Summary Report of Benefit-Risk Assessment

MYLOTARG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 5MG/ VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Gemtuzumab ozogamicin
Product Registrant	Pfizer Private Limited
Product Registration Number	SIN16243P
Application Route	Abridged evaluation
Date of Approval	21 June 2021

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A INTRODUCTION

Mylotarg is indicated in combination with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients aged 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).

The active substance, gemtuzumab ozogamicin (GO), is an antibody-drug conjugate composed of the CD33-directed monoclonal antibody that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. The antibody portion of GO binds to CD33 antigen present on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, forming a complex which is then internalised. Upon internalisation, calicheamicin is released and binds to DNA, resulting in DNA double strand breaks and subsequent cell death.

Mylotarg is available as powder for concentrate for solution for infusion containing 5 mg/vial of GO. The excipients include sucrose, dextran 40, sodium chloride, sodium dihydrogen phosphate monohydrate and disodium hydrogen phosphate anhydrous.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, GO, and the drug product, Mylotarg Powder for Concentrate for Solution for Infusion, are manufactured at Wyeth Pharmaceutical Division of Wyeth Holdings LLC, New York, USA.

Drug substance:

The drug substance, GO is an antibody-drug conjugate (ADC) composed of the CD33 directed monoclonal antibody that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin.

Adequate controls have been presented for the cell banks, raw materials, reagents, intermediates, gemtuzumab monoclonal antibody and the linker calicheamicin. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented were adequate to support the approved storage condition and shelf life. [redacted]

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are appropriately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 60 months when stored at 2 - 8ºC, protected from light. After reconstitution and dilution, the claimed in-use period of up to 18 hours at 2 - 8ºC, and up to 6 hours at room temperature (below 30ºC), is supported with appropriate data. The container closure system is a 20 mL amber Type 1 glass vial, with butyl elastomer rubber stopper treated with fluoropolymer film, aluminium seal with flip-off plastic cap.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Mylotarg in the treatment of previously untreated, de novo CD33 positive AML was primarily based on one pivotal Phase III study (ALFA0701) conducted in patients aged 50 to 70 years old, and supported by a publication based on a Phase III study (AAML0531) and an investigator-led Individual Patient Data (IPD) meta-analysis conducted at the Cardiff University which included adolescents and adults.

Pivotal study ALFA0701
Study ALFA0701 was a multicentre, randomised, open-label, comparative study of GO in addition to DNR + AraC versus DNR + AraC for induction and consolidation therapy in patients with previously untreated morphologically documented AML aged 50 to 70 years.

Patients in the study were randomised in a 1:1 ratio to receive either GO + DNR + AraC or DNR + AraC. The treatments consisted of the standard “3+7” DNR + AraC regimen for induction with/ without GO 3 mg/m^2 on days 1, 4, and 7 of induction and day 1 of consolidation course 1 and 2. The study subjects were followed up through 2 years from date of last inclusion. DNR + AraC is a standard induction and consolidation regimen recommended in current international clinical practice guidelines, hence the use of DNR + AraC as an active comparator was considered acceptable. Patients with APL were excluded from the study.

The primary efficacy endpoint was event free survival (EFS) defined as the time from date of randomisation to date of induction failure (failure to achieve complete response), relapse, or death due to any cause, whichever occurred first. The key secondary efficacy endpoints were overall survival (OS), relapse-free survival (RFS) and hematologic response rate (complete response [CR] and complete response without platelets [CRp]). The statistical plan for the analyses of the endpoints was standard and considered to be appropriate.

The study treatments were not blinded to the patients or the treating investigators as the individual drug component of the combination therapies employed different regimens and was

administered on different days of the treatment cycle. However, considering that the primary endpoint of EFS was determined by the occurrence of induction failure, relapse or death which are objective measures and the efficacy data was also retrospectively reviewed by a blinded independent review committee (BIRC), possible biases introduced by the local investigators could be reduced.

A total of 271 patients were randomised and were included in the intent-to-treat population: 135 patients in the DNR + AraC + GO arm and 136 patients in the DNR + AraC arm. The demographics and baseline characteristics were balanced across the arms. The median age was 62 years old (range 50 – 70 years old) with a similar proportion of males and females. 11.8% of the patients had Eastern Co-operative Oncology Group performance status of ≥2 indicating poorer performance at baseline. In terms of cytogenetics, 3.3% of patients had favourable, 66.4% of patients had intermediate, 21.0% of patients had unfavourable and 8.1% of patients had unknown risk profiles.

The primary analysis of EFS demonstrated a statistically significant improvement for subjects in the GO + DNR + AraC arm compared to DNR + AraC arm with a 44% reduction in induction failure, relapse or death (HR 0.562; 95% CI 0.415, 0.762; p=0.0002). The median time to an event was 17.3 months in the GO + DNR + AraC arm compared to 9.5 months in the DNR + AraC arm, demonstrating a 7.8-month improvement with addition of GO. The EFS results were consistent in the investigator and BIRC assessments.

In terms of the secondary endpoints, GO + DNR + AraC demonstrated a statistically significantly longer median RFS compared to DNR + AraC (28.0 months versus 11.4 months, HR = 0.526, 95%CI: 0.362, 0.764, p = 0.0006). GO + DNR + AraC also showed numerically higher response rate (CR + CRp) compared to DNR + AraC (81.5% versus 73.5%, p = 0.1457). While statistical significance was not achieved for OS, numerically longer median OS was observed with addition of GO compared to DNR + AraC (27.5 months versus 21.8 months) hence there was no detrimental effect (HR = 0.807, 95%CI: 0.596, 1.093, p = 0.1646).

Summary of key efficacy results

	GO + DNR + AraC	**DNR + AraC**
Primary endpoint		
EFS, n	135	136
Number of events, n (%)	73 (54.1)	102 (75.0)
Induction failure, n (%)	17 (12.6)	29 (21.3)
Relapse, n (%)	44 (32.6)	58 (42.6)
Death, n (%)	12 (8.9)	15 (11.0)
Event free at reference date, (%)	62 (45.1)	34 (25.0)
KM estimate of median time to event (months) [95%CI]	17.3 [13.4, 30.0]	9.5 [8.1, 12.0]
Probability of being event-free at 2 years [95%CI]	42.1 [32.9, 51.0]	18.2 [11.1, 26.7]
Probability of being event-free at 3 years [95%CI]	39.8 [30.2, 49.3]	13.6 [5.8, 24.8]
Versus DNR + AraC – unstratified		
Hazard ratio [95%CI]	0.562 [0.415, 0.762]	
p-value	0.0002	
Key secondary endpoints		
OS, n	135	136
Number of deaths, n (%)	80 (59.3)	88 (64.7)
Alive at reference date, n (%)	55 (40.7)	48 (35.3)
KM estimate of median time to event (months) [95%CI]	27.5 [21.4, 45.6]	21.8 [15.5, 27.4]

Survival probability at 2 years [95%CI]	52.6 [43.8, 60.6]	47.8 [39.2, 55.9]
Survival probability at 3 years [95%CI]	45.7 [37.2, 53.9]	37.0 [28.8, 45.11]
Versus DNR + AraC – unstratified		
Hazard ratio [95%CI]	0.807 [0.596, 1.093]	
p-value	0.1646	
Versus DNR + AraC – stratified by risk (NCCN guideline) [95%CI]	0.887 [0.647, 1.216]	
p-value	0.4547	
Versus DNR + AraC – stratified by risk (ELN guideline) [95%CI]	0.859 [0.635, 1.190]	
p-value	0.3824	
RFS, n	110	100
Relapse, n (%)	44 (40.0)	58 (58.0)
Death, n (%)	5 (4.5)	8 (8.0)
Event free at reference date, n (%)	61 (55.5)	34 (34.0)
KM estimate of median time to event (months) [95%CI]	28.0 [16.3, NE]	11.4 [10.0, 14.4]
Versus DNR + AraC – unstratified [95%CI]	0.526 [0.362, 0.764]	
p-value	0.0006	
Hematologic response, n	135	136
Overall response, n (%)	110 (81.5)	100 (73.5)
95%CI	[73.89, 87.64]	[65.28, 80.72]
Risk difference [95%CI]		7.95 [-3.79, 19.85]
Odds ratio [95%CI]		1.58 [0.86, 2.96]
Complete remission (CR), n (%)	95 (70.4)	95 (69.6)
Complete remission with incomplete platelet recovery (CRp), n (%)	15 (11.1)	5 (3.7)

Subgroup analyses showed consistent results in all subgroups except in patients with unfavourable cytogenetics at baseline (HR = 1.111, 95%CI: 0.633. 19.49, p = 0.715). Nonetheless, unfavourable cytogenetics is a known risk factor for poorer prognosis.

	GO + DNR + AraC	**DNR + AraC**
Cytogenetics (Unfavourable), n	27	30
Number of events, n (%)	23 (85.2)	26 (86.7)
Induction failure, n (%)	9 (33.3)	13 (43.3)
Relapse, n (%)	9 (33.3)	9 (30.0)
Death, n (%)	5 (18.5)	4 (13.3)
KM estimate of median time to event (months) [95%CI]	4.5 [1.1, 7.4]	2.8 [1.6, 8.7]
Hazard ratio [95%CI]	1.111 [0.633, 1.949]	
p-value	0.7151	

Supportive studies

Study AAML0531 was a prospective Phase III randomised, comparator-controlled trial conducted by the Children's Oncology Group which investigated GO in combination with conventional chemotherapy for the treatment of de novo AML in children, adolescents, and young adults. The patients were randomised equally into standard chemotherapy alone (No GO arm) or chemotherapy in combination with 3 mg/m^2 GO (GO arm). The primary efficacy endpoints were EFS at 3 years and OS.

A total of 1022 patients were randomised. 207 patients (20.3%) were 0 to 1 year old, 354 patients (34.6%) were 2 to 10 years old, 298 patients (29.2%) were 11 to 15 years old, 150 patients (14.7%) were 16 to 20 years old and 13 patients (1.3%) were 21 years and older.

There was a statistically significant improvement in EFS for subjects in the GO arm compared to the conventional chemotherapy arm at 3 years (HR = 0.83, 95%CI: 0.70, 0.99, p = 0.04). Although the effect on OS was not statistically significant, the survival rate at 3 years was numerically higher in the GO arm compared to the conventional chemotherapy arm (69.4% versus 64.4%, HR = 0.91, 95%CI: 0.74, 1.13, p = 0.39).

The other supportive study was an investigator-led IPD meta-analysis conducted at the Cardiff University which consisted of five randomised investigator-initiated research studies, including the pivotal study ALFA-0701 and four other studies (Medical Research Council AML15, National Cancer Research Institute AML16, Southwest Oncology Group S0106, and Groupe Ouest Est d'Etude des Leucémies aiguës et Autres Maladies du Sang AML2006IR) to investigate GO in combination with conventional chemotherapy for the treatment of de novo AML in paediatrics, adults and elderly. The studies were selected based on common design features including the administration of GO in combination with intensive induction chemotherapy in patients with untreated AML, and the primary efficacy endpoint was OS.

A total of 3331 patients was included in the meta-analysis. Of these, 1663 patients (49.9%) were randomised to the GO arm while 1668 patients (50.1%) were randomised to the chemotherapy arm without GO. 33.1% of patients were 60 to 69 years of age and 10.7% of the patients were 70 years old and older. 7.7% of the patients aged 15 to 29 years, with 22 patients under the age of 18 years. 88.1% of the patients were treated for de novo AML. The majority of the patients had favourable/intermediate cytogenetics or European Leukaemia Net (ELN) risk (44.9% to 62.2% with negative FMS-like tyrosine kinase 3 gene or nucleophosmin-1 gene status).

The odds ratio for the GO arm versus the chemotherapy alone arm ranged from 0.81 – 0.93 in favour of the GO arm, indicating OS benefit; and the median OS (95%CI) was also longer in the GO arm (23.62 [21.22, 27.33]) versus the chemotherapy alone arm (21.49 [19.42, 23.20]) across all the studies except in study SWOG S0106 which used a different GO dosing regimen (6mg/m^2) from the proposed.

OS in the meta-analysis and in the individual trials

Trial	Trial arm	Patients (n)	Patient deaths		Median OS (months) (95%CI)	Odds ratio
			n	%		
Meta-analysis	GO No GO	1663 1668	1101 1153	66.2 69.1	23.62 (21.22, 27.33) 21.49 (19.42, 23.20)	0.91
MRC AML 15	GO No GO	548 551	339 357	61.9 64.8	34.37 (28.98, 46.36) 27.50 (22.64, 36.50)	0.93
NCRI AML 16	GO No GO	559 556	472 494	84.4 88.8	14.00 (12.65, 15.34) 11.99 (10.58, 13.11)	0.87
ALFA-701	GO No GO	135 136	80 88	59.3 64.7	27.43 (21.39, 45,57) 21.77 (15.51, 27.37)	0.81
GOLAMS AML2006IR	GO No GO	126 125	56 63	44.4 50.4	NR (55.89, NE) 67.35 (27.24, NE)	0.86
SWOG S0106	GO No GO	295 300	154 151	52.2 30.3	43.56 (26.09, 110.4) 60.98 (34.63, NE)	1.09

Overall, the pivotal study ALFA0701 conducted in patients with previously untreated, de novo CD33 positive AML aged 50 to 70 years showed that DNR + AraC + GO resulted in a statistically significantly longer EFS compared to DNR + AraC. The improvement in EFS was supported by the secondary endpoints where DNR + AraC + GO demonstrated a statistically significantly longer median RFS compared to DNR + AraC. DNR + AraC + GO also showed

numerically higher overall response rate (CR + CRp) compared to DNR + AraC. While statistical significance was not achieved for OS, a numerical benefit was observed.

Although this study investigated only patients aged 50 to 70 years, the observed efficacy of GO seen in older patients could be extrapolated to patients less than 50 years old considering the similarity in disease pathogenesis across the age groups. This was further supported by the IPD meta-analysis which showed consistent results in adults and adolescents aged 15 years and older as well as elderly aged 70 years and older; as well as the supplemental evidence from the Phase III study AAML0531 conducted in adolescents aged 15 years and older.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of Mylotarg in patients with previously untreated, de novo CD33 positive AML was based on safety data derived from the pivotal Phase III study ALFA0701. The safety dataset comprised a total of 268 patients who received at least one dose of study treatment: 131 subjects in the GO + DNR + AraC arm and 137 patients in the DNR + AraC arm. The median duration of exposure was slightly longer in the GO + DNR + AraC arm compared to the DNR + AraC arm (12.14 months versus 11.71 months).

Overview of safety profile

AE	GO + DNR + AraC (N=131)	DNR + AraC (N=137)
Any AE	129 (98.5%)	129 (94.2%)
Treatment-related AE	129 (98.5%)	126 (92.0%)
Treatment-related SAE	80 (61.1%)	58 (42.3%)
Discontinuations due to AE	41 (31.3%)	10 (7.3%)
Deaths due to AE	80 (59.3%)	88 (64.7%)
Treatment-related deaths	7 (5.3%)	5 (3.6%)

98.5% of the patients in the GO + DNR + AraC arm experienced an adverse event (AE). The overall incidence of AEs and incidence of Grade 3 and 4 AEs such as mucosal toxicity, pain, nausea, vomiting and diarrhoea were higher (>5% difference) in the GO + DNR + AraC arm compared to the DNR + AraC arm, but the safety profile of the GO-combination was expected due to an addition of another drug to the chemotherapy backbone.

More patients experienced a related serious AE (SAE) in the GO + DNR + AraC arm compared to the DNR + AraC arm (61.1% vs 42.3%). The most common treatment-related SAEs were infections and infestations (38.2% vs 33.6%), blood and lymphatic system disorders (34.4% vs 10.9%) and hepatobiliary disorders (12.2% vs 3.6%) in the GO + DNR + AraC arm and the control arm, respectively. Treatment-related SAEs experienced by >5% of patients in either treatment arm included thrombocytopenia (24.4% vs 3.6%), bronchopulmonary aspergillosis (9.9% vs 7.3%), febrile bone marrow aplasia (9.2% vs 5.1%) and septic shock (6.9% vs 5.1%) in the GO + DNR + AraC arm and the control arm, respectively.

The AEs of special interest reported with Mylotarg included venous occlusive disease (VOD, 4.6%), haemorrhage (90.1%), neutropenia (92.4%) and reduced left ventricular ejection fraction (1.5%). The AEs of special interest have been adequately presented in warnings and precautions in the proposed package insert.

In study AAML0531 and the IPD meta-analysis, the safety profile in paediatric patients was similar with that observed in the studies of GO combined with intensive chemotherapy in adult patients with de novo AML.

Overall, the incidence of AEs was higher with the addition of Mylotarg to chemotherapy compared to chemotherapy alone. Nevertheless, the AEs were as expected due to the additional drug in combination with chemotherapy. The package insert has also included adequate warnings and information on the AEs and their management.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current standard of care for newly diagnosed AML involves induction and consolidation therapies with standard ‘‘3+7’’ regimen of DNR + AraC which consists of 3 consecutive daily infusions of DNR and 7 days of continuous infusion of cytarabine AraC. Despite these agents, 30% to 80% of patients with AML would have relapsed disease within 3 years. Mylotarg presents an additional treatment option for the management of AML.

In the pivotal study ALFA0701 conducted in patients with previously untreated, de novo CD33 positive AML aged 50 to 70 years old, the improvement in EFS of 7.8 months for GO + DNR + AraC was supported by statistically significantly longer median RFS (28.0 months versus 11.4 months, HR = 0.526, 95%CI: 0.362, 0.764, p = 0.0006) and numerically higher overall response rate (CR + CRp) (81.5% versus 73.5%, p = 0.1457) compared to DNR + AraC. While statistical significance was not achieved for OS, there was no detrimental effect (HR = 0.807, 95%CI: 0.596, 1.093, p = 0.1646) and numerical benefit favouring GO arm was demonstrated. Subgroup analyses showed consistent results in all subgroups except in patients with unfavourable cytogenetics at baseline (HR = 1.111, 95%CI: 0.633. 19.49, p = 0.715). Nonetheless, unfavourable cytogenetics is a known risk factor for poorer prognosis and the information on this subgroup of patients has been included in the package insert.

The efficacy of Mylotarg in the younger population aged 15 years and older was extrapolated from the results seen in older patients based on similarity in disease pathogenesis, EFS and OS across all age groups including adolescents, adults, and elderly.

In terms of safety, in the pivotal study, more patients experienced an AE (98.5% versus 94.2%) or AEs related the study drugs (96.5% versus 92.0%) in the GO + DNR + AraC arm compared to the DNR + AraC arm. The incidence of Grade 3 and 4 AEs such as mucosal toxicity, pain, nausea, vomiting, and diarrhoea were higher (>5% difference) in the GO + DNR + AraC arm compared to the DNR + AraC arm. Similar adverse events profile was observed in the younger patient population. The safety concerns and risk mitigation recommendations were adequately included in the package insert.

Overall, the benefits of Mylotarg outweighed the risks in the treatment of patients aged 15 years and above with previously untreated, de novo CD33 positive AML.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Mylotarg for the treatment of patients age 15 years and above with previously untreated, de novo CD33 positive AML, was deemed favourable and approval of the product registration was granted on 21 June 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

MYLOTARG

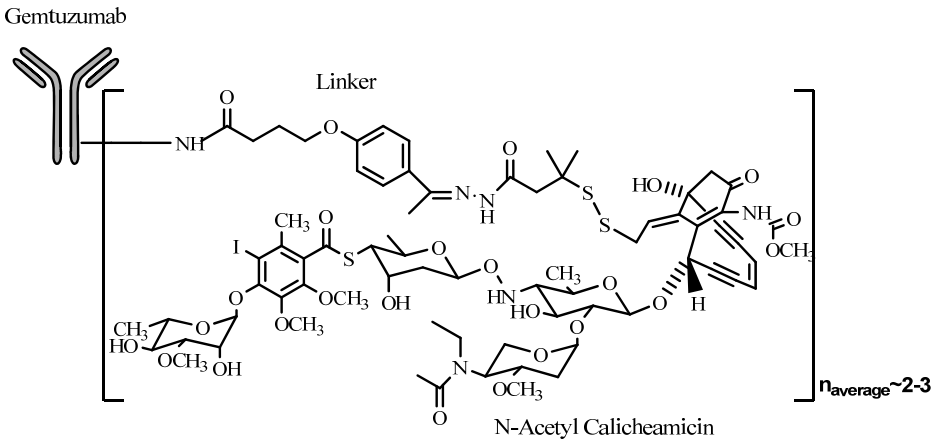
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial contains 5 mg gemtuzumab ozogamicin.

After reconstitution, the concentrated solution contains 1 mg/mL gemtuzumab ozogamicin (see Section 6.6).

For the full list of excipients, see Section 6.1.

Chemical structure:



Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (hP67.6; recombinant humanized immunoglobulin [Ig] G4, kappa antibody produced by mammalian cell culture in NS0 cells) that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. Gemtuzumab ozogamicin consists of conjugated and unconjugated gemtuzumab. The conjugated molecules differ in the number of activated calicheamicin derivative moieties attached to gemtuzumab. The number of conjugated calicheamicin derivatives per gemtuzumab molecule ranges from predominantly 0 to 6, with an average of 2 to 3 moles of calicheamicin derivative per mole of gemtuzumab.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MYLOTARG is indicated for:

- Newly-diagnosed acute myeloid leukemia (AML) (combination therapy)
    - Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive AML, except acute promyelocytic leukemia (APL) (see Sections 4.4 and 5.1).

4.2. Posology and method of administration

Premedication with a corticosteroid, antihistamine, and acetaminophen (or paracetamol) is recommended 1 hour prior to MYLOTARG dosing to help ameliorate infusion-related symptoms (see Section 4.4).

Appropriate measures to help prevent the development of tumor lysis-related hyperuricemia such as hydration, administration of antihyperuricemic or other agents for treatment of hyperuricemia must be taken (see Section 4.4).

For patients with hyperleukocytosis (leukocyte count >30,000/mm^3), cytoreduction is recommended prior to administration of MYLOTARG (see Table 2).

MYLOTARG must be reconstituted and diluted before administration (see Section 6.6).

Posology

Newly-diagnosed de novo CD33-positive AML (combination regimen)

A treatment course including MYLOTARG in combination therapy for adults with newly-diagnosed de novo CD33-positive AML consists of 1 induction cycle and 2 consolidation cycles.

Induction

The recommended dose of MYLOTARG is 3 mg/m^2/dose (up to a maximum of one 5 mg vial) infused over a 2-hour period on Days 1, 4, and 7 in combination with DNR 60 mg/m^2/day infused over 30 minutes on Day 1 to Day 3, and AraC 200 mg/m^2/day by continuous infusion on Day 1 to Day 7.
If a second induction is required, MYLOTARG should not be administered during second induction therapy. Only DNR and AraC should be administered during the second induction cycle, at the following recommended dosing: DNR 35 mg/m^2/day on Days 1 and 2, and AraC 1 g/m^2 every 12 hours, on Day 1 to Day 3.

Consolidation

For patients experiencing a complete remission (CR) following induction, defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count (ANC) of more than 1.0×10^9 cells/L with a platelet count of 100×10^9/L or more in the peripheral blood in the absence of transfusion, up to 2 consolidation courses of intravenous DNR (60 mg/m^2 for 1 day [first course] or 2 days [second course]) in combination with intravenous AraC (1 g/m^2 per 12 hours, infused over 2 hours on Day 1 to Day 4) with intravenous MYLOTARG (3 mg/m^2/dose infused over 2 hours up to a maximum dose of one 5 mg vial on Day 1) are recommended. Table 1 shows dosing regimens for MYLOTARG in combination with chemotherapy.

Table 1. Dosing Regimens for MYLOTARG in Combination With Chemotherapy

Treatment Course	**MYLOTARG**	**Daunorubicin**	**Cytarabine**
Induction[a]	3 mg/m^2/dose (up to a maximum of 5 mg/dose) on Days 1, 4, and 7	60 mg/m^2/day on Days 1-3	200 mg/m^2/day on Days 1-7
Second induction (if required)	MYLOTARG should not be administered during second induction.	35 mg/m^2/day on Days 1- 2	1 g/m^2/every 12 hours on Days 1-3
Consolidation Course 1[a,b]	3 mg/m^2/dose (up to a maximum of 5 mg/dose) on Day 1	60 mg/m^2/day on Day 1	1 g/m^2/every 12 hours from Days 1-4
Consolidation Course 2[a,b]	3 mg/m^2/dose (up to a maximum of 5 mg/dose) on Day 1	60 mg/m^2/day on Days 1-2	1 g/m^2/every 12 hours from Days 1-4

a. See Table 2 and Table 3 for dose modification information.
b. For patients experiencing a complete remission following induction.

Dose and schedule modifications

Schedule modification for hyperleukocytosis

In patients with hyperleukocytic (leukocyte count >30,000/mm^3) AML, cytoreduction is recommended either with leukapheresis, oral hydroxyurea (previously untreated AML), or AraC with or without hydroxyurea (previously untreated AML) to reduce the peripheral white blood cell (WBC) count 48 hours prior to administration of MYLOTARG (see Section 4.4).

If AraC is used for leukoreduction with or without hydroxyurea in patients with previously untreated, de novo hyperleukocytic AML receiving MYLOTARG in combination therapy, apply the following modified schedule (Table 2):

Table 2. Schedule Modification for the Treatment of Hyperleukocytosis With Cytarabine

Treatment Course	MYLOTARG	Daunorubicin	Cytarabine	Hydroxyurea
Induction[a]	3 mg/m^2/dose (up to a maximum of 5 mg/dose) on Days 3, 6, and 9	60 mg/m^2/day on Days 3-5	200 mg/m^2/day on Days 1-7	Day 1 (as per standard medical practice)

[a.] See Table 3 for additional dose modification information.

Dose modification for adverse reactions

Dose modification of MYLOTARG is recommended based on individual safety and tolerability (see Section 4.4). Management of some adverse reactions may require dose interruptions or permanent discontinuation of MYLOTARG (see Sections 4.4 and 4.8).

Table 3 shows the dose modification guidelines for hematologic and nonhematologic toxicities.

Table 3. Dosage Modifications for Hematologic and Nonhematologic Toxicities

Hematologic and Nonhematologic Toxicities	Recommended Action
For patients receiving MYLOTARG in combination therapy	
Persistent thrombocytopenia	• If platelet count does not recover to greater than or equal to 100,000 mm^3 within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles).
Persistent neutropenia	• If neutrophil count does not recover to greater than 500 mm^3 within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles).
For all patients receiving MYLOTARG (combination therapy)	
VOD/SOS	• Discontinue MYLOTARG (see Section 4.4).
Total bilirubin greater than 2 × ULN, or AST and/or ALT greater than 2.5 × ULN	• Delay treatment with MYLOTARG until recovery of total bilirubin to less than or equal to 2 × ULN and AST and ALT to less than or equal to 2.5 × ULN prior to each dose. • Omit scheduled dose if delayed more than 2 days between sequential infusions.
Infusion related reactions	• Interrupt the infusion and institute appropriate medical management based on the severity of symptoms. Patients should be monitored until signs and symptoms completely

Table 3. Dosage Modifications for Hematologic and Nonhematologic Toxicities

Hematologic and Nonhematologic Toxicities	Recommended Action
	resolve and infusion may resume. • Consider permanent discontinuation of treatment for severe or life-threatening infusion reactions (see Section 4.4).
Other severe or life-threatening nonhematologic toxicities	• Delay treatment with MYLOTARG until recovery to a severity of no more than mild. • Consider omitting scheduled dose if delayed more than 2 days between sequential infusions.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease; ULN=upper limit of normal.

Special populations

Use in patients with hepatic impairment

No adjustment to dose of MYLOTARG is required in patients with mild to moderate hepatic impairment. MYLOTARG has not been studied in patients with severe hepatic impairment.

Use in patients with renal impairment

No adjustment to dose of MYLOTARG is required in patients with mild to moderate renal impairment. MYLOTARG has not been studied in patients with severe renal impairment.

Elderly patients

No adjustment to dose of MYLOTARG is required in elderly patients (≥65 years) (see Section 5.2).

Pediatric population

The safety and efficacy of MYLOTARG in combination with chemotherapy in the pediatric population (<15 years) with newly-diagnosed AML have not been established.

Method of administration

Administer MYLOTARG intravenously by infusion over a 2-hour period under close clinical monitoring, including pulse, blood pressure, and temperature. Do not administer MYLOTARG as an intravenous push or bolus (see Section 6.6).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4. Special warnings and precautions for use

Hepatotoxicity, including hepatic venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS)

In clinical studies with MYLOTARG in patients with previously untreated de novo AML, hepatotoxicity, including life-threatening, and sometimes fatal hepatic VOD/SOS events, was reported (see Section 4.8).

Hepatotoxicity, including VOD/SOS events, has been reported in association with the use of MYLOTARG as part of a combination chemotherapy regimen, in patients without a history of liver disease or hematopoietic stem cell transplant (HSCT).

Death from liver failure and from VOD/SOS have been reported in patients who received MYLOTARG. Due to the risk of VOD/SOS, monitor closely for signs and symptoms of VOD/SOS; these may include elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase, which should be monitored prior to each dose of MYLOTARG, hepatomegaly (which may be painful), rapid weight gain, and ascites. Monitoring only total bilirubin may not identify all patients at risk of VOD/SOS. For patients who develop abnormal liver tests, more frequent monitoring of liver tests and clinical signs and symptoms of hepatotoxicity is recommended for patients who proceed to HSCT. Close monitoring of liver tests is recommended during the post-HSCT period, as appropriate. The ALFA-0701 study recommended an interval of 2 months between the last dose of MYLOTARG and HSCT.

Management of signs or symptoms of hepatic toxicity may require a dose interruption or discontinuation of MYLOTARG (see Section 4.2). In patients who experience VOD/SOS, discontinue MYLOTARG and treat according to standard medical practice.

Infusion related reactions (including anaphylaxis)

There have been reports of fatal infusion reactions in the postmarketing setting. Signs and symptoms of infusion related reactions may include fever and chills, and less frequently hypotension, tachycardia, and respiratory symptoms that may occur during the first 24 hours after administration. Perform infusion of MYLOTARG under close clinical monitoring, including pulse, blood pressure, and temperature.

Premedication with a corticosteroid, antihistamine, and acetaminophen (or paracetamol) is recommended 1 hour prior to MYLOTARG dosing (see Section 4.2). Interrupt infusion immediately for patients who develop evidence of severe reactions, especially dyspnea, bronchospasm, 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 signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension (see Section 4.2).

Myelosuppression

In clinical studies with MYLOTARG, neutropenia, thrombocytopenia, anemia, leukopenia, febrile neutropenia, lymphopenia, and pancytopenia, some of which were life-threatening or fatal, were reported (see Section 4.8). Complications associated with neutropenia and thrombocytopenia may include infections and bleeding/hemorrhagic events, respectively.

Infections and bleeding/hemorrhagic events were reported, some of which were life-threatening or fatal.

Monitor complete blood counts prior to each dose of MYLOTARG and monitor patients for signs and symptoms of infection, bleeding/hemorrhage, or other effects of myelosuppression during treatment with MYLOTARG. Routine clinical and laboratory surveillance testing during and after treatment with MYLOTARG is indicated.

Management of patients with severe infection, bleeding/hemorrhage, or other effects of myelosuppression, including severe neutropenia or persistent thrombocytopenia, may require a dose delay or permanent discontinuation of MYLOTARG (see Section 4.2).

Tumor lysis syndrome (TLS)

In clinical studies with MYLOTARG, TLS was reported (see Section 4.8). Fatal reports of TLS complicated by acute renal failure have been reported in the postmarketing setting. In patients with hyperleukocytic AML, leukoreduction should be considered with hydroxyurea or leukapheresis to reduce the peripheral WBC count to below 30,000/mm^3 prior to administration of MYLOTARG to reduce the risk of inducing TLS (see Section 4.2).

Patients should be monitored for signs and symptoms of TLS and treated according to standard medical practice. Appropriate measures to help prevent the development of tumor lysis-related hyperuricemia such as hydration, administration of antihyperuricemic (e.g., allopurinol) or other agents for treatment of hyperuricemia (e.g., rasburicase) must be taken.

Use in AML with adverse-risk cytogenetics

The efficacy of MYLOTARG has been shown in AML patients with favorable- and intermediate-risk cytogenetics, with uncertainty regarding the effect in patients with adverse cytogenetics (see Section 5.1). For patients being treated with MYLOTARG in combination with DNR and AraC for newly-diagnosed de novo AML, when cytogenetics testing results become available consider whether the potential benefit of continuing treatment with MYLOTARG outweighs the risks for the individual patient.

4.5. Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies have been performed with MYLOTARG (see Section 5.2).

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving MYLOTARG.

Advise women to use effective contraception during treatment with MYLOTARG and for at least 7 months after the last dose. Advise men with female partners of childbearing potential to use effective contraception during treatment with MYLOTARG and for at least 4 months after the last dose.

Pregnancy

There are no or limited amount of data from the use of gemtuzumab ozogamicin in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3).

MYLOTARG must not be used during pregnancy unless the potential benefit to the mother outweighs the potential risks to the foetus. Pregnant women, or patients becoming pregnant whilst receiving gemtuzumab ozogamicin, or treated male patients as partners of pregnant women, must be apprised of the potential hazard to the foetus.

Breastfeeding

There is no information regarding the presence of MYLOTARG in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for adverse reactions in breastfed infants, women should not breastfeed during treatment with MYLOTARG and for at least 1 month after the final dose (see Section 5.3).

Fertility

Based on nonclinical findings, male and female fertility may be compromised by treatment with MYLOTARG (see Section 5.3). Both men and women should seek advice for fertility preservation before treatment.

4.7. Effects on ability to drive and use machines

No studies on the effect of MYLOTARG on the ability to drive and use machines have been performed. Fatigue has been reported during treatment with MYLOTARG (see Section 4.8). Therefore, caution should be exercised when driving or operating machines.

4.8. Undesirable effects

Summary of the safety profile

Combination therapy in previously untreated AML

The overall safety profile of MYLOTARG is based on data from patients with AML from the combination therapy study ALFA-0701, and from postmarketing experience. In the combination therapy study, safety data consisting of selected treatment emergent adverse events (TEAEs) considered most important for understanding the safety profile of MYLOTARG consisted of all grades haemorrhages, all grades VOD, and severe infections. All of these TEAEs were determined to be adverse drug reactions.

In the combination therapy study ALFA-0701, clinically relevant serious adverse reactions were hepatotoxicity, including VOD/SOS (3.8%), haemorrhage (9.9%), severe infection (41.2%), and TLS (1.5%).

The most common adverse reactions (>30%) in the combination therapy study were haemorrhage and infection.

The most frequent (≥1%) adverse reactions that led to permanent discontinuation in the combination therapy study were thrombocytopenia, VOD, haemorrhage, and infection.

Tabulated list of adverse reactions

Tables 4 show the adverse reactions reported in patients with previously untreated de novo AML who received MYLOTARG in a combination study.

The adverse drug reactions are presented by system organ class (SOC). Within each SOC, adverse drug reactions are presented in order of decreasing seriousness.

Table 4: Selected Adverse Drug Reactions Captured During a Retrospective Review of Predefined Events by SOC and CIOMS Frequency Category Listed in Order of Decreasing Medical Seriousness Within Each Frequency Category and SOC (Combination Therapy ALFA-0701)

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10
Infections and infestations	Infection*,a	
Vascular disorders	Haemorrhage*,b	
Hepatobiliary disorders		Venoocclusive liver disease*

CIOMS=Council for International Organizations of Medical Sciences; SOC=System Organ Class.
*Including fatal outcome.
a. Infection includes any reported preferred terms for gemtuzumab ozogamicin retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 System Organ Class Infections and infestations, and includes fatal events.
b. Haemorrhage includes any reported preferred terms for gemtuzumab ozogamicin retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 Standard MedDRA Query (narrow) for Haemorrhage terms (excluding laboratory terms).

Postmarketing experience

The following adverse drug reactions have been identified during post-approval use of MYLOTARG. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: Neutropenic colitis*
Infections and infestations: Fungal lung infections including Pulmonary mycosis and Pneumocystis jirovecii pneumonia*; and bacterial infections including Stenotrophomonas infection
Renal and urinary disorders: Haemorrhagic cystitis
Respiratory, thoracic and mediastinal disorders: Interstitial pneumonia

* Including fatal events

Description of selected adverse drug reactions

Hepatotoxicity, including hepatic VOD/SOS

In the combination therapy study in patients with previously untreated de novo AML treated with fractionated doses of MYLOTARG in combination with chemotherapy (N=131),

hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic VOD/SOS events, was reported. Hepatotoxicity with fatal outcome occurred in 5 (3.7%) patients in the combination therapy study.

In the combination therapy study (N=131), VOD events were reported in 6 (4.6%) patients during or following treatment, 2 (1.5%) of these events were fatal. Five (3.8%) of these VOD events occurred within 28 days of last dose of MYLOTARG. One VOD event occurred more than 28 days of last dose of MYLOTARG; with 1 of these events occurring a few days after having started a HSCT conditioning regimen. The median time from the last MYLOTARG dose to onset of VOD was 9 days (range: 2-298 days).

Patients should be monitored for hepatotoxicity as recommended in Section 4.4. Management of signs or symptoms of hepatic toxicity may require a dose interruption or discontinuation of MYLOTARG (see Section 4.2).

Myelosuppression

In the combination therapy study in patients with previously untreated de novo AML treated with fractionated doses of MYLOTARG in combination with chemotherapy, Grade 3/4 decreases in leukocytes, neutrophils, and platelets were observed in 131 (100%), 124 (96.1%), and 131 (100%) patients, respectively.

During the induction phase, 109 (83.2%) and 99 (75.6%) patients had platelet recovery to counts of 50,000/mm^3 and 100,000/mm^3, respectively. The median times to platelet recovery to counts of 50,000/mm^3 and 100,000/mm^3 were 34 and 35 days, respectively. During the Consolidation 1 phase, 92 (94.8%) and 71 (73.2%) patients had a platelet recovery to counts of 50,000/mm^3, and 100,000/mm^3, respectively. The median times to platelet recovery to counts of 50,000/mm^3 and 100,000/mm^3 were 32 and 35 days, respectively. During the Consolidation 2 phase, 80 (97.6%) and 70 (85.4%) patients had a platelet recovery to counts of 50,000/mm^3 and 100,000/mm^3, respectively. The median times to platelet recovery to counts of 50,000/mm^3 and 100,000/mm^3 were 36.5 and 43 days, respectively.

Thrombocytopenia with platelet counts <50,000/mm^3 persisting 45 days after the start of therapy for responding patients (CR and complete remission with incomplete platelet recovery [CRp]) occurred in 22 (20.4%) patients. The number of patients with persistent thrombocytopenia remained similar across treatment courses (8 [7.4%] patients at the induction phase, 8 [8.5%] patients at the Consolidation 1 phase, and 10 [13.2%] patients at the Consolidation 2 phase).

During the induction phase, 121 (92.4%) and 118 (90.1%) patients had a documented neutrophil recovery to ANC of 500/mm^3 and 1000/mm^3, respectively. The median time to neutrophil recovery to ANC of 500/mm^3 and 1000/mm^3 was 25 days. In the Consolidation 1 phase of therapy, 94 (96.9%) patients had neutrophil recovery to counts of 500/mm^3, and 91 (94%) patients recovered to counts of 1000/mm^3. The median times to neutrophil recovery to ANC of 500/mm^3 and 1000/mm^3 were 21 and 25 days, respectively. In the Consolidation 2 phase of therapy, 80 (97.6%) patients had neutrophil recovery to counts of 500/mm^3, and 79 (96.3%) patients recovered to counts of 1000/mm^3. The median times to neutrophil recovery to ANC of 500/mm^3 and 1000/mm^3 were 22 and 27 days, respectively.

In the combination therapy study, in patients with de novo AML treated with fractionated doses of MYLOTARG in combination with chemotherapy (N=131), 102 (77.9%) patients experienced all-causality severe (Grade ≥3) infections. Treatment-related death due to septic shock was reported in 1 (0.8%) patient.

In the combination therapy study (N=131), all grades and Grade 3/4 bleeding/haemorrhagic events were reported in 118 (90.1%) and 27 (20.6%) patients, respectively. The most frequent Grade 3 bleeding/haemorrhagic events were epistaxis (1.5%), haemoptysis (3.1%), and haematuria (2.3%). Grade 4 bleeding/haemorrhagic events were reported in 4 (3.1%) patients (gastrointestinal haemorrhage, haemorrhage, and pulmonary alveolar haemorrhage [2 patients]). Fatal bleeding/haemorrhagic events were reported in 3 (2.3%) patients (cerebral haematoma, intracranial haematoma, and subdural haematoma).

Management of patients with severe infection, bleeding/haemorrhage, or other effects of myelosuppression, including severe neutropenia or persistent thrombocytopenia, may require a dose delay or permanent discontinuation of MYLOTARG (see Sections 4.2 and 4.4).

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity.

Patients in the Phase 2 trials did not develop antidrug antibodies (ADAs) and only 2 patients in a Phase 1 trial developed antibodies against the calicheamicin-linker complex, 1 of whom had reduced hP67.6 plasma concentrations. Overall, the incidence rate of ADA development after MYLOTARG treatment was <1% across the 4 clinical studies with ADA data. Definitive conclusions cannot be drawn between the presence of antibodies and potential impact on efficacy and safety due to the limited number of patients with positive antidrug antibodies.

The detection of ADAs is highly dependent on the sensitivity and specificity of the assay. The incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, circulating drug concentrations, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to MYLOTARG with the incidence of antibodies to other products may be misleading.

4.9. Overdose

No cases of overdose with MYLOTARG were reported in clinical experience. Single doses higher than 9 mg/m^2 in adults were not tested. Treatment of MYLOTARG overdose should consist of general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

Gemtuzumab ozogamicin is a CD33-targeted ADC. Gemtuzumab is a humanized immunoglobulin class G subtype 4 (IgG4) antibody which specifically recognizes human

CD33. The antibody portion (hP67.6) binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of myeloid leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells. The small molecule, N-acetyl gamma calicheamicin, is a cytotoxic semisynthetic natural product. N-acetyl gamma calicheamicin is covalently attached to the antibody via an AcBut (4-(4-acetylphenoxy) butanoic acid) linker. Nonclinical data suggest that the anticancer activity of gemtuzumab ozogamicin is due to the binding of the ADC to CD33-expressing tumor cells, followed by internalization of the ADC-CD33 complex, and the intracellular release of N-acetyl gamma calicheamicin dimethyl hydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl gamma calicheamicin dimethyl hydrazide induces double-stranded DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

In vitro studies have also shown that after a 3 mg/m^2 dose, re-expression of available CD33 sites occurred every 72 hours to nearly pretreatment levels before the next dose. This observation led to the hypothesis that repeated administration of lower doses of gemtuzumab ozogamicin may be able to enhance the internalization process and thereby the intracellular accumulation of the drug, while improving safety as compared with the higher unfractionated dosing regimen.

Pharmacodynamic (PD) effects

In vitro cytotoxicity assays showed that gemtuzumab ozogamicin was effective at selectively killing human leukemia cell line (HL-60) target cells. In nonclinical murine models, gemtuzumab ozogamicin demonstrates antitumor effects in the HL-60 human promyelocytic leukemia xenograft tumor in athymic mice. Combining DNR and AraC chemotherapy with gemtuzumab ozogamicin was effective in eliminating disease and prolonging survival in nonclinical AML models.

Clinical efficacy and safety

Studies of previously untreated patients with de novo AML

The efficacy and safety of MYLOTARG were evaluated in a multicenter, randomized, open-label, Phase 3 study (ALFA-0701) comparing the addition of MYLOTARG to a standard chemotherapy induction regimen of daunorubicin and cytarabine (DA) versus DA alone. Eligible patients were between 50 and 70 years of age with previously untreated de novo AML.

Patients were randomized (1:1) to receive induction therapy consisting of DNR (60 mg/m^2 on Days 1 to 3) and AraC (200 mg/m^2 on Days 1 to 7) (DA) with (N=135) or without (N=136) MYLOTARG 3 mg/m^2 (up to maximum of one vial) on Days 1, 4, and 7. Patients who did not achieve a response after first induction could receive a second induction with DNR and AraC alone. Patients with response received consolidation therapy with 2 courses of treatment including DNR (60 mg/m^2 on Day 1 of consolidation course 1; 60 mg/m^2 on Days 1 and 2 of consolidation course 2) and AraC (1 g/m^2 every 12 hours on Days 1 to 4) with or without MYLOTARG 3 mg/m^2 (up to a maximum of one vial) on Day 1 according to their initial randomization. Patients who experienced remission were also eligible for allogeneic transplantation. An interval of at least 2 months between the last dose of MYLOTARG and transplantation was recommended.

The primary endpoint was event-free survival (EFS). The secondary endpoints included CR and CRp rates, relapse-free survival (RFS), overall survival (OS), and safety of the combination DA with or without MYLOTARG.

In total, 271 patients were randomized in this study with 135 to induction treatment of 3+7 DA plus fractionated 3 mg/m^2 × 3 doses of MYLOTARG and 136 to 3+7 DA alone (see Section 4.2). A second course of induction therapy with DA but without MYLOTARG, regardless of the randomization arm, was allowed. Patients in either arm who did not receive the second course of induction therapy and did not achieve a CR after induction could receive a salvage course comprised of idarubicin, AraC, and granulocyte colony-stimulating factor (G-CSF).

Patients with CR or CRp received consolidation therapy with 2 courses of treatment including DNR and AraC with or without MYLOTARG according to their initial randomization. Patients who experienced remission were also eligible for allogeneic transplantation. An interval of at least 2 months between the last dose of MYLOTARG and transplantation was recommended.

Safety data consisting of selected TEAEs considered most important for understanding the safety profile of MYLOTARG as well as all adverse events (AEs) that led to the permanent discontinuation of treatment were retrospectively collected. The selected TEAEs consisted of all grades hemorrhages, all grades VOD/SOS and severe infections.

Overall, the median age of patients was 62 years and most patients (87.8%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 at baseline. Baseline characteristics were balanced between treatment arms with the exception of gender as a higher percentage of males were enrolled in the MYLOTARG arm (54.8%) than in the DA alone arm (44.1%). Overall, 59.0% and 65.3% of patients had documented favorable/intermediate risk disease by the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) 2010 risk classifications, respectively. CD33 expression on AML blasts by flow cytometry harmonized from local laboratory results was determined in 194/271 (71.6%) patients overall. Few patients (13.7%) had low CD33 expression (less than 30% of blasts).

The trial met its primary objective of demonstrating that MYLOTARG added in fractionated doses (3 mg/m^2 × 3) to standard induction chemotherapy for patients with previously untreated de novo AML resulted in a statistically significant and clinically meaningful improvement in EFS. Median EFS was 17.3 months (95% CI: 13.4, 30.0) in the MYLOTARG arm versus 9.5 months (95% CI: 8.1, 12.0) in the DA alone arm; hazard ratio (HR) 0.562 (95% CI: 0.415, 0.762); 2-sided p=0.0002 by log-rank test. EFS results derived from investigator assessment are summarized in Table 5 and the Kaplan-Meier plot is shown in Figure 1.

Table 5. Efficacy Results from Study ALFA-0701 (mITT population)

	MYLOTARG + Daunorubicin + Cytarabine	**Daunorubicin + Cytarabine**
Event-free survival (by Investigator)	**N=135**	**N=136**
Number of events, n (%)	73 (54.1)	102 (75.0)

Table 5. Efficacy Results from Study ALFA-0701 (mITT population)

	MYLOTARG + Daunorubicin + Cytarabine	Daunorubicin + Cytarabine
Median EFS in months [95% CI][a,]	17.3 [13.4, 30.0]	9.5 [8.1, 12.0]
2-year EFS probability [95% CI][b]	42.1 [32.9, 51.0]	18.2 [11.1, 26.7]
3-year EFS probability [95% CI][b]	39.8 [30.2, 49.3]	13.6 [5.8, 24.8]
Hazard ratio [95% CI][c]	0.562 [0.415, 0.762]	
p-value[d]	0.0002	
Relapse-free survival (by Investigator)	**N=110**	**N=100**
Number of events, n (%)	49 (44.5)	66 (66.0)
Median RFS in months [95% CI][a]	28.0 [16.3, NE]	11.4 [10.0, 14.4]
Hazard ratio [95% CI][c]	0.526 [0.362, 0.764]	
p-value[d]	0.0006	
Overall survival	**N=135**	**N=136**
Number of deaths, n (%)	80 (59.3)	88 (64.7)
Median OS in months [95% CI][a]	27.5 [21.4, 45.6]	21.8 [15.5, 27.4]
Hazard ratio [95% CI][c]	0.807 [0.596, 1.093]	
p-value[d]	0.1646	
Response rate (by Investigator)	**N=135**	**N=136**
Overall response % [95% CI][e]	81.5 [73.89, 87.64]	73.5 [65.28, 80.72]
CR	70.4	69.9
CRp	11.1	3.7
Risk difference [95% CI][f]	7.95 [-3.79, 19.85]	
p-value[g]	0.1457	

Based on the primary definition of EFS: event dates (induction failure, relapse, or death) determined by investigator assessment.

The mITT population included all patients who were randomized, unless withdrawal of consent prior to start of treatment and were analyzed according to initial randomization arm.

Abbreviations: CI=confidence interval; CR=complete remission; CRp=complete remission with incomplete platelet recovery; EFS=event-free survival; mITT=modified intent-to-treat; n=number; N=number; NE=not estimable; OS=overall survival; RFS=relapse-free survival.

a. Median estimated by Kaplan-Meier method; CI based on the Brookmeyer-Crowley method with log-log transformation.

b. Estimated from Kaplan-Meier curve. Probability (%) calculated by the product-limit method; CI calculated from the log-log transformation of survival probability using a normal approximation and the Greenwood formula.

c. Based on the Cox proportional hazards model versus daunorubicin + cytarabine.

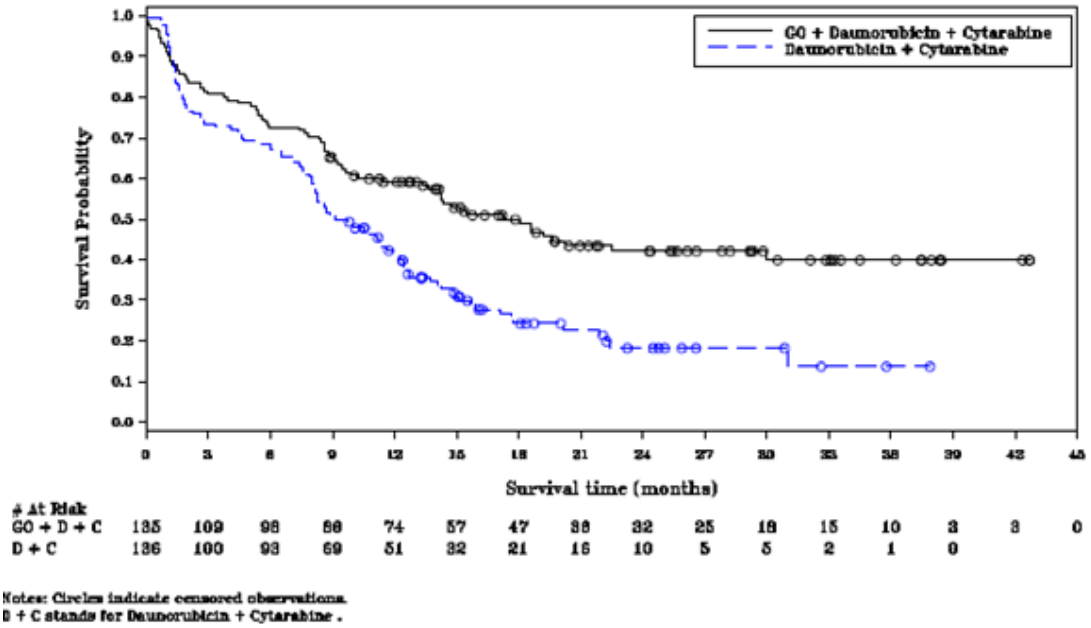
d. 2-sided p-value from the log-rank test.

e. Response defined as CR+CRp.

f. Overall response difference; CI based on Santner and Snell method.

g. Based on Fisher's exact test.

Figure 1. Kaplan-Meier Plot of Event-Free Survival (mITT Population)



Notes: Circles indicate censored observations.
D + C stands for Daunorubicin + Cytarabine .

Abbreviations: C=cytarabine; D=daunorubicin; GO=gemtuzumab ozogamicin; mITT=modified intent-to-treat.

Use in AML with adverse-risk cytogenetics

In subgroup analyses in ALFA-0701, the addition of MYLOTARG to standard combination chemotherapy did not improve EFS in the subgroup of patients having adverse-risk cytogenetics (HR 1.11; 95% CI: 0.63, 1.95). EFS and OS analyzed by cytogenetic risk classification and cytogenetic/molecular risk classification are presented in Table 6 and Table 7.

Table 6. Event-Free Survival by AML Risk Classifications (mITT Population)

	MYLOTARG + Daunorubicin + Cytarabine	**Daunorubicin + Cytarabine**
Cytogenetics (Favorable/Intermediate), N	94	95
Number of events, n (%)	44 (46.8)	68 (71.6)
Median EFS in months [95% CI][a,b]	22.5 [15.5, NE]	11.6 [8.3, 13.7]
Hazard ratio[c] [95% CI] p-value[d]	0.460 [0.313, 0.676] <0.0001	
Cytogenetics (Unfavorable), N	27	30
Number of events, n (%)	23 (85.2)	26 (86.7)
Median EFS in months [95% CI][a,b]	4.5 [1.1, 7.4]	2.8 [1.6, 8.7]
Hazard ratio[c] [95% CI] p-value[d]	1.111 [0.633, 1.949] 0.7151	
ELN (Favorable/Intermediate), n	86	91
Number of events, n (%)	40 (46.5)	63 (69.2)

Table 6. Event-Free Survival by AML Risk Classifications (mITT Population)

Median EFS in months [95% CI][a,b]	22.5 [15.5, NE]	12.2 [8.5, 14.3]
Hazard ratio[c] [95% CI] p-value[d]	0.485 [0.325, 0.724] 0.0003	
ELN (Poor/Adverse), n	37	36
Number of events, n (%)	27 (73.0)	32 (88.9)
Median EFS in months [95% CI][a,b]	7.4 [3.7, 14.3]	4.0 [1.7, 8.6]
Hazard ratio[c] [95% CI] p-value[d]	0.720 [0.430, 1.205] 0.2091	

Method (A1): Event date determined by investigator assessment.
The modified intent-to-treat (mITT) population included all patients who were randomized, unless withdrawal of consent prior to start of treatment and were analyzed according to initial randomization arm.
Abbreviations: AML=acute myeloid leukemia; CI=confidence interval; EFS=event-free survival; ELN=European LeukemiaNet; KM=Kaplan-Meier; mITT=modified intent-to-treat; n=number; N=number; NE=not estimable.

a. Based on the Brookmeyer and Crowley Method with log-log transformation.
b. Estimated from the KM curve.
c. Based on the Cox Proportional Hazards Model.
d. 2-sided p-value from the log-rank test.

Table 7. Overall Survival by AML Risk Classifications from Study ALFA-0701 (mITT Population)

	MYLOTARG + Daunorubicin + Cytarabine	Daunorubicin + Cytarabine
Cytogenetics (favorable/intermediate), N	**94**	**95**
Number of deaths, n (%)	51 (54.3)	57 (60.0)
Median OS in months [95% CI][a]	38.6 [24.4, NE]	26.0 [18.9, 39.7]
Hazard ratio [95% CI][Error! Reference source not found.]	0.747 [0.511, 1.091]	
p-value[c]	0.1288	
Cytogenetics (unfavorable), N	**27**	**30**
Number of deaths, n (%)	24 (88.9)	24 (80.0)
Median OS in months [95% CI][a]	12.0 [4.2, 14.2]	13.5 [9.4, 27.3]
Hazard ratio [95% CI][Error! Reference source not found.]	1.553 [0.878, 2.748]	
p-value[c]	0.1267	
ELN (favorable/intermediate), N	**86**	**91**
Number of deaths, n (%)	44 (51.2)	53 (58.2)
Median OS in months [95% CI][a]	45.6 [25.5, NE]	26.9 [19.3, 46.5]
Hazard ratio [95% CI][Error! Reference source not found.]	0.730 [0.489, 1.089]	
p-value[c]	0.1216	
ELN (poor/adverse), N	**37**	**36**
Number of deaths, n (%)	31 (83.8)	29 (80.6)
Median OS in months [95% CI][a]	13.2 [7.0, 18.5]	13.5 [10.8, 19.8]
Hazard ratio [95% CI][Error! Reference source not found.]	1.124 [0.677, 1.867]	
p-value[c]	0.6487	

The ALFA-0701 trial was not designed to prospectively evaluate the benefit of MYLOTARG in subgroups; analyses are presented for descriptive purposes only.
The mITT population included all patients who were randomized, unless withdrawal of consent prior to start of treatment and were analyzed according to initial randomization arm.
Abbreviations: AML=acute myeloid leukemia; CI=confidence interval; ELN=European LeukemiaNet; mITT=modified intent-to-treat; n=number; N=number; NE=not estimable; OS=Overall Survival.

a. Median estimated by Kaplan-Meier method; CI based on the Brookmeyer and Crowley Method with log-log transformation.
b. Based on the Cox Proportional Hazards Model Versus daunorubicin + cytarabine.
c. 2-sided p-value from the log-rank test.

Cardiac electrophysiology

There are limited data available to describe the effects of gemtuzumab ozogamicin on cardiac electrophysiology.

5.2. Pharmacokinetic properties

Gemtuzumab ozogamicin is an ADC composed of CD33-directed monoclonal antibody (hP67.6) that is covalently linked to the cytotoxic agent N-acetyl-gamma calicheamicin. The pharmacokinetics (PK) of gemtuzumab ozogamicin is described by measuring PK

characteristics of the antibody (hP67.6) as well as total and unconjugated calicheamicin derivatives. Given that the hP67.6 portion renders target selectivity on the intact molecule, and that MYLOTARG dosages are reported in terms of milligrams of protein (hP67.6), the hP67.6 concentration results are reported as the primary PK measures. After gemtuzumab ozogamicin binds to the target it is internalized and N-acetyl calicheamicin is released by hydrolytic cleavage. Determination of PK parameters for unconjugated calicheamicin was limited due to the low systemic concentration levels.

No clinical PK data have been collected using the fractionated regimen; however, the PK have been simulated using the population PK model. Although the total dose of the fractionated dosing regimen is half of that of the original dosing regimen (9 versus 18 mg/m^2), the predicted total area under the plasma concentration time curve (AUC) of hP67.6 over the course of treatment is 25%, and maximum observed concentration (C_{max}) is 24%, of the values for original 9 mg/m^2 dosing regimen, since the PK is nonlinear. When gemtuzumab ozogamicin is administered at 3 mg/m^2 on Days 1, 4, and 7, the C_{max} of hP67.6, which would occur at the end of infusion, is predicted to be 0.38 mg/L following the first dose and increased to 0.63 mg/L after the third dose.

Distribution

In vitro, the binding of N-acetyl gamma calicheamicin dimethyl hydrazide to human plasma proteins is approximately 97%. In vitro, N-acetyl gamma calicheamicin dimethyl hydrazide is a substrate of P-glycoprotein (P-gp). Population PK analyses found the total volume of distribution of hP67.6 antibody (sum of V1 [10 L] and V2 [15 L]) to be approximately 25 L.

Biotransformation

The primary metabolic pathway of gemtuzumab ozogamicin is anticipated to be hydrolytic release of N-acetyl gamma calicheamicin dimethyl hydrazide. In vitro studies demonstrated that N-acetyl gamma calicheamicin dimethyl hydrazide is extensively metabolized, primarily via nonenzymatic reduction of the disulfide moiety. The activity (cytotoxicity) of the resultant metabolites is expected to be significantly attenuated. In patients, unconjugated calicheamicin plasma levels were typically low, with a predicted geometric mean C_{max} of 1.5 ng/mL (95% CI: 1.4, 1.6) following the third dose.

Elimination

Based on population PK analyses, the predicted clearance (CL) value of hP67.6 from plasma was 3 L/h immediately after the first dose and then 0.3 L/h. The terminal plasma half-life ($t_{½}$) for hP67.6 was predicted to be approximately 160 hours for a typical adult male patient at the recommended dose level (3 mg/m^2) of MYLOTARG.

Effect of other drugs on gemtuzumab ozogamicin

In vitro, N-acetyl gamma calicheamicin dimethyl hydrazide is primarily metabolized via nonenzymatic reduction. Therefore, coadministration of MYLOTARG with inhibitors or inducers of cytochrome P450 (CYP) or uridine diphosphate glucuronosyltransferase (UGT) drug metabolizing enzymes are unlikely to alter the exposure to N-acetyl gamma calicheamicin dimethyl hydrazide.

Based on population PK analyses, the combination of gemtuzumab ozogamicin with hydroxyurea, DNR, and AraC is not predicted to cause clinically meaningful changes in the PK of hP67.6 or unconjugated calicheamicin.

Effect of gemtuzumab ozogamicin on other drugs

Effect on CYP substrates

In vitro, N-acetyl gamma calicheamicin dimethyl hydrazide and gemtuzumab ozogamicin had a low potential to inhibit the activities of CYP1A2, CYP2A6 (tested only using gemtuzumab ozogamicin), CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 at clinically relevant concentrations. In vitro, N-acetyl gamma calicheamicin dimethyl hydrazide and gemtuzumab ozogamicin had a low potential to induce the activities of CYP1A2, CYP2B6, and CYP3A4 at clinically relevant concentrations.

Effect on UGT substrates

In vitro, N-acetyl gamma calicheamicin dimethyl hydrazide had a low potential to inhibit the activities of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 at clinically relevant concentrations.

Effect on drug transporter substrates

In vitro, N-acetyl gamma calicheamicin dimethyl hydrazide had a low potential to inhibit the activities of P-gp, breast cancer resistance protein (BCRP), bile salt export pump (BSEP), multidrug resistance associated protein (MRP) 2, multidrug and toxin extrusion protein (MATE)1 and MATE2K, organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT) 1 and OCT 2, and organic anion transporting polypeptide (OATP)1B1 and OATP1B3 at clinically relevant concentrations.

Effect on AraC and DNR

Based on population PK analyses, the combination of gemtuzumab ozogamicin with DNR and AraC is not predicted to cause clinically meaningful changes in the PK of these agents.

Pharmacokinetics in specific groups of subjects or patients

Age, race, and gender

Based on a population PK analysis, age, race, and gender did not significantly affect MYLOTARG disposition.

Hepatic impairment

No formal PK studies of MYLOTARG have been conducted in patients with hepatic impairment.

Based on a population PK analysis, the clearance of gemtuzumab ozogamicin (hP67.6 antibody and unconjugated calicheamicin) is not expected to be affected by mild or moderate hepatic impairment status, as defined by National Cancer Institute Organ Dysfunction

Working Group (NCI ODWG). The analysis included 405 patients in the following NCI ODWG impairment status categories: mild (B1, n=58 and B2, n=19), moderate (C, n=6) and normal hepatic function (n=322). The PK of gemtuzumab ozogamicin has not been studied in patients with severe hepatic impairment (see Section 4.2).

Renal impairment

No formal PK studies of gemtuzumab ozogamicin have been conducted in patients with renal impairment.

Based on population PK analysis in 406 patients, the clearance of gemtuzumab ozogamicin in patients with mild renal impairment (CL_{cr} 60-89 mL/min; n=149) or moderate renal impairment (CL_{cr} 30-59 mL/min; n=47), was similar to patients with normal renal function (CL_{cr} ≥90 mL/min; n=209). The impact of severe renal impairment on PK of gemtuzumab ozogamicin could not be assessed, since data are available from a single patient only (CL_{cr} 15-29 mL/min; n=1).

Geriatric use

Use of MYLOTARG in combination with DNR and AraC in newly-diagnosed adult patients with de novo AML is supported by a randomized, controlled trial that included 50 patients greater than or equal to 65 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Pediatric use

The safety and efficacy of MYLOTARG in combination with chemotherapy have not been established in the pediatric patients aged <15 years with newly-diagnosed de novo AML.

5.3. Preclinical safety data

Repeat-dose toxicity

In repeat-dose toxicity studies in rats and/or monkeys up to 12 weeks in duration, the important toxicities occurred in the liver (liver enzyme elevations, hepatocellular alterations, oval cell/bile duct hyperplasia, and sinusoidal dilation with hepatocyte atrophy), bone marrow and lymphoid organs (hypocellularity), hematology parameters (decreased red blood cell [RBC] mass and WBC counts, mainly lymphocytes), kidney (tubular and/or glomerular alterations, and proteinuria), eye (degeneration and pigmentation of corneal epithelium, and peripapillary swelling of the optic nerve) and male (atrophy of seminiferous tubules, oligospermia, and mammary gland atrophy) and female (atrophy of ovary, oviduct, uterus, and cervix) reproductive organs. Effects on liver, kidney, and male reproductive organs in rats, and on lymphoid tissues in monkeys were not reversible in the 6-week studies following a 4-week nondosing period (approximately 18 times for rats, and 36 times for monkeys, the human clinical exposure after the third dose of 3 mg/m^2 based on AUC_{168}). Effects on female reproductive organs and the eye in monkeys were adverse in the 12-week study (approximately 193 and 322 times, respectively, the human clinical exposure after the third dose of 3 mg/m^2 based on AUC_{168}).

Genotoxicity

Gemtuzumab ozogamicin was clastogenic in vivo in the bone marrow of mice at ≥22.1 mg/m^2. This is consistent with the known induction of DNA breaks by calicheamicin and other enediyne antitumour antibiotics. N-acetyl gamma calicheamicin dimethyl hydrazide (the released cytotoxin) was mutagenic in the bacterial reverse mutation assay and clastogenic in the in vitro micronucleus assay in human TK6 cells.

Carcinogenicity

Formal carcinogenicity studies have not been conducted with gemtuzumab ozogamicin. After 6 weeks of administration of gemtuzumab ozogamicin to rats, preneoplastic lesions (minimal to slight oval cell hyperplasia) were observed in the liver at 7.2 mg/m^2/week (approximately 54 times the human clinical exposure after the third dose of 3 mg/m^2 based on AUC_{168}). There were no preneoplastic or neoplastic lesions observed in monkeys up to 22 mg/m^2/week (approximately 115 times the human clinical exposure after the third dose of 3 mg/m^2 based on AUC_{168}). Preneoplastic and neoplastic lesions have been observed in the livers of rats with other antibody-calicheamicin conjugates.

Reproductive toxicity

In the female fertility study where treated female rats were mated with untreated male rats at the end of the dosing period, no gemtuzumab ozogamicin–related effects on copulation or fertility were observed; however, slightly lower numbers of corpora lutea at 1.08 mg/m^2/day and increased embryolethality at ≥0.36 mg/m^2/day were observed in the presence of maternal toxicity. Gemtuzumab ozogamicin-related findings in the reproductive tract of female monkeys were observed after 12 weeks of dosing at ≥2.2 mg/m^2/week (atrophy in the ovary, oviduct, uterus, and cervix; approximately 66 times the human clinical exposure after the third dose of 3 mg/m^2 based on AUC_{168}). Female reproductive tract findings were adverse at ≥6.6 mg/m^2/week (approximately 193 times the human clinical exposure after the third dose of 3 mg/m^2 based on AUC_{168}) due to the anticipated potential for disruption or loss of a normal menstrual cycle and thereby normal reproductive function.

In the male fertility study where treated male rats were mated with untreated female rats at the end of the dosing period, gemtuzumab ozogamicin-related effects on male reproduction included lower spermatogonia and spermatocytes, decreases in testicular spermatids and epididymal sperm, vacuolation of the nucleus in spermatids, and/or appearance of giant cells at ≥0.12 mg/m^2/day. Additional findings included effects on the testes (≥0.12 mg/m^2/day) and epididymides (≥0.36 mg/m^2/day); both organs were macroscopically small and decreased in weight as well as fertility (1.08 mg/m^2/day). When male rats were mated again after a 9-week nondosing period, effects on sperm and fertility were worse but there was partial recovery of the lower spermatogonia and spermatocytes in the testes. In the 6-week toxicity study with gemtuzumab ozogamicin, effects on male reproductive organs (testes, epididymides, and mammary gland) were observed at ≥2.4 mg/m^2/week (approximately 18 times the human clinical exposure after the third human dose of 3 mg/m^2 based on AUC). Effects on rat male reproductive organs were partially reversible or not reversible following a 4-week nondosing period. Effects on male monkey reproductive organs in a 6-week toxicity study included findings in the testes and epididymides and decreased mean testes weight at 18 mg/m^2/week (approximately 81 times the human clinical exposure after the third human dose of 3 mg/m^2 based on AUC_{168}). During the 12-week study in monkeys, adverse findings in the reproductive tract of sexually mature males were observed at ≥2.2 mg/m^2/week

(approximately 66 times the human clinical exposure after the third dose of 3 mg/m^2 based on AUC_{168}) and consisted of slight to marked degeneration of seminiferous tubules in the testis; minimal or slight luminal cellular debris and oligospermia and minimal to moderate epithelial degeneration in the epididymis; and slight epithelial atrophy, slight duct ectasia, and minimal or slight sperm stasis in the seminal vesicle.

Developmental toxicity

In an embryo-fetal development study in rats, pregnant animals received daily intravenous doses up to 1.2 mg/m^2/day gemtuzumab ozogamicin during the period of organogenesis. Lower fetal body weight, higher incidence of fetal wavy ribs, and lower incidence of fetal skeletal ossification were observed at ≥0.15 mg/m^2/day. Increased embryolethality and fetal morphological anomalies (digital malformations, absence of the aortic arch, anomalies in the long bones in the forelimbs, misshapen scapula, absence of a vertebral centrum, and fused sternebrae) were observed at 0.36 mg/m^2/day. Increased embryolethality was also observed in the presence of maternal toxicity at ≥0.36 mg/m^2/day in female fertility and early embryonic development studies. All doses with embryo-fetal effects were observed in the presence of maternal toxicity. The lowest dose with embryo-fetal effects in rats (0.15 mg/m^2/day) was 9.7 times the human clinical exposure after the third human dose of 3 mg/m^2 based on AUC_{168}.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dextran 40
Sucrose
Sodium chloride
Sodium dihydrogen phosphate monohydrate
Disodium hydrogen phosphate anhydrous

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

Unopened vials

Refer to outer carton for expiration date.

Reconstituted and diluted solution

Protect the reconstituted and diluted MYLOTARG solutions from light. The solutions should be used immediately. Do not freeze the reconstituted or diluted solution.

If the product cannot be used immediately:

- Following reconstitution, the original vial may be stored up to 16 hours in a refrigerator (2°C to 8°C) or up to 3 hours at room temperature (below 30°C).
- The diluted solution may be stored up to 18 hours in a refrigerator (2°C to 8°C) and up to 6 hours at room temperature (below 30°C). The allowed time at room temperature (below 30°C) includes the time required for preparation of the diluted solution, equilibration, if needed, and administration to the patient. The maximum time from preparation of the diluted solution through administration should not exceed 24 hours.

6.4. Special precautions for storage

Unopened vials

Store in refrigerator (2°C to 8°C; 36°F to 46°F).
Do not freeze.
Store the vial in the original carton to protect from light.

For storage conditions after reconstitution and during dilution, see Section 6.3.

6.5. Nature and contents of container

Amber Type 1 glass vial, with butyl rubber stopper and crimp seal with flip-off cap containing 5 mg gemtuzumab ozogamicin. Each carton contains 1 vial.

6.6. Special precautions for disposal and other handling

Use appropriate aseptic technique for the reconstitution and dilution procedures. MYLOTARG is light sensitive and should be protected from ultraviolet light during reconstitution, dilution, and administration.

Reconstitution

- Calculate the dose (mg) of MYLOTARG required.
- Prior to reconstitution, allow the vial to reach room temperature (below 30°C) for approximately 5 minutes. Reconstitute each 5 mg vial with 5 mL of water for injections to obtain a single-use solution of 1 mg/mL of gemtuzumab ozogamicin.
- Gently swirl the vial to aid dissolution. Do not shake.
- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution may contain small white to off-white, opaque to translucent, and amorphous to fiber-like particles.
- MYLOTARG contains no bacteriostatic preservatives.
- If the reconstituted solution cannot be used immediately, it may be stored in the original vial for up to 16 hours in a refrigerator (2°C to 8°C) or up to 3 hours at room temperature (below 30°C). Protect from light and do not freeze.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial using a syringe. MYLOTARG vials contain 5 mg of drug product with no overfill. When reconstituted to a 1 mg/mL concentration as directed, the extractable content of the vial is 4.5 mg (4.5 mL). Protect from light. Discard any unused reconstituted solution left in the vial.
- Doses must be mixed to a concentration between 0.075 mg/mL to 0.234 mg/mL according to the following instructions:
    - Doses less than 3.9 mg must be prepared for administration by syringe. Add the reconstituted MYLOTARG solution to a syringe with sodium chloride 9 mg/mL (0.9%) solution for injection to a final concentration between 0.075 mg/mL to 0.234 mg/mL. Protect from light.
    - Doses greater than or equal to 3.9 mg are to be diluted in a syringe or an intravenous bag in an appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure a final concentration between 0.075 mg/mL to 0.234 mg/mL. Protect from light.
- Gently invert the infusion container to mix the diluted solution. Do not shake.
- Following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, MYLOTARG solution should be infused immediately. If not used immediately, the diluted solution may be stored up to 18 hours in a refrigerator (2°C to 8°C) and up to 6 hours at room temperature (below 30°C). The allowed time at room temperature (below 30°C) includes the time required for preparation of the diluted solution, equilibration, if needed, and administration to the patient. The maximum time from preparation of the diluted solution through administration should not exceed 24 hours. Protect from light and do not freeze.
- It is recommended that the infusion container be made of polyvinyl chloride (PVC) with DEHP, ethylene vinyl acetate (EVA) or polyolefin (polypropylene and/or polyethylene).

Administration

- Filtration of the diluted solution is required. An in-line, low protein-binding 0.2 micron polyethersulphone (PES) filter must be used for infusion of MYLOTARG.
- Doses administered by syringe must utilize small bore infusion lines (microbore) with an in-line, low protein-binding 0.2 micron polyethersulphone (PES) filter.
- During the infusion, the intravenous bag or syringes needs to be protected from light using a light (including ultraviolet light) blocking cover. The infusion line does not need to be protected from light.
- Infuse the diluted solution for 2 hours. The infusion must be completed prior to the end of the allowed 6-hour storage of the diluted solution at room temperature (below 30°C).
- Infusion lines made of PVC (DEHP- or non DEHP-containing), polyurethane or polyethylene are recommended.

Do not mix MYLOTARG with, or administer as an infusion with, other medicinal products.

See also Section 6.3 for dilution, storage, and infusion information.

Disposal

Toxic waste disposal procedures prescribed for anticancer drugs must be used.

7. PRODUCT OWNER

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