PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMYLOTARG®

gemtuzumab ozogamicin for injection

lyophilized powder for solution for intravenous infusion only
4.5 mg single-use vial

Anti-neoplastic Agent

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Quebec
H9J2M5

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PrMYLOTARG®

gemtuzumab ozogamicin for injection

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MYLOTARG (gemtuzumab ozogamicin for injection) is indicated for:

- Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia (AML), except acute promyelocytic leukemia

1.1 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of MYLOTARG in combination with chemotherapy in pediatric patients with newly-diagnosed AML has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

1.2 Geriatrics

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 in this trial between these subjects and younger subjects (see **WARNINGS AND PRECAUTIONS**, **Special Populations**).

2 CONTRAINDICATIONS

MYLOTARG (gemtuzumab ozogamicin for injection) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **Dosage Forms, Strengths, Composition and Packaging**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hepatotoxicity, including venoocclusive disease/sinusoidal obstruction syndrome (VOD/SOS) which may be severe, life-threatening or fatal, has been observed in patients receiving MYLOTARG (gemtuzumab ozogamicin). Monitor frequently for signs and symptoms of VOD after treatment with MYLOTARG (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic,** Hepatotoxicity, including VOD/SOS)
- Myelosuppression/cytopenias, and complications including infections and bleeding/hemorrhagic events, which may be severe, life-threatening or fatal, were reported in patients receiving MYLOTARG (see **WARNINGS AND PRECAUTIONS, Hematologic,** Myelosuppression/cytopenia)
- Tumor lysis syndrome (TLS), which may be severe, life-threatening or fatal, has been observed in patients receiving MYLOTARG (see **WARNINGS AND PRECAUTIONS**, **General**, Tumor lysis syndrome)
- Infusion-related reactions (see **WARNINGS AND PRECAUTIONS, General,** Infusion-related reactions)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- MYLOTARG (gemtuzumab ozogamicin for injection) should be administered under the supervision of a physician experienced in the use of anticancer medicinal products and in an environment where full resuscitation facilities are immediately available.

- MYLOTARG should be used only in patients eligible to receive intensive induction chemotherapy.

- Premedication with a corticosteroid, antihistamine, and acetaminophen is recommended 1 hour prior to MYLOTARG dosing to help ameliorate infusion related symptoms (see **WARNINGS AND PRECAUTIONS**).

- 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 **WARNINGS AND PRECAUTIONS**).

- 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. For instructions on reconstitution and dilution of the medicinal product before administration, see **DOSAGE AND ADMINISTRATION, Reconstitution**.

4.2 Recommended Dose and Dosage Adjustment

A treatment course including MYLOTARG in combination therapy for adults with newly diagnosed de novo CD33-positive acute myeloid leukemia (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 4.5 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.

For patients requiring a second induction cycle, do NOT administer MYLOTARG during the second induction cycle. 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 with no Auer rods in the bone marrow and the absence of peripheral blood leukemic blasts, full recovery of peripheral blood counts (absolute neutrophil count [ANC] of more than 1.0 x 10^9 cells/L, and platelet count of more than 100 x 10^9/L), transfusion independence and resolution of any extramedullary disease, 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 (1000 mg/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 4.5 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,c]	3 mg/m^2/dose (up to a maximum dose of one 4.5 mg vial) 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)	Do NOT administer MYLOTARG during the second induction cycle.	35 mg/m^2/day on Day 1 to Day 2	1 g/m^2/every 12 hours Day 1 to Day 3
Consolidation Course 1[a,b,c]	3 mg/m^2/dose (up to a maximum dose of one 4.5 mg vial) 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,c]	3 mg/m^2/dose (up to a maximum dose of one 4.5 mg vial) 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.
c. See Table 3 for dose modification information.

Dose and schedule modifications

Hepatic Impairment:
No adjustment to dose of MYLOTARG is required in patients with hepatic impairment defined by total bilirubin ≤2-times the ULN, and AST and/or ALT ≤2.5-times ULN. Delay treatment with MYLOTARG until recovery of total bilirubin to ≤2-times ULN and, AST and ALT to ≤2.5-times ULN prior to each dose. MYLOTARG has not been studied in patients with hepatic impairment defined by total bilirubin >2-times the ULN, or AST or ALT >2.5-times ULN (see ***Dose modification for adverse reactions*** **and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

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 (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Pediatric Population:
MYLOTARG dosing has not been established in pediatric patients with de novo AML (see **INDICATIONS)**.

Schedule modification for hyperleukocytosis

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

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 dose of one 4.5 mg vial) 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

Monitor blood counts frequently through resolution of cytopenias. Monitor blood counts and chemistries at least three times per week through recovery from treatment-related toxicities. Dose modification of MYLOTARG is recommended based on individual safety and tolerability (see **WARNINGS AND PRECAUTIONS**). Management of some adverse reactions may require dose interruptions or permanent discontinuation of MYLOTARG (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

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
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).

Table 3. Dosage Modifications for Hematologic and Nonhematologic Toxicities

Hematologic and Nonhematologic Toxicities	Recommended Action
VOD/SOS	• Discontinue MYLOTARG (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**, Hepatotoxicity).
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 resolve and infusion may resume. • Permanently discontinue MYLOTARG upon occurrence of a severe or life-threatening infusion reactions (see **WARNINGS AND PRECAUTIONS, General**).
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.

4.3 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.

4.4 Reconstitution

Use appropriate aseptic technique for the reconstitution and dilution procedures. MYLOTARG is light sensitive and should be protected from 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 25°C) for approximately 5 minutes. Reconstitute each vial with 5 mL of water for injections to obtain a single-use solution of 1 mg/mL of gemtuzumab ozogamicin that delivers 4.5 mL (4.5 mg).
- 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-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 are filled with 5 mg of drug product with a 0.5 mL overfill. When reconstituted to a 1 mg/mL concentration as directed, the minimum 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 (2-8°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 need 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.
- Flush the intravenous line after each dose with 0.9% sodium chloride.

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

4.5 Missed Dose

Management of some adverse reactions may require dose interruptions or permanent discontinuation of MYLOTARG (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**, Table 3).

5 OVERDOSAGE

Treatment of MYLOTARG (gemtuzumab ozogamicin for injection) overdose should consist of general supportive measures.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	White to off-white lyophilized cake or powder containing one 4.5 mg single-use vial	Dextran 40; Dibasic sodium phosphate, anhydrous; Monobasic sodium phosphate, monohydrate; Sodium chloride; Sucrose

The container is an amber Type 1 glass vial, with butyl rubber stopper and crimp seal with flip-off cap. Each carton contains 1 vial.

7 DESCRIPTION

MYLOTARG (gemtuzumab ozogamicin for injection) 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 zero to 6, with an average of 2 to 3 moles of calicheamicin derivative per mole of gemtuzumab.

8 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the Beginning of Part 1: Health Professional Information.

General

Infusion-related reactions (including anaphylaxis)

Life-threatening or fatal infusion-related reactions, including anaphylaxis, have been reported in clinical studies and in the postmarketing setting with MYLOTARG (gemtuzumab ozogamicin for injection; see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**). These can occur during or within 24 hours following infusion of MYLOTARG. Signs and symptoms of infusion-related reactions may include fever and chills, and less frequently hypotension, tachycardia, and respiratory symptoms. Perform infusion of MYLOTARG under close clinical monitoring, including pulse, blood pressure, and temperature.

Premedication with a corticosteroid, antihistamine, and acetaminophen is recommended 1 hour

prior to MYLOTARG dosing (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**). Interrupt infusion immediately for patients who develop evidence of severe reactions, especially dyspnea, bronchospasm, or clinically significant hypotension. Patients should be monitored during infusion and for at least 1 hour following infusion, or until signs and symptoms completely resolve. Discontinue MYLOTARG treatment in patients who develop signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension (see **DOSAGE AND ADMINISTRATION, Dose and schedule modifications**).

Tumor lysis syndrome (TLS)

Fatal reports of TLS complicated by acute renal failure with MYLOTARG have been reported in the postmarketing setting. In clinical studies with MYLOTARG, TLS was reported (see **ADVERSE REACTIONS**). In patients with hyperleukocytic acute myeloid leukemia (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 **DOSAGE AND ADMINISTRATION, Dose and schedule modifications**).

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.

Carcinogenesis and Mutagenesis
Formal carcinogenicity studies have not been conducted with gemtuzumab ozogamicin (see **NON-CLINICAL TOXICOLOGY**).

Cardiovascular
QT interval prolongation has been observed in patients treated with other drugs containing calicheamicin. QT interval prolongation has been observed in patients that have been treated with MYLOTARG. No clinical study has been performed to determine the risk of QT interval prolongation with MYLOTARG. When administering MYLOTARG to patients who have a history of or predisposition for QTc prolongation, who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances, obtain electrocardiograms (ECGs) and electrolytes prior to the start of treatment and as needed during administration.

Driving and Operating Machinery
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 **ADVERSE REACTIONS**). MYLOTARG may affect one's ability to drive or operate a vehicle or potentially dangerous machinery.

Hematologic
Myelosuppression/cytopenia

With MYLOTARG treatment, life-threatening or fatal infections and bleeding/hemorrhagic events were reported. 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 **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**). Complications associated with neutropenia and thrombocytopenia may include infections and bleeding/hemorrhagic events, respectively.

Persistent thrombocytopenia and more frequent platelet transfusions have been observed in patients treated with MYLOTARG.

Monitor complete blood counts prior to and following each dose of MYLOTARG and monitor patients for signs and symptoms of infection, bleeding/hemorrhage, or other effects of myelosuppression during treatment with MYLOTARG. Blood counts should be frequently monitored after treatment with MYLOTARG until resolution of cytopenias. 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 **DOSAGE AND ADMINISTRATION,** Dose and schedule modifications).

Hepatic/Biliary/Pancreatic

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

Life-threatening or fatal hepatotoxicity events, including VOD/SOS and hepatic failure, have been reported in patients treated with MYLOTARG (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions).**

Hepatotoxicity, including VOD/SOS events, has been reported in association with the use of MYLOTARG as a single agent, and as part of a combination chemotherapy regimen, in patients without a history of liver disease or hematopoietic stem cell transplant (HSCT). Based on an analysis of potential risk factors, adult patients who received MYLOTARG as monotherapy, either before or after an HSCT, and patients with moderate or severe hepatic impairment are at increased risk for developing VOD/SOS (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**).

Due to the risk of VOD/SOS, monitor patients 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. In addition, monitor for 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. Although no definitive relationship was found between VOD/SOS and time of HSCT relative to higher MYLOTARG monotherapy doses, 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 **DOSAGE AND ADMINISTRATION**, **Dose and schedule modifications**). In patients who experience VOD/SOS, discontinue MYLOTARG and treat according to standard medical practice.

Monitoring and Laboratory Tests

Hepatic

Due to the risk of VOD/SOS, monitor closely for signs and symptoms of VOD/SOS. These may include ALT, AST, total bilirubin, and alkaline phosphatase, which should be monitored prior to each dose of MYLOTARG. In addition, monitor for 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 (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**, **Hepatotoxicity, including VOD/SOS**).

Hematologic

Monitor complete blood counts prior to and following each dose of MYLOTARG and monitor patients for signs and symptoms of infection, bleeding/hemorrhage, or other effects of myelosuppression during treatment with MYLOTARG. Blood counts should be frequently monitored after treatment with MYLOTARG until resolution of cytopenias. Routine clinical and laboratory surveillance testing during and after treatment with MYLOTARG is indicated (see **WARNINGS AND PRECAUTIONS, Hematologic, Myelosuppression/cytopenia**).

Infusion-related reactions

Perform infusion of MYLOTARG under close clinical monitoring, including pulse, blood pressure, and temperature. Infusion-related reactions should be monitored during the infusion and for at least 1 hour after the end of the infusion, or until signs and symptoms have completely resolved. (see **WARNINGS AND PRECAUTIONS, General, Infusion related reactions**).

Tumor Lysis Syndrome

Patients should be monitored for signs and symptoms of TLS and treated according to standard medical practice (see **WARNINGS AND PRECAUTIONS, General, Tumor lysis syndrome**).

Sexual Health

Reproduction

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

Advise women of childbearing potential to use 2 methods of 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 2 methods of effective contraception during treatment with MYLOTARG and for at least 4 months after the last dose.

Fertility

There is no information regarding the effects of MYLOTARG on the fertility in patients. Based on nonclinical findings in animals, male and female fertility may be compromised by treatment with MYLOTARG (see **NON-CLINICAL TOXICOLOGY, Reproductive Toxicity**). Both men and women should seek advice for fertility preservation before treatment.

8.1 Special Populations

8.1.1 Pregnant Women

There are very limited data for the use of MYLOTARG (gemtuzumab ozogamicin for injection) in pregnant patients. Based on its mechanism of action and nonclinical safety findings in animals, MYLOTARG could cause embryo-fetal harm when administered to a pregnant woman. In addition, studies in animals have shown developmental toxicity (see **NON-CLINICAL TOXICOLOGY, Developmental Toxicity**).

MYLOTARG is not recommended during pregnancy and in women of childbearing potential not using contraception.

8.1.2 Breast-feeding

There is no information regarding the presence of MYLOTARG or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk precaution should be exercised. Due to 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.

8.1.3 Pediatrics

The safety and efficacy of MYLOTARG in combination with chemotherapy in the pediatric population with newly-diagnosed AML have not been established. Based on the data submitted and reviewed by Health Canada, the safety and efficacy of MYLOTARG in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see **INDICATIONS**).

8.1.4 Geriatrics

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

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

The following adverse reactions associated with MYLOTARG (gemtuzumab ozogamicin for injection) are discussed in detail under **WARNINGS AND PRECAUTIONS**. Appropriate management and dosing considerations regarding these adverse events are outlined under **DOSAGE AND ADMINISTRATION:** ***Dose modification for adverse reactions***.

- Infusion-related reactions
- Tumour lysis syndrome (TLS)
- Myelosuppression/cytopenia, including infection and bleeding/haemorrhagic events
- Hepatotoxicity, including VOD/SOS

In the combination therapy study ALFA-0701, in patients who received MYLOTARG in combination with DNR and AraC, 67.2% experienced a serious adverse reaction. Selected 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 (>2%)

serious adverse reactions with MYLOTARG included: thrombocytopenia, bronchopulmonary aspergillosis, septic shock, febrile bone marrow aplasia, bacterial sepsis, acute kidney injury, pneumonia, sepsis, acute respiratory distress syndrome, Escherichia sepsis, acute myeloid leukemia, venooclusive disease, hepatocellular injury, cholestatic liver injury, febrile neutropenia, mucosal inflammation, disease progression, and enterococcal sepsis.

The most common selected adverse reactions (>30%, grouped terms) in the combination therapy study were haemorrhage and infection. The most frequently (≥10%) reported adverse reactions were epistaxis, purpura, haematoma, device-related infection, petechiae, catheter site haemorrhage, blood blister, haematuria, gingival bleeding, mouth haemorrhage, thrombocytopenia, haemoptysis, device-related sepsis and bronchopulmonary aspergillosis. The most frequent (≥1%) adverse reactions that led to permanent discontinuation in the combination therapy study were thrombocytopenia, VOD, haemorrhage, and infection.

Fatal adverse reactions were experienced by 7 (5.3%) patients who received MYLOTARG and 5 (3.6 %) patients in the control arm. In the MYLOTARG arm, these deaths were due to: VOD, septic shock, subdural haematoma, cerebral haematoma, and intracranial haematoma. In the control arm, these deaths were due to septic shock and cerebral haemorrhage. The occurrence of deaths within 28 days of last dose of any study treatment was 6 events (4.6%) in the MYLOTARG arm and 5 events (3.6%) in the control arms.

Information about adverse drug reactions from monotherapy studies is presented in order to provide full characterization of adverse drug reactions. In monotherapy studies, clinically relevant serious adverse reactions also included infusion related reactions (2.5%), thrombocytopenia (21.7%), and neutropenia (34.3). In monotherapy studies the most common adverse reactions (>30%) included pyrexia, nausea, infection, chills, haemorrhage, vomiting, thrombocytopenia, fatigue, headache, stomatitis, diarrhoea, abdominal pain, and neutropenia. The most frequent (≥1%) adverse reactions that led to permanent discontinuation in monotherapy studies were infection, haemorrhage, multi-organ failure, and VOD.

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The overall safety profile of MYLOTARG is based on data from patients with acute myeloid leukaemia (AML) from the combination therapy study ALFA-0701, monotherapy studies, and from post-marketing 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 included all grades haemorrhages, all grades venoocclusive disease (VOD), and severe infections. All of these TEAEs were determined to be adverse drug reactions.

The safety evaluation of MYLOTARG (3 mg/m^2 on Days 1, 4 and 7) in combination with daunorubicin and cytarabine in adult patients with previously untreated de novo acute myeloid leukemia (AML) is based on data from the ALFA-0701 (n=271) study (see **CLINICAL TRIALS**). The study was designed to compare the clinical efficacy and safety of patients treated with MYLOTARG in combination with daunorubicin (DNR) and cytarabine (AraC; MYLOTARG arm; N=135) versus patients treated with DNR and AraC alone (control arm; N=136). The age of patients in this study ranged from 50-70, with a median of 62 years. In this study, 131 patients

were treated with MYLOTARG plus DNR and AraC. During the induction course, 123 (93.9%) received the 3 fractionated doses. MYLOTARG was received by 91 (69.5%) of patients during the first consolidation course and 64 (48.9%) of patients during the second consolidation course.

Table 5 shows the adverse drug reactions occurring ≥1% from the ALFA-0701 study reported in patients with previously untreated de novo AML who received MYLOTARG in combination.

Table 5. Summary of Adverse Drug Reactions occurring ≥1% from the ALFA-0701 study

	MYLOTARG + Daunorubicin + Cytarabine (N=131)		Daunorubicin + Cytarabine (N=137)	
System Organ Class Adverse Reaction	**All Grades %**	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
Blood and lymphatic system disorders				
Thrombocytopenia	15.3	14.5	0	0
Ear and labyrinth disorders				
Ear haemorrhage	1.5	0	0	0
Eye disorders				
Conjunctival haemorrhage	8.4	0	2.2	0
Eye haemorrhage	3.1	0	0.7	0
Retinal haemorrhage	2.3	1.5	0	0
Gastrointestinal disorders				
Anal haemorrhage	1.5	0	0.7	0
Gingival bleeding	17.6	1.5	8.8	0
Haematemesis	5.3	3.1	2.2	0
Haematochezia	4.6	0.8	5.8	0
Haemorrhoidal haemorrhage	2.3	0	2.2	0
Lip haemorrhage	3.8	0	1.5	0.7
Melaena	5.3	1.5	0	0
Mouth haemorrhage	16.0	0.8	4.4	0
Rectal haemorrhage	6.9	1.5	6.6	0.7
Tongue blistering	1.5	0	0	0
Tongue haematoma	2.3	0.8	0.7	0
General disorders and administration site conditions				
Catheter site haematoma	8.4	0	5.1	0
Catheter site haemorrhage	22.1	1.5	20.4	0.7
Infusion site haemorrhage	1.5	0	0	0
Puncture site haemorrhage	5.3	0.8	2.2	0
Hepatobiliary disorders				
Venoocclusive liver disease	4.6	2.3	0	0
Infections and infestations				
Device related infection	24.43	24.43	24.09	24.09
Bronchopulmonary aspergillosis	10.69	10.69	6.57	6.57
Device related sepsis	10.69	10.69	10.95	10.95

	MYLOTARG + Daunorubicin + Cytarabine (N=131)		Daunorubicin + Cytarabine (N=137)	
System Organ Class Adverse Reaction	**All Grades %**	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
Bacterial sepsis	9.16	9.16	2.92	2.92
Septic shock	9.16	7.63	5.84	8.76
Staphylococcal sepsis	6.87	6.87	10.22	10.22
Streptococcal sepsis	6.87	6.87	2.92	2.92
Enterococcal sepsis	4.58	4.58	0.73	0.73
Escherichia bacteraemia	4.58	4.58	2.92	2.92
Escherichia sepsis	4.58	4.58	3.65	3.65
Sepsis	4.58	4.58	2.92	2.92
Klebsiella sepsis	3.82	3.82	2.92	2.92
Pneumonia	3.82	3.82	4.38	4.38
Clostridium difficile colitis	3.05	3.05	2.19	2.19
Staphylococcal bacteraemia	3.05	3.05	1.46	1.46
Aspergillus infection	2.29	2.29	2.19	2.19
Candida sepsis	2.29	2.29	2.92	2.92
Cellulitis	2.29	2.29	1.46	1.46
Clostridium difficile infection	2.29	2.29	3.65	3.65
Escherichia urinary tract infection	2.29	2.29	1.46	1.46
Candida infection	1.53	1.53	0	0
Lung infection	1.53	1.53	1.46	1.46
Pseudomonal sepsis	1.53	1.53	0	0
Streptococcal bacteraemia	1.53	1.53	0.73	0.73
Streptococcal infection	1.53	1.53	0.73	0.73
Urinary tract infection	1.53	1.53	6.57	6.57
Anal abscess	1.53	1.53	0.73	0.73
Injury, poisoning, and procedural complications				
Contusion	3.8	0	2.2	0
Post-procedural haemorrhage	6.9	0	2.9	0.7
Procedural haemorrhage	1.5	0	0.7	0
Subdural haematoma	1.5	0	0	0
Wound haemorrhage	1.5	0.8	2.2	0
Investigations				
Blood urine present	1.5	0	0.7	0
Renal and urinary disorders				
Haematuria	19.1	2.3	10.2	0.7
Reproductive system and breast disorders				
Metrorrhagia	2.3	0	4.4	0
Vaginal haemorrhage	1.5	0.8	0	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	62.6	1.5	36.5	0
Haemoptysis	14.5	3.1	9.5	1.5
Pulmonary alveolar haemorrhage	3.1	2.3	0.7	0

	MYLOTARG + Daunorubicin + Cytarabine (N=131)		Daunorubicin + Cytarabine (N=137)	
System Organ Class Adverse Reaction	**All Grades %**	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
Skin and subcutaneous tissue disorders				
Blood blister	22.1	0.8	8.0	0
Petechiae	22.9	1.5	16.8	1.5
Purpura	26.0	1.5	14.6	2.2
Vascular disorders				
Haematoma	25.2	1.5	17.5	0.7
Haemorrhage	4.6	1.5	4.4	0

Table 6 summarizes the selected adverse reactions reported in patients with previously untreated de novo AML who received MYLOTARG in a combination.

Table 6. Selected Adverse Reactions Captured During a Retrospective Review of Predefined Events in Patients With Previously Untreated AML Who Received MYLOTARG (Combination Therapy ALFA-0701

System Organ Class Adverse Reaction	MYLOTARG + Daunorubicin + Cytarabine (N=131)		Daunorubicin + Cytarabine (N=137)	
	All Grades %	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
Infections and infestations				
Infection*,[a]	77.9	76.3	77.4	74.5
Vascular disorders				
Haemorrhage*,[b]	90.1	20.6	78.1	8.8
Hepatobiliary disorders				
Venoocclusive liver disease*,[c]	4.6	2.3	1.5	1.5

AML=acute myeloid leukemia; N=number of patients; PT=preferred term.

* 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. Infection includes Sepsis and Bacteraemia (53.4%), Fungal infection (15.3%), Lower respiratory tract infection (5.3%), Bacterial infection (9.2%), Gastrointestinal infection (8.4%), Skin infection (2.3%), and Other infections (28.4%).

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). Haemorrhage includes Central nervous system haemorrhage (3.1%), Upper gastrointestinal haemorrhage (33.6%), Lower gastrointestinal haemorrhage (17.6%), Subcutaneous haemorrhage (60.3%), Other haemorrhage (64.9%), and Epistaxis (62.6%).

c. Venoocclusive liver disease includes the following reported PTs: Venoocclusive disease and Venoocclusive liver disease*.

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 and in 1 (0.7%) patient in the control arm.

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). VOD was also reported in 2 patients who received MYLOTARG as a follow-up therapy following relapse of AML after chemotherapy treatment in the control arm of the combination therapy study. Both of these patients experienced VOD more than 28 days after the last dose of MYLOTARG treatment. One of these patients experienced VOD 25 days after the subsequent HSCT. In the control arm receiving chemotherapy without ever receiving MYLOTARG, there were zero VOD events.

Based on an analysis of potential risk factors, adult patients who received MYLOTARG as monotherapy, patients who had received an HSCT prior to gemtuzumab ozogamicin exposure were 2.6 times more likely (95% CI: 1.448, 4.769) to develop VOD compared to patients without HSCT prior to treatment with gemtuzumab ozogamicin; patients who had received an HSCT following treatment with gemtuzumab ozogamicin were 2.9 times more likely (95% CI: 1.502, 5.636) to develop VOD compared to patients without HSCT following treatment with gemtuzumab ozogamicin; and patients who had moderate/severe hepatic impairment at baseline were 8.7 times more likely (95% CI: 1.879, 39.862) to develop VOD compared to patients without moderate/severe hepatic impairment at baseline.

Patients should be monitored for hepatotoxicity (see **WARNINGS AND PRECAUTIONS**). Management of signs or symptoms of hepatic toxicity may require a dose interruption or discontinuation of MYLOTARG (see **DOSAGE AND ADMINISTRATION, Dose and schedule modifications**).

Myelosuppression/cytopenia

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. In the control group (N=137), Grade 3/4 decreases in leukocytes, neutrophils, and platelets were observed in 135 (99.3%), 131 (97.0%), and 136 (100.0%), respectively.

During the induction phase, 109 (83.2%) and 99 (75.6%) patients receiving Mylotarg had platelet recovery to counts of 50,000/mm^3 and 100,000/mm^3, respectively. In the control arm, 118 patients (86.1%) had platelet recovery to 50,000/mm^3 and 111 patients (81.0%) had platelet recovery to 100,000/mm^3.The median times to platelet recovery to counts of 50,000/mm^3 and 100,000/mm^3 were 34 and 35 days, respectively for patients receiving MYLOTARG, and 29.0 and 30.0 days for the patients in the control arm. During the Consolidation 1 phase, 92 (94.8%) and 71 (73.2%) patients receiving MYLOTARG had a platelet recovery to counts of 50,000/mm^3,

and 100,000/mm^3, respectively, while 86 (88.7%) and 80 (82.5%) patients in the control arm had platelet recovery to counts of 50,000/mm^3, and 100,000/mm^3. The median times to platelet recovery to counts of 50,000/mm^3 and 100,000/mm^3 were 32 and 35 days, respectively for patients receiving MYLOTARG and 27.0 and 28.0 days for those in the control arm. During the Consolidation 2 phase, 80 (97.6%) and 70 (85.4%) patients receiving Mylotarg 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. In the control arm during the Consolidation 2 phase, 85 (95.5%) and 82 (92.1%) 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 30.0 and 32.0 days, respectively. Platelet recovery to both counts of 50,000/mm^3 and 100,000/mm^3 was longer for patients who received MYLOTARG through all treatment phases compared to patients in the control arm.

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 receiving MYLOTARG and 2 (2.0%) patient in the control arm. 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 the control arm, persistent thrombocytopenia was experienced by 1 (1.0%) patient in the induction phase, no patients at the Consolidation 1 phase, and 2 (2.4%) 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 control arm during the induction phase, 125 (91.2%) and 120 (87.6%) 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 24.0 and 25.0 days, respectively. 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 control arm during the Consolidation 1 phase, 94 (96.9%) and 89 (91.8%) 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 22.0 and 24.0 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 control arm during the Consolidation 2 phase, 88 (98.9%) and 88 (98.9%) 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 22.0 and 26.0 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. In the control arm, 106 (77.4%) patients experienced all-causality severe (Grade ≥3) infections. Treatment-related death due to septic shock was reported in 1 (0.8%) patient receiving MYLOTARG and in 3 patients (2.2%) in the control arm.

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 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 control arm, all grades and Grade 3/4 bleeding/haemorrhagic events were reported in 107 (78.1%) and 12 (8.8%) patients, respectively. The most frequent Grade 3 bleeding/haemorrhagic event was purpura (2.2%). Fatal bleeding/haemorrhagic events were reported in 1 (0.7%) patient (cerebral haemorrhage).

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 **DOSAGE AND ADMINISTRATION, Dose and schedule modifications** and **WARNINGS AND PRECAUTIONS, Hematologic**).

Immunogenicity

Immunogenicity was not assessed in the ALFA-0701 study of patients treated with MYLOTARG in combination with DNR and AraC. The data regarding immunogenicity with MYLOTARG is limited. As with all therapeutic proteins, there is potential for immunogenicity. In clinical studies of MYLOTARG in patients with relapsed or refractory AML, the immunogenicity of MYLOTARG was evaluated using 2 enzyme-linked immunosorbent assays (ELISAs).

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.

9.3 Less Common Clinical Trial Adverse Reactions

Additional clinically significant less common events include the following adverse drug reactions and discontinuations due to adverse events:

Blood and lymphatic system disorders: Febrile neutropenia
Cardiac disorders: Acute coronary syndrome
Hepatobiliary disorders: Cholecystitis acute, Hepatitis cholestatic, Hepatotoxicity
Nervous system disorders: Cerebral hematoma, Peripheral neuropathy
Renal and urinary disorders: Acute kidney injury, Renal failure

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 7 summarizes hematologic and chemistry laboratory abnormalities by treatment arm for patients treated in ALFA-0701.

Table 7. Clinically Relevant Laboratory Abnormalities in Patients With Previously Untreated AML Who Received MYLOTARG (Combination Therapy-ALFA-0701)

Laboratory Abnormality	N	MYLOTARG + Daunorubicin + Cytarabine		N	Daunorubicin + Cytarabine	
		All Grades %	Grade 3/4 %		All Grades %	Grade 3/4 %
Haematology						
Activated partial thromboplastin time prolonged	125	80.0	6.4	127	57.5	5.5
Haemoglobin decreased	130	100	86.2	136	100	89.7
Lymphocytes (absolute) decreased	129	98.5	90.7	135	97.8	89.6
Neutrophils decreased	129	97.7	96.1	135	98.5	97.0
Platelets decreased	131	100	100	136	100	100
Prothrombin time increased	92	84.8	3.3	92	89.1	0
White blood cells decreased	131	100	100	136	99.3	99.3
Chemistry						
Alanine aminotransferase (ALT) increased	129	78.3	10.9	134	81.3	15.7
Alkaline phosphatase increased	128	79.7	13.3	132	68.9	5.3
Aspartate aminotransferase (AST) increased	129	89.2	14.0	134	73.9	9.0
Blood bilirubin increased	126	51.6	7.1	132	50.8	3.8
Glucose decreased	125	23.2	0.8	135	11.9	1.5
Hyperglycaemia	125	92.0	19.2	135	91.1	17.8
Hyperuricemia	117	32.5	2.6	123	28.5	0
Phosphate decreased	129	89.2	65.1	134	69.4	40.3
Potassium decreased	130	93.1	57.7	135	82.2	31.1
Sodium decreased	130	90.0	44.6	135	85.9	27.4

AML=acute myeloid leukemia; N=number of patients.

9.5 Post-Market Adverse Reactions

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

10 DRUG INTERACTIONS

10.1 Overview
No clinical drug interaction studies have been performed with MYLOTARG (gemtuzumab ozogamicin for injection).

10.2 Drug-Drug Interactions
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.

No clinical drug interaction studies have been performed. Based on population PK analyses, the combination of gemtuzumab ozogamicin with hydroxyurea, daunorubicin (DNR) and cytarabine (AraC) is not predicted to cause clinically meaningful changes in the pharmacokinetics (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

No clinical drug interaction studies have been performed. 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.

10.3 Drug-Food Interactions
Interactions with food have not been established.

10.4 Drug-Herb Interactions
Interactions with herbal products have not been established.

10.5 Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action
MYLOTARG (gemtuzumab ozogamicin for injection) is a CD33-directed ADC. Gemtuzumab is a humanized immunoglobulin class G subtype 4 (lgG4) 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 dimethyl hydrazide, is a cytotoxic semisynthetic natural product. N-acetyl gamma calicheamicin dimethyl hydrazide 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.

11.2 Pharmacodynamics
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 acute myeloid leukemia (AML) models.
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/m2 and above.

11.3 Pharmacokinetics
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 dimethyl hydrazide. The pharmacokinetic (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 dimethyl hydrazide 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.

Metabolism: 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) parameter 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 (t½) 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.

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 parameter of gemtuzumab ozogamicin (hP67.6 antibody and unconjugated calicheamicin) is not expected to be affected by mild 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 DOSAGE AND ADMINISTRATION, Dosing Considerations).

Renal Impairment: No formal PK studies of gemtuzumab ozogamicin have been conducted in patients with renal impairment (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

Based on population PK analysis in 406 patients, the clearance parameter 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).

12 STORAGE, STABILITY AND DISPOSAL

Store in refrigerator (2°C to 8°C).

Do not freeze.

Store the vial in the original carton to protect from light.

Following reconstitution and dilution, the solution should be protected from light and should be used immediately. If the product cannot be 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 (see **DOSAGE AND ADMINISTRATION, Reconstitution)**.

13 SPECIAL HANDLING INSTRUCTIONS

Use appropriate aseptic technique for the reconstitution and dilution procedures (see **DOSAGE AND ADMINISTRATION, Reconstitution**). MYLOTARG (gemtuzumab ozogamicin for injection) is light sensitive and should be protected from light during reconstitution, dilution, and administration.

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: gemtuzumab ozogamicin

Chemical name:

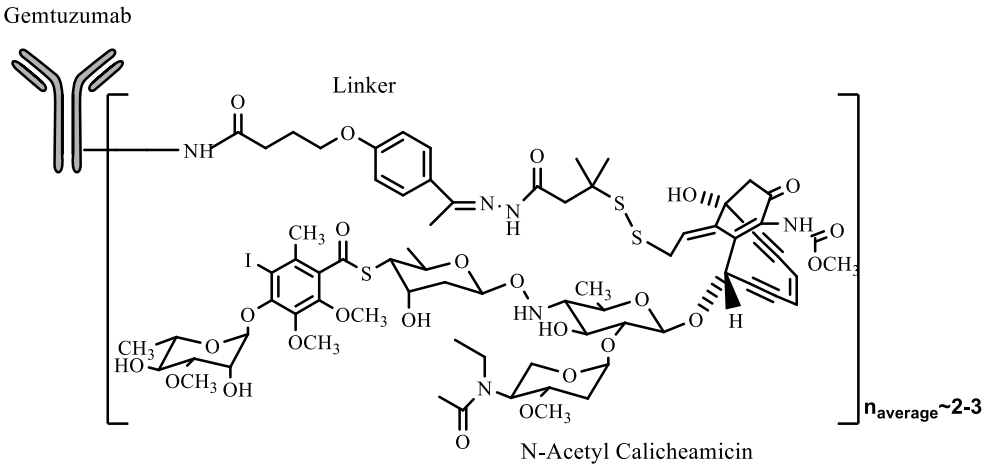
(1) Immunoglobulin G4, anti-(human CD33 antigen) human-mouse monoclonal hP67.6 γ4-chain), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer, methyl [(l*R*,4*Z*, 8*S*, 13*E*)-[8-[[2-*O*-[4-(acetylethylamino)-2,4-dideoxy-3-*O*-methyl-α-L-*threo*-pentopyranosyl]-4,6-dideoxy-4-[[[2,6-dideoxy-4-*S*-[4- [(6-deoxy-3-*O*-methyl-α-L-mannopyranosyl)oxy]-3-iodo-5,6-dimethoxy-2-methylbenzoyl]-4-thio-β-D-*ribo*-hexopyranosyl]oxy]amino]- β-D-glucopyranosyl]oxy]-13-[2-[[3-[2-[1-[4-(4-amino-4-oxobutoxy)phenyl] ethylidene]hydrazino]-1,1-dimethyl-3-oxopropyl]dithio]ethylidene]-1-hydroxy-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyn-10-yl]carbamate conjugate;

(2) Immunoglobulin G4 (human-mouse monoclonal hP67.6 γ4-chain anti-human antigen CD33), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer, conjugate with methyl (1*R*, 4*Z*, 8*S*, 13*E*)-13-[2-[[2-[[[*p*-(3-carbamoylpropoxy)- α-methylbenzylidene]hydrazino] carbonyl]-1,1-dimethylethyl]dithio]ethylidene]-8-[[4,6-dideoxy-4-[[[2,6-dideoxy-4-*S*-[4-[(6-deoxy-3-*O*-methyl-α-L-mannopyranosyl)oxy]-3-iodo-5,6-dimethoxy-*o*-toluoyl]-4-thio-β-D-*ribo*-hexopyranosyl]oxy]amino]-2-*O*-[2,4-dideoxy-4-(*N*-ethylacetamido)-3-*O*-methyl-α-L-*threo*-pentopyranosyl]- β-D-glucopyranosyl]oxy]-1-hydroxy-11-oxobicyclo[7.3.1] trideca-4,9-diene-2,6-diyne-10-carbamate.

Molecular formula and molecular mass:

Gemtuzumab ozogamicin drug substance has heterogeneity in composition of glycans and number of calicheamicin derivative conjugated per gemtuzumab molecule. As a result, definitive molecular mass is not applicable. For the predominant N-glycoform of gemtuzumab ozogamicin with 2 and 3 calicheamicin derivative moieties attached, the theoretical molecular masses are 151,520 Da and 153,185 Da, respectively.

Structural formula:



Physicochemical properties:

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.

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

ALFA-0701 Trial

The efficacy and safety of MYLOTARG (gemtuzumab ozogamicin for injection) were evaluated in a multicenter, randomized, open-label, Phase 3 study (ALFA-0701) of 271 patients comparing the addition of MYLOTARG to a standard chemotherapy induction regimen of daunorubicin (DNR) and cytarabine (AraC) versus DNR and AraC alone. Eligible patients were between 50 and 70 years of age with previously untreated de novo acute myeloid leukemia (AML).

A total of 280 patients were enrolled across 26 centers in France between January 2008 and November 2010. Following publication of the initial AFLA-0701 results, showing significant improvement in investigator-assessed event-free survival, the Centre Hospitalier de Versailles, in collaboration with Pfizer, performed a retrospective, independent, blinded review of the efficacy endpoints of the study and provided a more complete assessment of the safety profile of MYLOTARG.

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) with (MYLOTARG arm; N=135) or without

(Control arm; 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 at the following 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. Patients with response received consolidation therapy with 2 courses of treatment (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**) 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), measured from the date of randomization until induction failure, relapse, or death by any cause. Induction failure and relapse were assessed by independent review with the date of induction failure set at the randomization date. The key secondary endpoint was overall survival (OS). Overall response, defined by patients who had a complete remission (CR) or complete remission with incomplete platelet recovery was also assessed in this study.

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).

15.2 Study Results

ALFA-0701 Trial

Study ALFA-0701 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 improvement in EFS. The findings for EFS and OS are summarized in Table 8 and the Kaplan-Meier plot for EFS is shown in Figure 1. There was no statistically significant difference between treatment arms in overall survival.

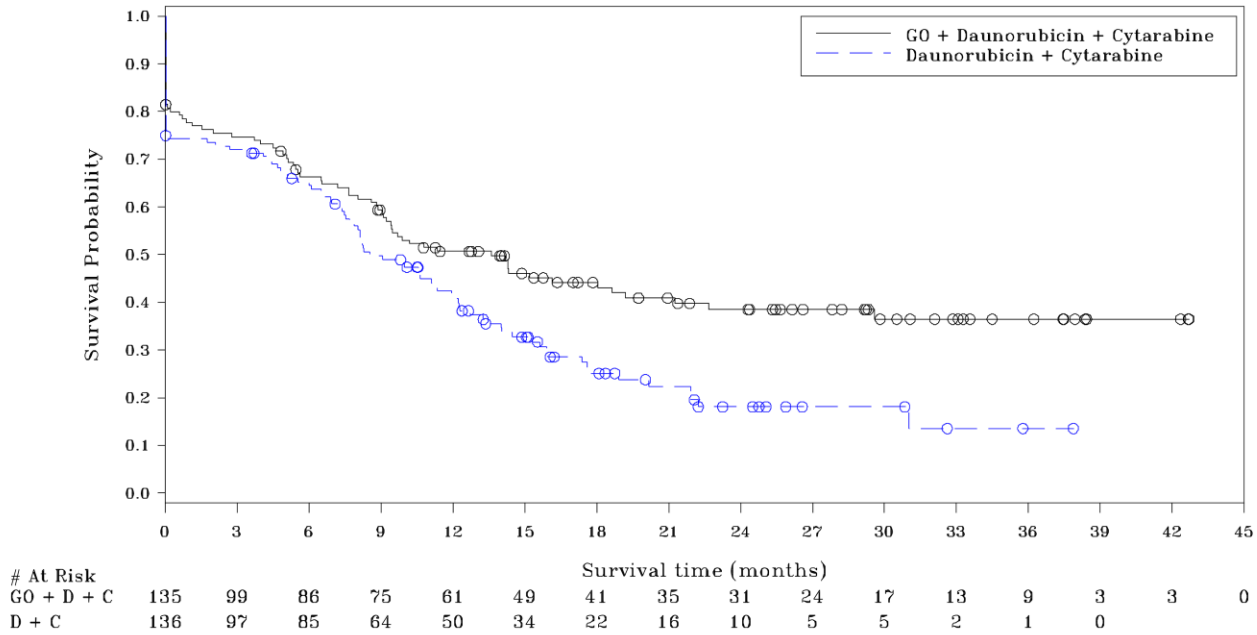
Table 8. Efficacy Results from Study ALFA-0701 (mITT population)

	MYLOTARG + Daunorubicin + Cytarabine	Daunorubicin + Cytarabine
Event-free survival	**N=135**	**N=136**
Number of events, n (%)	78 (57.8)	100 (73.5)
Median EFS in months [95% CI][a]	13.6 [9.0, 19.2]	8.5 [7.5, 12.0]
Hazard ratio [95% CI][b]	0.661 [0.491, 0.891]	
p-value[c]	0.0059	
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][b]	0.807 [0.596, 1.093]	

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; EFS=event-free survival; mITT=modified intent-to-treat; n=number of events; N=number of patients; OS=overall survival.

a. Median estimated by Kaplan-Meier method; CI based on the Brookmeyer-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.

Figure 1. Kaplan-Meier Plot of Event-Free Survival (Determined by Independent Review, ITT 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.

The results of EFS by investigator assessment were consistent with the results for EFS by independent review (median EFS of 17.3 months in the MYLOTARG arm and of 9.5 months in the control arm; HR: 0.562, 95% CI: 0.415-0.762).

Among the 271 randomized patients, 100/135 (74.1%) of patients in the MYLOTARG arm and 96/136 (70.6%) of patients in the control arm experienced an overall response (defined as CR+ CRp) as assessed per investigator assessment.

Studies in children, adolescents, and young adults with previously untreated de novo AML

In a randomized, open-label study (COG AAML0531), 1,063 pediatric and young adult patients, aged 1 month to 29 years, with newly diagnosed de novo AML were randomly assigned to either standard 5-course chemotherapy alone (cytarabine, daunorubicin, and etoposide) or to the same chemotherapy with 2 doses of MYLOTARG (3 mg/m^2/dose). MYLOTARG was administered once during induction treatment (Course 1) and once during intensification treatment (Course 2). The estimated HR for EFS was 0.84 (95% CI: 0.71, 1.0). The estimated HR for OS was 0.90 (95% CI: 0.72, 1.33). During the second intensification period, a larger proportion of patients in the MYLOTARG arm experienced prolonged neutrophil recovery time (> 59 days) as compared with the comparator arm (21.0% versus 11.5%), and while there were more deaths due to the disease under study in the comparator arm (83 [15.6%] versus 57 [10.7%] patients in the MYLOTARG arm), there were more deaths due to infection in the MYLOTARG arm (26 [4.9%] versus 16 [3.0%] patients in the comparator arm). Therefore, the optimal dose of MYLOTARG for use in pediatric patients has not been established and the results of this study require cautious interpretation.

16 NON-CLINICAL TOXICOLOGY

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 3.7 and 18 times, respectively for rats, and 7.4 and 36 times, respectively for monkeys, the human clinical exposure after the second dose of 9 mg/m^2, or after the third dose of 3 mg/m^2 based on AUC_{168}, respectively). 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, and approximately 39 and 66 times, respectively, the human clinical exposure after the second dose of 9 mg/m^2, based on AUC_{168}).

Genotoxicity

Gemtuzumab ozogamicin was clastogenic in vivo in the bone marrow of mice at ≥22.1 mg/m2. This is consistent with the known induction of DNA breaks by calicheamicin and other enediyneantitumour antibiotics. N-acetyl gamma calicheamicin dimethyl hydrazide (the releasedcytotoxin) was mutagenic in the bacterial reverse mutation assay and clastogen ic 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 11 and 54 times the human clinical exposure after the second dose of 9 mg/m^2 or after the third dose of 3 mg/m^2, respectively, based on AUC_{168}). There were no preneoplastic or neoplastic lesions observed in monkeys up to 22 mg/m^2/week (approximately 23 and 115 times, respectively, the human clinical exposure after the second dose of 9 mg/m^2, or after the third dose of 3 mg/m^2, respectively, 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/m2/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 13 and 66 times the human clinical exposure after the second dose of 9 mg/m^2, or after the third dose of 3 mg/m^2, respectively, based on AUC_{168}). Female reproductive tract findings were adverse at ≥6.6 mg/m2/week (approximately 39 and 193 times the human clinical exposure after the second dose of 9 mg/m^2, or after the third dose of 3 mg/m^2, respectively, 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/m2/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 3.7 or 18 times the human clinical exposure after the second human dose of 9 mg/m^2 or after the third human dose of 3 mg/m^2, respectively, 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 17 or 81 times the human clinical exposure after the second human dose of 9 mg/m^2 or after the third human dose of 3 mg/m^2, respectively, 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 13 and 66 times the human clinical exposure after the second dose of 9 mg/m^2, or after the third dose of 3 mg/m^2, respectively, 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 2.0 or 9.7 times the human clinical exposure after the second human dose of 9 mg/m^2 or after the third human dose of 3 mg/m^2, respectively, based on AUC_{168}.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrMYLOTARG®

gemtuzumab ozogamicin for injection

Read this carefully before you start **MYLOTARG**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MYLOTARG.**

Serious Warnings and Precautions

- Liver toxicity, including a condition called venoocclusive disease (VOD), in which the blood vessels in the liver become damaged because of blood clots
- Low number of blood cells known as neutrophils, red blood cells, white blood cells, lymphocytes, or a low number of blood cells known as platelets (with signs and symptoms such as infection, fever, bruising easily or bleeding)
- Tumor lysis syndrome (complications occurring after cancer treatment leading to increased blood levels of potassium, uric acid, and phosphorus and decreased blood levels of calcium)
- Infusion-related reactions (with signs and symptoms such as fever and chills during or shortly after the MYLOTARG infusion)

What is MYLOTARG used for?

- MYLOTARG is used to treat a certain type of cancer called acute myeloid leukaemia (AML) in which the bone marrow makes abnormal white blood cells. MYLOTARG is intended for the treatment of AML in adult patients who have not tried other treatments. MYLOTARG is not for use in patients with a type of cancer called acute promyelocytic leukaemia (APL).

How does MYLOTARG work?

MYLOTARG acts by attaching to cells with a protein called CD33. AML cells have this protein. Once attached to the AML cells, MYLOTARG delivers a substance into the cells that targets the cells' DNA and eventually kills them.

What are the ingredients in MYLOTARG?

Medicinal ingredients: gemtuzumab ozogamicin
Non-medicinal ingredients: Dextran 40; Dibasic sodium phosphate, anhydrous; Monobasic sodium phosphate, monohydrate; Sodium chloride; Sucrose

MYLOTARG comes in the following dosage forms:

MYLOTARG is supplied as a white to off-white lyophilized cake or powder in a glass vial for solution for infusion. The container is an amber Type 1 glass vial, with butyl rubber stopper and crimp seal with flip-off cap.

Do not use MYLOTARG if:

- You are allergic to gemtuzumab ozogamicin or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive MYLOTARG. Talk about any health conditions or problems you may have, including if you:

- have a history of liver problems or liver diseases. MYLOTARG may cause a serious life-threatening condition called hepatic venoocclusive disease (VOD), a condition in which the blood vessels in the liver become damaged and obstructed by blood clots. The signs and symptoms of VOD include, rapid weight gain, pain in the upper right side of your abdomen (belly), increase in the size of the liver, build-up of fluid causing abdominal swelling, and blood tests showing increases in bilirubin and/or liver enzymes. This condition may occur during and following treatment with MYLOTARG.
- have or think you have an infection or fever or are bruising easily or are getting frequent nose bleeds. MYLOTARG may cause a low number of blood cells known as neutrophils (sometimes accompanied with fever), red blood cells, white blood cells, lymphocytes, or a low number of blood cells known as platelets.
- have a high-pitched whistling sound during breathing (wheezing), difficulty breathing, shortness of breath, cough with or without mucous, hives, itching, swelling or have a fever and chills during or shortly after the MYLOTARG infusion.
- have symptoms in the stomach and intestines (for example, nausea, vomiting, diarrhea), heart (for example, changes in the rhythm), kidney (for example, decreased urine, blood in urine), and nerves and muscles (for example, muscular spasms, weakness, cramps), during or shortly after the MYLOTARG infusion. These may be a serious and life-threatening syndrome known as tumour lysis syndrome.

Other warnings you should know about:

Pregnancy, breast-feeding and fertility:

- If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.
- You must avoid becoming pregnant or fathering a child. Women must use 2 methods of effective contraception during treatment and for at least 7 months after the last dose of treatment. Men must use 2 methods of effective contraception during treatment and for at least 4 months after the last dose of treatment. Contact your doctor immediately if you or your partner becomes pregnant while taking this medicine.
- Seek advice regarding fertility preservation before treatment.
- If you need treatment with MYLOTARG, you must stop breast-feeding during treatment and for at least 1 month after treatment. Talk to your doctor.

Driving and using machines:

- If you feel unusually tired, dizzy or have a headache (these are very common side effects of MYLOTARG) you should not drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How Mylotarg is given

- Your doctor will decide on the correct dose.
- A doctor or nurse will give you MYLOTARG through a drip in your vein (intravenous infusion [IV]) gradually over 2 hours.
- Mylotarg is given in combination with chemotherapy on day 1, 4 and 7 of the first induction cycle.
- If the medicine works well, MYLOTARG can be given on day 1 of up to 2 consolidation cycles in combination with chemotherapy.
- Your doctor may change your dose, interrupt, or completely stop treatment with MYLOTARG if you have certain side effects.
- Your doctor will do blood tests during the treatment to check for side effects and for response to treatment.
- Before you receive MYLOTARG, you may be given some medicines (a corticosteroid, antihistamine, and acetaminophen) to help reduce infusion reactions symptoms such as fever and chills, which may occur during or shortly after the MYLOTARG infusion.

Usual dose:
Your doctor will decide on the correct dose.

Overdose:

If you think you have received too much MYLOTARG, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Speak with your healthcare professional as soon as possible if you miss a dose of MYLOTARG.

What are possible side effects from using MYLOTARG?

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some of the side effects could be serious and may occur during or after treatment with MYLOTARG. Immediately contact your doctor if you experience any of the following serious side effects:

- Liver problems
- Bleeding
- Infections
- Complications known as tumor lysis syndrome
- Infusion reaction

Other side effects may include:

Very common (may affect more than 1 in 10 people):

- Infections (including serious infections)
- Reduced number of blood platelets (cells that help blood to clot)
- Reduced number of white blood cells which may result in general weakness and a tendency to develop infections
- Reduced number of red blood cells (anaemia) which may result in fatigue and shortness of breath
- High blood sugar

- Decreased appetite
- Headache
- Rapid heartbeat
- Bleeding
- Low blood pressure
- High blood pressure
- Shortness of breath
- Vomiting
- Diarrhoea
- Pain in the abdomen
- Feeling sick (nausea)
- Mouth inflammation
- Constipation
- Abnormalities in liver blood tests (which can be indicators of liver injury)
- Skin rash
- Fever
- Oedema (excess fluid in body tissue, causing swelling of the hands and feet)
- Fatigue
- Chills
- Changes in the levels of different enzymes in the blood (may show in your blood tests)
- Prolonged clotting time
- High level of uric acid in the blood

Common (may affect up to 1 in 10 people):
- Signs of an infusion reaction, such as a rash, shortness of breath, difficulty breathing, a tight chest, chills or fever, back pain during or after MYLOTARG infusion
- Signs of an enlarged liver (hepatomegaly), such as an enlarged belly
- Abnormal liver function
- Excessive accumulation of fluid in the abdomen/stomach
- Indigestion
- Inflammation of the oesophagus (swallowing tube)
- Liver venoocclusive disease (VOD), which includes signs of enlarged liver, pain in the upper right belly, yellowing of the skin and the whites of the eyes, accumulation of fluid in the abdomen, weight gain, abnormal liver blood tests
- Yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice)
- Redness of the skin
- Itchy skin
- Organ failure

Uncommon (may affect up to 1 in 100 people):
- Liver failure
- Budd Chiari syndrome, which includes pain in the upper right part of the belly, an abnormally large liver, and/or accumulation of fluid in the belly associated with blood clots in the liver. Symptoms may also include feeling sick (nausea) and/or vomiting.

Frequency unknown (frequency cannot be estimated from the available data):
- Interstitial pneumonia (inflammation of the lungs causing coughing and difficulty breathing)
- Inflammation of the bowel in association with low white blood cell counts

- Inflammation of the urinary bladder resulting in bleeding from the bladder

These are not all the possible side effects you may feel when taking MYLOTARG. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Bleeding (reduced number of platelets, cells that help blood to clot): if you bruise easily or get nose bleeds on a regular basis, or have black tarry stools, coughing up of blood, bloody sputum, or change in your mental status		√	
Infections (reduced number of white blood cells known as neutrophils): may result in general weakness and a tendency to develop infections		√	
COMMON			
Infusion reactions: such as rash, shortness of breath, difficulty breathing, a tight chest, chills or fever, back pain during or after MYLOTARG infusion		√	
Tumor lysis syndrome: if you experience dizziness, decreased urination, confusion, vomiting, nausea, swelling, shortness of breath, or heart rhythm disturbances		√	
Liver problems (potentially life-threatening disease called venoocclusive disease): which includes sign of enlarged liver, pain in the upper right belly, yellowing of the skin and the whites of the eyes, accumulation of in the abdomen, weight gain, abnormal liver blood tests		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Reporting Suspected Side Effects

For the general public: Should you experience a side effect following treatment, please report it to your doctor, nurse, or pharmacist.

Should you require information related to the management of the side effect, please contact your healthcare provider. The Public Health Agency of Canada, Health Canada and Pfizer Canada ULC cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following treatment, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:

Unopened Vial

Store in a refrigerator (2-8°C). Do not freeze.

Store in the original carton in order to protect from light.

MYLOTARG will be prepared in an infusion container by a pharmacist and then delivered to the healthcare professional who will administer the medication to you as an intravenous infusion at the hospital.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your doctor how to throw away medicines you no longer use. These measures will help protect the environment.

Keep out of reach and sight of children.

If you want more information about MYLOTARG

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.pfizer.ca or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC

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