## 1. NAME OF THE MEDICINAL PRODUCT

MYLOTARG

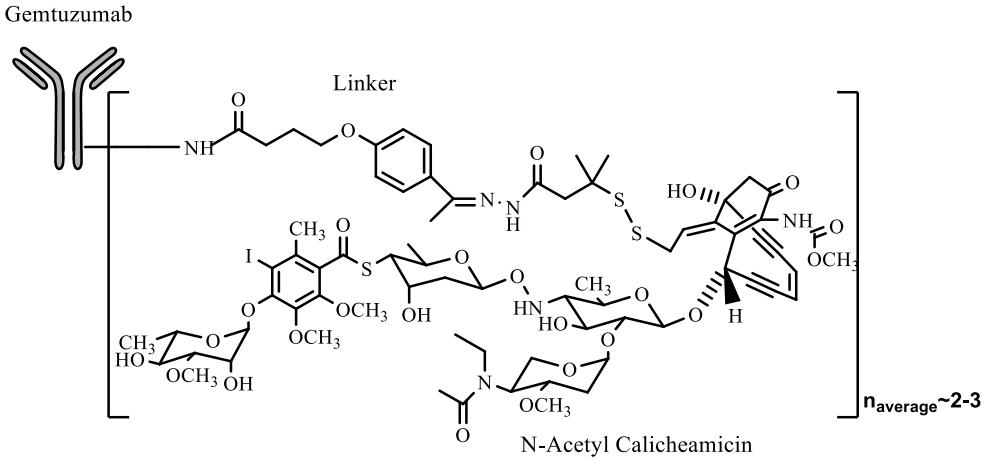
## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 the treatment of newly-diagnosed, de novo CD33-positive acute myeloid leukemia in adults and pediatric patients 1 month and older, 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)*

*Patients 15 years and above*

The recommended dose of MYLOTARG is 3 mg/$m^2$. A treatment course including MYLOTARG in combination therapy 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 daunorubicin (DNR) 60 mg/$m^2$/day infused over 30 minutes on Day 1 to Day 3, and cytarabine (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 $1.0 \times 10^9$ cells/L with a platelet count of $100 \times 10^9$/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.

*Pediatric patients (1 month and older)*

The recommended dose of MYLOTARG in pediatric patients 1 month and older with previously untreated de novo AML is:

- 3 mg/$m^2$ for patients with body surface area (BSA) greater than or equal to 0.6 $m^2$
- 0.1 mg/kg for patients with BSA less than 0.6 $m^2$

For Induction 1, MYLOTARG is given once in combination with standard chemotherapy. No MYLOTARG is given in the second induction cycle.

No MYLOTARG is given in the first or third intensification cycles. For Intensification 2, MYLOTARG is given once in combination with standard chemotherapy. Consider the risks and potential benefits before giving MYLOTARG during Intensification 2.

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 drug reactions*

Dose modification of MYLOTARG is recommended based on individual safety and tolerability (see Section 4.4). Management of some adverse drug 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 | • Adults: 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).<br>• Pediatrics: Patients should have a platelet count of 75,000/$mm^3$ before the next cycle (induction or intensification). |
| Persistent neutropenia | • Adults: 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).<br>• Pediatrics: Patients should have a neutrophil count of 1,000/$mm^3$ before the next cycle (induction or intensification). |
| **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.<br>• 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 resolve and infusion may resume.<br>• 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.<br>• 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=veno-occlusive 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 hepatic impairment

defined by total bilirubin ≤ 2 × upper limit of normal (ULN) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN. Postpone MYLOTARG until recovery of total bilirubin to ≤ 2 × ULN and AST and ALT to ≤ 2.5 × ULN prior to each dose (see Table 3 and Section 5.2). 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 (<1 month) 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 veno-occlusive 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/haemorrhagic events, respectively. Infections and bleeding/haemorrhagic 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/haemorrhage, 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/haemorrhage, 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/Contraception in males and females

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 drug 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

The overall safety profile of MYLOTARG is based on data from patients with AML from the combination therapy studies ALFA-0701, AAML0531, and from postmarketing experience.

*Combination therapy in previously untreated AML*

*Adult*

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

The most common adverse drug reactions (>30%) in the adult combination therapy study ALFA-0701 were haemorrhage and infection.

The most frequent (≥1%) adverse drug reactions that led to permanent discontinuation in the adult combination therapy study ALFA-0701 were thrombocytopenia, VOD, haemorrhage, and infection.

*Pediatric*

In the pediatric combination therapy study AAML0531, safety data collected included Grade 3 and 4 nonhematologic adverse events, deaths, VOD/SOS, and prolongation of neutropenia and thrombocytopenia.

The most common adverse drug reactions (>30%) in the pediatric combination therapy study AAML0531 were infection (35.8%) and febrile neutropenia (32.1%) during Induction 1 and infection (67.5%) during Intensification 2.

*Tabulated list of adverse drug reactions*

Tables 4 and 5 show the adverse drug reactions reported in patients with previously untreated de novo AML who received MYLOTARG in combination studies ALFA-0701 and AAML0531, respectively.

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 | | Veno-occlusive 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).

**Table 5. Adverse Drug Reactions During Induction 1 and Intensification 2 in Pediatric Patients With Previously Untreated De Novo AML Receiving MYLOTARG (Combination Therapy-AAML0531)**

| System Organ Class | Adverse Drug Reactions |
|---|---|
| Infections and infestations | Infection[*,a] |
| Blood and lymphatic system disorders | Febrile neutropenia<br>Thrombocytopenia[b]<br>Neutropenia[c] |
| Immune system disorders | Infusion related reaction[d] |
| Metabolism and nutrition disorders | Tumor lysis syndrome<br>Hyperglycaemia<br>Decreased appetite |
| Nervous system disorders | Headache |

**Table 5. Adverse Drug Reactions During Induction 1 and Intensification 2 in Pediatric Patients With Previously Untreated De Novo AML Receiving MYLOTARG (Combination Therapy-AAML0531)**

| | |
|---|---|
| Cardiac disorders | Tachycardia[e] |
| Vascular disorders | Haemorrhage[*,f]<br>Hypotension<br>Hypertension |
| Respiratory, thoracic and mediastinal disorders | Dyspnea |
| Gastrointestinal disorders | Ascites<br>Vomiting<br>Diarrhoea<br>Abdominal pain<br>Nausea<br>Mucositis[g]<br>Dyspepsia[#] |
| Hepatobiliary disorders | Veno-occlusive liver disease[#,h]<br>Transaminases increased[i]<br>Hyperbilirubinaemia |
| Skin and subcutaneous tissue disorders | Rash[#,j]<br>Pruritus[#] |
| General disorders and administration site conditions | Multi-organ failure[*,#]<br>Pyrexia<br>Oedema[#]<br>Fatigue[#]<br>Chills |

Abbreviations: AML=acute myeloid leukemia; PT=preferred term.

[*]Including fatal outcome.

[#]Single case

[**]Observed only in Intensification 2.

a. Infection includes any reported preferred terms for gemtuzumab ozogamicin retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 System Organ Class Infections and infestations, and includes fatal events.

b. Thrombocytopenia includes the following reported PT: Platelet count decreased.

c. Neutropenia includes the following reported PT: Neutrophil count decreased.

d. Infusion related reaction includes the following reported PTs: Infusion related reaction, Urticaria[#,**], Bronchospasm, Drug hypersensitivity.

e. Tachycardia includes the following reported PT: Sinus tachycardia.

f. Haemorrhage includes any reported preferred terms for gemtuzumab ozogamicin retrieved by applying the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 Standard MedDRA Query (narrow) for Haemorrhage terms (excluding laboratory terms).

g. Mucositis includes the following reported PTs: Stomatitis, Oral pain, Anal inflammation, Pharyngeal inflammation, enteritis[#,**].

h. Veno-occlusive liver disease includes the following reported PT: Veno-occlusive disease[#].

i. Transaminases increased includes the following reported PTs: Alanine aminotransferase, Aspartate aminotransferase.

j. Rash includes the following reported PT: Rash papular[#].

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 reactions

*Hepatotoxicity, including hepatic VOD/SOS*

In the adult combination therapy study ALFA-0701, 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 adult combination therapy study ALFA-0701 (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).

In the pediatric combination therapy study AAML0531, VOD events were reported in 25/520 (5%) patients in the MYLOTARG arm. VOD was fatal in 2 patients. Among 187 patients who had a HSCT in the MYLOTARG arm, VOD occurred within 30 days post-HSCT in 20 (11%) patients.

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 adult combination therapy study ALFA-0701 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.

*Platelet and neutrophil recovery*

During the induction phase in study ALFA-0701, 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).

In study ALFA-0701, 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 study AAML0531, the addition of MYLOTARG to chemotherapy was associated with a higher incidence of prolonged thrombocytopenia and neutropenia particularly when used in Intensification 2. During Intensification 2, prolonged thrombocytopenia (platelets <50,000/mm$^3$ lasting past cycle Day 42 in the absence of active leukemia) was reported in 64% (190/297) of patients in the MYLOTARG + chemotherapy arm compared with 55% (146/264) in the chemotherapy alone arm. Prolonged neutropenia (neutrophils <500/mm$^3$ lasting past cycle Day 42 in the absence of active leukemia) occurred in 47% (142/300) versus 43% (118/275) of patients, respectively. The prolonged cytopenias were associated with more deaths in remission in the MYLOTARG + chemotherapy arm (29 [5%]) compared to the chemotherapy alone arm (15 [3%]).

*Infections*

In the adult combination therapy study ALFA-0701, 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.

*Bleeding/haemorrhagic events*

In the adult combination therapy study ALFA-0701 (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 haematemesis (3.1), 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).

In the combination pediatric study AAML0531, fatal bleeding occurred in 3/520 (<1%) of the pediatric patients. Grade 3 or 4 bleeding was reported in 66/520 (13%) of patients in the MYLOTARG arm.

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.

The incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) was 6 (12.0%) and 1 (2.0%), respectively. The presence of ADA had no statistically significant or clinically relevant effects on PK of total hP67.6 antibody or conjugated calicheamicin. None of the patients experienced anaphylaxis, hypersensitivity or other clinical sequelae related to ADA. There was no evidence that the presence of ADA had a direct association with any potential safety issues.

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-directed 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 cancer 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.

Saturation of a high percentage of CD33 antigenic sites is presumed to be required for maximum delivery of calicheamicin to leukemic blast cells. Near maximal peripheral CD33 saturation was observed across studies after gemtuzumab ozogamicin dosing at dose levels of 2 mg/m$^2$ and above.

*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*

*Study ALFA-0701*

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 haemorrhages, 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 doses) 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 6 and the Kaplan-Meier plot is shown in Figure 1.

**Table 6. 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) |
| 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.

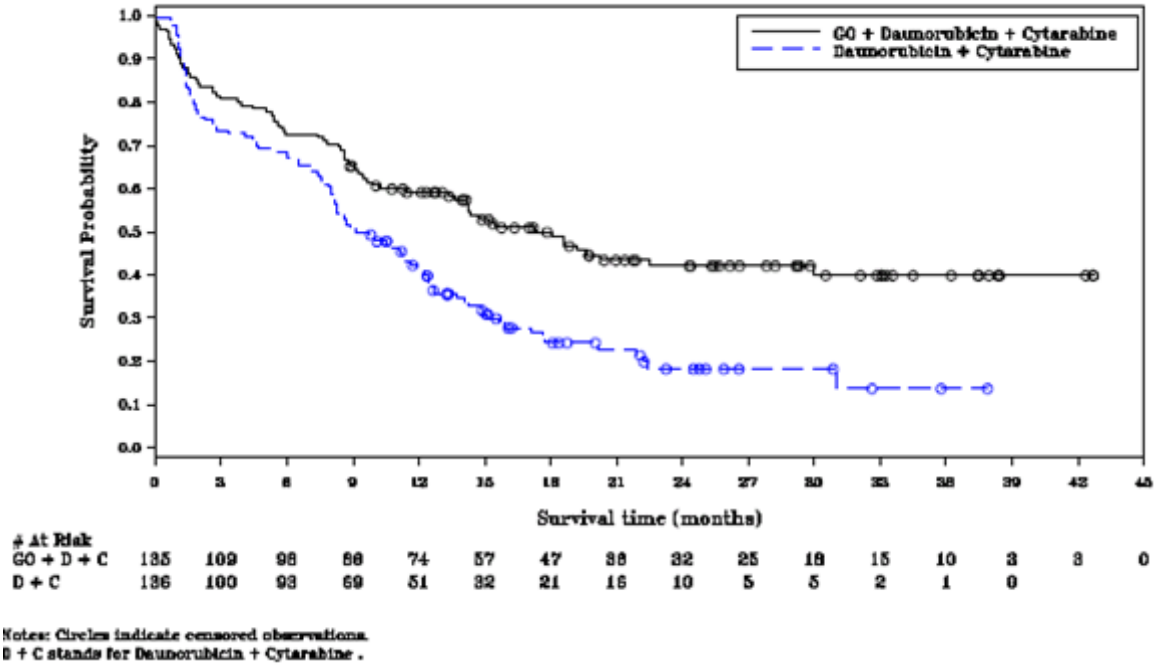
d. 2-sided p-value from the log-rank test.

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)**




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 7 and Table 8.

**Table 7. 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]<br>p-value[d] | 0.460 [0.313, 0.676]<br><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]<br>p-value[d] | 1.111 [0.633, 1.949]<br>0.7151 | |
| **ELN (Favorable/Intermediate), n** | 86 | 91 |
| Number of events, n (%) | 40 (46.5) | 63 (69.2) |

**Table 7. 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]<br>p-value[d] | 0.485 [0.325, 0.724]<br>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]<br>p-value[d] | 0.720 [0.430, 1.205]<br>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 8. 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][b] | 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][b] | 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][b] | 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][b] | 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.

*Study AAML0531*

MYLOTARG in combination with chemotherapy was evaluated in AAML0531 (NCT00372593), a multicenter, randomized study of 1,063 patients with newly-diagnosed AML ages 0 to 29 years.

Patients were randomized to 5-cycle chemotherapy alone or with a single dose of MYLOTARG (3 mg/m$^2$/dose) administered once on Day 6 in Induction 1 and once on Day 7 in Intensification 2. All patients proceeded to Induction 2 regardless of remission status after Induction 1. In the absence of active disease, a neutrophil count (ANC) >1,000/mm$^3$ and a platelet count >75,000/mm$^3$ was recommended before proceeding with subsequent cycles of therapy. Patients not in remission after Induction 2 discontinued protocol therapy permanently. All other patients proceeded to Intensification 1. Patients with high-and intermediate-risk disease with 5/6 or 6/6 matched family donors (MFD) proceeded to HSCT

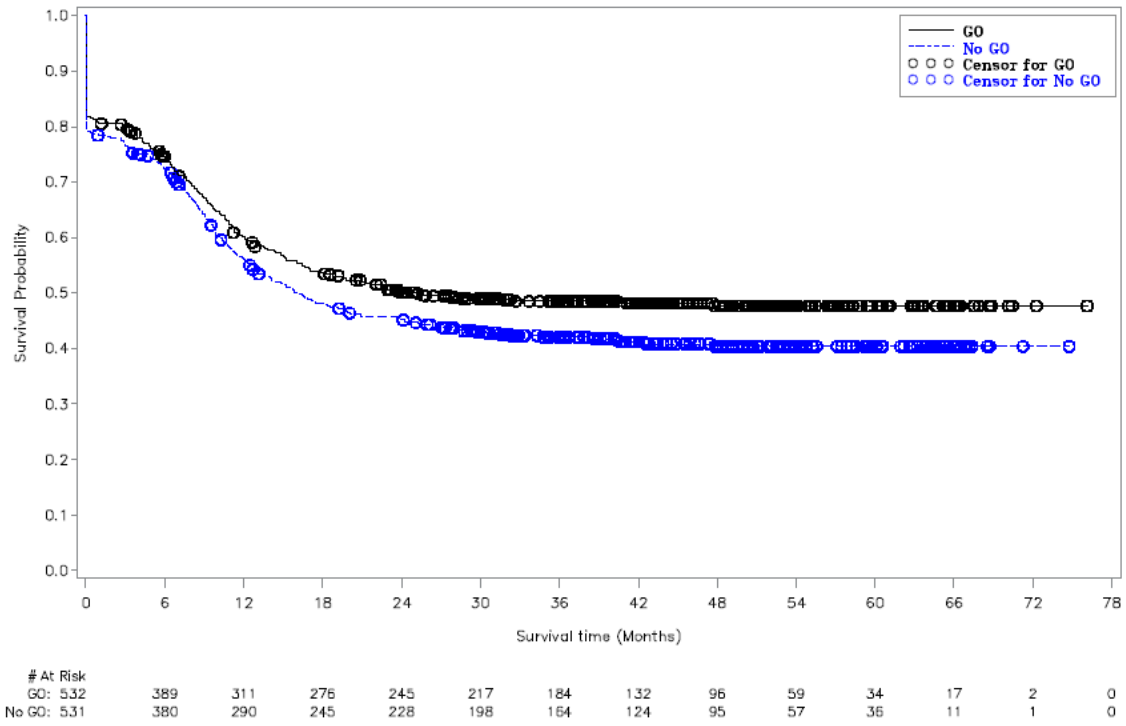
following Intensification 1. Patients with high-risk disease proceeded to HSCT with an alternative donor if no MFD was available. All patients with low-risk disease and any high- and intermediate-risk patients without appropriate donors proceeded with Intensification 2 with or without MYLOTARG according to their initial randomization, followed by Intensification 3. All patients in remission were to proceed on to Intensification 2 or allogeneic HSCT. In Intensification 2, patients received MYLOTARG according to the initial randomization. Patients in remission after Intensification 2 proceeded to Intensification 3.

There were 532 patients randomized to treatment with MYLOTARG + chemotherapy and 531 to chemotherapy alone. Overall, 94% of patients were <18 years of age, and 6% were adults; median age was 9 years (range: 0-29 years). The patients were 49% male, 51% female, 73% White, 11% Black, 5% Asian, 11% other or missing race, and 18% Hispanic. The proportion of patients in each disease risk group: low-risk (23% vs 23%), intermediate-risk (57% vs 57%), and high-risk (15% vs 17%).

Efficacy was assessed by event-free survival (EFS), measured from the date of study entry until induction failure, relapse, or death by any cause. Induction failure was defined as failure to achieve CR by the end of Induction 2 period, and date of induction failure was defined as Day 1 on study. The EFS hazard ratio was 0.84 (95% CI: 0.71, 0.99). The estimated percentage of patients free of induction failure, relapse, or death at five years was 48% (95% CI: 43%, 52%) in the MYLOTARG + chemotherapy arm versus 40% (95% CI: 36%, 45%) in the chemotherapy alone arm.

The Kaplan-Meier plot for EFS is shown in Figure 2. No difference between treatment arms in overall survival was demonstrated.

**Figure 2. Kaplan-Meier Plot of Event-Free Survival (Full Analysis Set) Study AAML0531 Trial**[169]




Abbreviations: GO=gemtuzumab ozogamicin.

Cardiac electrophysiology

Based on the concentration-QTc interval analysis, the expected median change in QTcF from baseline for total hP67.6 antibody was 0.842 msec (95% CI: -1.93, 3.51 msec) at an average observed plasma $C_{max}$. For unconjugated calicheamicin, the expected median change in QTcF from baseline was 0.602 msec (95% CI: -2.17, 2.72 msec) at an average observed plasma $C_{max}$ following administration at the recommended dosing regimen of MYLOTARG.

## 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 conjugated 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 [13.0 L] and V2 [6.91 L]) to be approximately 20 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.

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 effectiveness of MYLOTARG in combination with standard chemotherapy have been established in pediatric patients 1 month and older with newly-diagnosed de novo AML. The use of MYLOTARG for this indication is supported by evidence of effectiveness from adequate and well-controlled studies in adults with supportive data on safety and effectiveness in Study AAML0531 (NCT00372593). AAML0531 included patients in the following age groups: 2 patients less than 27 days old, 94 patients 28 days to less than 2 years old, 225 patients 2 years to less than 12 years old, 175 patients 12 years old to less than 18 years old, and 36 patients 18 years or older in the MYLOTARG plus chemotherapy arm. The

safety and effectiveness of MYLOTARG with standard chemotherapy in pediatric patients less than 1 month of age with newly-diagnosed de novo AML have not been established.

## 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 antitumor 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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