat dose patients was in a Phase 1 study and received a first course of 3 doses at 1 mg/m^2 and 2 doses of a second course at 6 mg/m^2. This patient was discontinued from further dose administration as a result of an immune response to the calicheamicin/calicheamicin-linker portion of gemtuzumab ozogamicin. The 4 other retreated patients did not experience an immune response.

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 6.

TABLE 6. NUMBER (%) OF PATIENTS REPORTING TREATMENT-EMERGENT ADVERSE EVENTS[a] -ALL GRADES (INCIDENCE ≥ 10%[b])

Adverse Event	Efficacy and Safety Studies	
	All Patients (n = 142)	Age ≥ 60 (n = 80)
Body as a whole		
Abdomen enlarged	13 (9)	9 (11)
Abdominal pain	52 (37)	23 (29)
Asthenia	63 (44)	36 (45)
Back pain	22 (15)	14 (18)
Chills	104 (73)	53 (66)
Fever	121 (85)	64 (80)
Headache	50 (35)	21 (26)
Neutropenic fever	30 (21)	16 (20)
Pain	30 (21)	20 (25)
Sepsis	36 (25)	19 (24)
Cardiovascular system		
Hemorrhage	14 (10)	6 (8)
Hypertension	29 (20)	16 (20)
Hypotension	28 (20)	13 (16)
Tachycardia	15 (11)	8 (10)
Digestive system		
Anorexia	41 (29)	25 (31)
Constipation	36 (25)	22 (28)
Diarrhea	54 (38)	30 (38)
Dyspepsia	16 (11)	9 (11)
Nausea	100 (70)	51 (64)
Stomatitis	45 (32)	20 (25)
Vomiting	89 (63)	44 (55)
Hemic and lymphatic system		
Ecchymosis	18 (13)	12 (15)
Metabolic		
Hypokalemia	44 (31)	24 (30)
Hypomagnesemia	14 (10)	3 (4)
Lactic dehydrogenase increased	19 (13)	14 (18)
Musculoskeletal system		
Arthralgia	12 (8)	8 (10)
Nervous system		
Depression	13 (9)	8 (10)
Dizziness	22 (15)	9 (11)
Insomnia	22 (15)	14 (18)
Respiratory system		
Cough increased	28 (20)	15 (19)
Dyspnea	46 (32)	29 (36)
Epistaxis	44 (31)	23 (29)
Pharyngitis	20 (14)	11 (14)
Pneumonia	14 (10)	8 (10)
Pulmonary physical finding[c]	16 (11)	10 (13)
Rhinitis	14 (10)	8 (10)
Skin and appendages		
Herpes simplex	31 (22)	12 (15)
Rash	31 (22)	18 (23)
Local reaction	35 (25)	20 (25)
Peripheral edema	23 (16)	17 (21)
Petechiae	28 (20)	17 (21)
Urogenital system[c]		
Hematuria	14 (10)	8 (10)

TABLE 6. NUMBER (%) OF PATIENTS REPORTING TREATMENT-EMERGENT ADVERSE EVENTS [a] -ALL GRADES (INCIDENCE ≥ 10%[b])

Adverse Event	Efficacy and Safety Studies All Patients (n = 142)	Age ≥ 60 (n = 80)
Vaginal hemorrhage	7 (12)	2 (7)

a: Does not include changes in laboratory values reported as adverse events for events included in the NCI common toxicity scale.

b: ≥ 10% limit specifies the minimum percentage threshold from at least 1 column for an event to be displayed in the table.

c: Includes rales, rhonchi, and changes in breath sounds.

d: Percentages for sex-specific adverse events are based on the number of patients of the relevant sex.

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284 TEAE with a Grade 3 or 4 severity are listed in Table 7

TABLE 7. PERCENT (%) OF PATIENTS REPORTED TO HAVE SEVERE OR NCI GRADE 3 OR 4 TREATMENT-EMERGENT ADVERSE EVENTS [a] (INCIDENCE ≥ 5%)[b]

Body system Adverse event	Efficacy and safety studies Grades 3 - 4 All Patients (n = 142	Age ≥ 60 (n = 80)
Any adverse event	129 (91)	70 (88)
Body as a whole		
Asthenia	10 (7)	8 (10)
Chills	18 (13)	12 (15)
Fever	21 (15)	11 (14)
Neutropenic fever	10 (7)	4 (5)
Sepsis	23 (16)	12 (16)
Cardiovascular system		
Hypertension	13 (9)	9 (11)
Hypotension	11 (8)	6 (8)
Digestive system		
Nausea	13 (9)	6 (8)
Metabolic		
Hypokalemia	4 (3)	4 (5)
Lactic dehydrogenase increased	6 (4)	6 (8)
Respiratory system		
Dyspnea	13 (9)	10 (13)
Pneumonia	10 (7)	5 (6)

a: Does not include changes in laboratory values reported as adverse events for events included in the NCI common toxicity scale.

b: ≥ 5% limit specifies the minimum percentage threshold from at least 1 column for an event to be displayed in the table.

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Clinically important laboratory abnormalities with a Grade 3 or 4 severity are listed in Table 8.

TABLE 8. NUMBER (%[a]) OF PATIENTS WITH LABORATORY TEST RESULTS OF GRADE 3 OR 4 SEVERITY[b]

	Efficacy and safety studies Grades 3 - 4	
Test	All Patients (n = 142	Age ≥ 60 (n = 80)
Hematologic		
Hemoglobin	66/141 (47)	36/80 (45)
WBC	136/141 (96)	75/80 (94)
Total neutrophils, absolute	137/140 (98)	78/79 (99)
Lymphocytes	130/140 (93)	70/79 (89)
Platelet count	139/141 (99)	79/80 (99)
Prothrombin time	2/ 47 (4)	1/23 (4)
Partial thromboplastin time	1/ 79 (1)	1/42 (2)
Non-hematologic		
Glucose	17/140 (12)	9/79 (11)
Creatinine	2/141 (1)	0/80
Total bilirubin	33/141 (23)	18/80 (23)
AST	24/141 (17)	12/80 (15)
ALT	12/141 (9)	7/80 (9)
Alkaline phosphatase	5/141 (4)	1/80 (1)
Calcium	17/141 (12)	5/80 (6)

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. Laboratory parameters associated with hepatic dysfunction (e.g., elevated levels of bilirubin, AST, and ALT) were more consistently observed in patients ≥ 60 years old than in those < 60 years old.

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

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 9mg/m^2, administered as a 2-hour intravenous infusion. 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. Mylotarg may be administered in an outpatient setting.

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 the fluorescent light off**. Prior to reconstitution, allow drug vials to come to room temperature. 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 solution and for particulate. The final concentration of drug in the vial is 1 mg/mL. While in the vial, the reconstituted drug may be stored refrigerated (2-8°C) and protected from light for up to 8 hours.

Instructions for Dilution

Withdraw the desired volume from each vial and inject into a 100 mL IV bag of 0.9% Sodium Chloride Injection. Place the 100-mL IV bag into an UV protectant bag. The resulting drug solution in the IV bag should be used immediately.

Administration

DO NOT ADMINISTER AS AN INTRAVENOUS 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. A separate IV line equipped with a low protein-binding 1.2-micron terminal filter must be used for administration of the drug. Mylotarg may be given peripherally or through a central line. Pre-medication, 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:** Mylotarg should be stored refrigerated (2 - 8° C, 36 - 46° F and protected from light).

Instructions for use, handling and for disposal: Mylotarg should be inspected visually for particulate matter and discoloration, following reconstitution and prior to administration. Protect from light and use an UV protective bag over the IV bag during infusion. Procedures for handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1,2,3]

HOW SUPPLIED

Mylotarg is supplied as a single vial package with an amber glass vial containing 5mg of Mylotarg lyophilized powder. Single unit 5mg package: each 20mL vial contains 5 mg of Mylotarg. NDC 0008-4510-01

REFERENCES

[1] Recommendation for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For Sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

[2] AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985; 253 (11): 1590-1592.

[3] National Study Commission on Cytotoxic Exposure–Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.