▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – MYLOTARG® (GEMTUZUMAB OZOGAMICIN) POWDER FOR INJECTION

1. NAME OF THE MEDICINE

Gemtuzumab ozogamicin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial contains 5 mg gemtuzumab ozogamicin.

After reconstitution, the concentrated solution contains 1 mg/mL gemtuzumab ozogamicin (see Section 4.2 Dose and method of administration).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection.

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MYLOTARG is indicated for combination therapy with standard anthracycline and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, *de novo* CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL) (see Section 4.4 Special warnings and precautions for use, and Section 5.1 Pharmacodynamic properties).

4.2 Dose and method of administration

MYLOTARG 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.

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

Appropriate measures to help prevent the development of tumour lysis-related hyperuricaemia such as hydration, administration of antihyperuricaemic or other agents for treatment of hyperuricaemia must be taken (see Section 4.4 Special warnings and precautions for use).

MYLOTARG must be reconstituted and diluted before administration (see Section 4.2 Dose and method of administration, Instructions for use and handling).

Traceability

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient file.

Dosage

Induction

The recommended dose of MYLOTARG is 3 mg/m^2/dose (up to a maximum of one 5 mg vial) infused over a 2-hour period on Days 1, 4, and 7 of the induction chemotherapy cycle.

If a second induction is required, MYLOTARG should not be administered during second induction therapy. Only standard anthracycline and cytarabine (AraC) should be administered during the second induction cycle.

Consolidation

For patients experiencing a complete remission (CR) following induction, defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count (ANC) of more than 1.0×10^9 cells/L with a platelet count of 100×10^9/L or more in the peripheral blood in the absence of transfusion, the recommended dose of MYLOTARG is 3 mg/m^2/dose (up to a maximum dose of one 5 mg vial) infused over a 2-hour period on Day 1 of the consolidation chemotherapy cycle.

Table 1. Dosing Regimens for MYLOTARG in Combination with Chemotherapy

Treatment Course	**MYLOTARG**	**Standard Anthracycline and Cytarabine Combination Chemotherapy**
Induction[a]	3 mg/m^2/dose (up to a maximum of one 5 mg vial) on Days 1, 4, and 7	According to current medical standard[c]
Second induction (if required)	MYLOTARG should not be administered during second induction.	According to current medical standard

Consolidation Course 1[a,b]	3 mg/m^2/dose (up to a maximum of one 5 mg vial) on Day 1	According to current medical standard[d]
Consolidation Course 2[a,b]	3 mg/m^2/dose (up to a maximum of one 5 mg vial) on Day 1	According to current medical standard[d]

a. See Table 2 and Table 3 for dose modification information.
b. For patients experiencing a complete remission following induction.
c. Induction therapy is usually 7 days
d. Consolidation therapy is usually 4 days

Method of administration

MYLOTARG is for intravenous use and must be reconstituted and diluted before administration (see Section 4.2 Dose and method of administration). Administer MYLOTARG intravenously by infusion over a 2-hour period under close clinical monitoring, including pulse, blood pressure, and temperature. Do not administer MYLOTARG as an intravenous push or bolus (see Section 4.2 Dose and method of administration, Instructions for use and handling).

Dosage adjustment

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 Section 4.4 Special warnings and precautions for use).

If AraC is used for leukoreduction with or without hydroxyurea in patients with previously untreated, *de novo* hyperleukocytic AML receiving MYLOTARG in combination therapy, treatment of hyperleukocytosis with AraC should begin on Day 1 with Mylotarg given at 3 mg/m^2/dose (up to a maximum of one 5 mg vial) on days 3, 6, and 9 of standard induction chemotherapy, adapted in accordance with standard medical practice (see Table 2 and Table 3 for additional dose modification information).

Dose modification for adverse reactions

Dose modification of MYLOTARG is recommended based on individual safety and tolerability (see Section 4.4 Special warnings and precautions for use). Management of some adverse reactions may require dose interruptions or permanent discontinuation of MYLOTARG (see Section 4.4 Special warnings and precautions for use, and Section 4.8 Adverse effects (undesirable effects)).

Tables 2 and 3 show the dose modification guidelines for haematologic and non-haematologic toxicities, respectively.

Table 2. Dose modifications for haematologic toxicities

Haematologic toxicities	Dose modifications
Persistent thrombocytopenia	• If platelet count does not recover to ≥ 100,000/ mm^3 within 14 days following the planned start date of the consolidation cycle (14 days after haematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles).
Persistent neutropenia	• If neutrophil count does not recover to > 500/mm^3 within 14 days following the planned start date of the consolidation cycle (14 days after haematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles).

Abbreviations: AML=acute myeloid leukaemia; AraC=cytarabine; BMA= bone marrow aspirate;

Table 3. Dose modifications for non-haematologic toxicities

Non-haematologic toxicities	Dose modifications
VOD/SOS	Discontinue MYLOTARG (see Section 4.4 Special warnings and precautions for use).
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. Consider permanent discontinuation of treatment for severe or life-threatening infusion reactions (see Section 4.4 Special warnings and precautions for use).
Other severe or life-threatening non-haematologic 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; ULN=upper limit of normal; VOD=venoocclusive disease.

Special populations

Use in patients with hepatic impairment

No adjustment of the starting dose is required in patients with hepatic impairment defined by total bilirubin ≤ 2 × upper limit of normal (ULN) and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 × ULN. Postpone MYLOTARG until recovery of total bilirubin to ≤ 2 × ULN and AST and ALT to ≤ 2.5 × ULN prior to each dose (see Table 3, Section 4.4 Special warnings and precautions for use, and Section 5.2 Pharmacokinetic properties).

Use in patients with renal impairment

No adjustment to dose of MYLOTARG is required in patients with mild to moderate renal impairment. MYLOTARG has not been studied in patients with severe renal impairment. MYLOTARG does not undergo renal clearance, the pharmacokinetics in patients with severe renal impairment is unknown (see section 5.2 Pharmacokinetic properties)

Elderly patients

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

Paediatric population

The safety and efficacy of MYLOTARG in combination with chemotherapy in the paediatric population (<15 years) with newly-diagnosed AML have not been established. Currently available data are described in Section 4.8 Adverse effects (undesirable effects), Section 5.1 Pharmacodynamic properties, and Section 5.2 Pharmacokinetic properties, but no recommendation on a posology can be made.

Instructions for use and handling

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

Reconstitution

- Calculate the dose (mg) of MYLOTARG required.
- Prior to reconstitution, allow the vial to reach room temperature (below 25°C) for approximately 5 minutes. Reconstitute each 5 mg vial with 5 mL of water for injections to obtain a single-use solution of 1 mg/mL of gemtuzumab ozogamicin.
- Gently swirl the vial to aid dissolution. Do not shake.
- Inspect the reconstituted solution for particulates and discolouration. The reconstituted solution may contain small white to off-white, opaque to translucent, and amorphous to fibre-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 6 hours in a refrigerator (2°C - 8°C) with not more than 3 hours at room temperature (below 25°C). Protect from light and do not freeze.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial using a syringe. MYLOTARG vials contain 5 mg of drug product with no overfill. When reconstituted to a 1 mg/mL concentration as directed, the extractable content of the vial is 4.5 mg (4.5 mL). Protect from light. Product is for single use in one patient only. Discard any residue.
- 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 can be stored up to 18 hours from the start of reconstitution, with no more than 6 hours at room temperature (below 25°C) and the remainder in a refrigerator (2°C-8°C). MYLOTARG solution is administered over 2 hours, and the infusion must be completed prior to the end of the 6 hour room temperature storage period. The diluted solution must be protected from light for the duration of the storage period. Do not freeze.
- It is recommended that the infusion container be made of polyvinyl chloride (PVC) with DEHP, 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 syringe must be protected from light (including ultraviolet light) using a light blocking cover. The infusion line does not need to be protected from light.
- Infuse the diluted solution for 2 hours. Infusion lines made of PVC (DEHP- or non DEHP-containing), or polyethylene are recommended.
- The total in-use period for MYLOTARG should not exceed 18 hours from the start of reconstitution through completion of administration.

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

For information on dilution, storage, and infusion, see Section 6.4 Special precautions for storage.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Hepatotoxicity, including life-threatening, and sometimes fatal hepatic VOD/SOS events, was reported (see Section 4.8 Adverse effects (undesirable effects)).

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 haematopoietic 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 section 4.8 Adverse effects (undesirable effects)).

Death from liver failure and from VOD/SOS have been reported in patients who received MYLOTARG. Due to the risk of VOD/SOS, monitor closely for signs and symptoms of VOD/SOS; these may include elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase, which should be monitored prior to each dose of MYLOTARG, hepatomegaly (which may be painful), rapid weight gain, and ascites. Monitoring only total bilirubin may not identify all patients at risk of VOD/SOS. For patients who develop abnormal liver tests, more frequent monitoring of liver tests and clinical signs, and symptoms of hepatotoxicity is recommended for patients who proceed to HSCT. Close monitoring of liver tests is recommended during the post-HSCT period, as appropriate. No definitive relationship was found between VOD/SOS and time of HSCT relative to higher MYLOTARG monotherapy doses, however, the ALFA-0701 study recommended an interval of 2 months between the last dose of MYLOTARG and HSCT.

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

Infusion related reactions (including anaphylaxis)

In clinical studies with MYLOTARG, infusion related reactions, including anaphylaxis were reported (see Section 4.8 Adverse effects (undesirable effects)). There have been reports of fatal infusion reactions in the postmarketing setting. Signs and symptoms of infusion related reactions may include fever and chills, and less frequently hypotension, tachycardia, and respiratory symptoms that may occur during the first 24 hours after administration. Perform infusion of MYLOTARG under close clinical monitoring, including pulse, blood pressure, and temperature. Premedication with a corticosteroid, antihistamine, and acetaminophen (or

paracetamol) is recommended 1 hour prior to MYLOTARG dosing (see Section 4.2 Dose and method of administration). Interrupt infusion immediately for patients who develop evidence of severe reactions, especially dyspnea, bronchospasm, or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of MYLOTARG treatment should be strongly considered for patients who develop signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension (see Section 4.2 Dose and method of administration).

Myelosuppression

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

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

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

Tumour lysis syndrome (TLS)

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

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 tumour lysis-related hyperuricaemia such as hydration, administration of antihyperuricaemic (e.g., allopurinol) or other agents for treatment of hyperuricaemia (e.g., rasburicase) must be taken.

Use in AML with adverse-risk cytogenetics

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

Use in the elderly

See Section 4.2 Dose and method of administration, and Section 5.2 Pharmacokinetic properties.

Paediatric use

See Section 4.2 Dose and method of administration, and Section 5.2 Pharmacokinetic properties.

Effects on laboratory tests

No formal drug-laboratory interaction studies have been conducted with MYLOTARG.

4.5 Interactions with other medicines and other forms of interactions

No clinical drug interaction studies have been performed with MYLOTARG.

Effect of other drugs on gemtuzumab ozogamicin

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

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

Effect of MYLOTARG 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 co-administered chemotherapeutic agents

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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Marked impairment of male fertility was observed in rats at all dose levels of gemtuzumab ozogamicin tested (≥ 0.12 mg/m^2/day intravenously), associated with decreased sperm count, reduced sperm motility and increased abnormal sperm. Effects were more severe 9 weeks post-treatment compared to immediately after the end of treatment, related to damage to spermatogonia and spermatocytes during dosing and the time-course for spermatogenesis, but there was evidence of reversibility. Toxicity to the male reproductive tract was observed with gemtuzumab ozogamicin in rats and monkeys with no NOAEL established. Findings included degeneration of seminiferous tubules in the testis; luminal cellular debris, oligospermia and epithelial degeration in the epididymis; and atrophy, duct ectasia, and sperm stasis in the seminal vesicle.

In female rats, the incidence of pregnancy was unaffected following treatment with gemtuzumab ozogamicin at intravenous doses up to 1.08 mg/m^2/day. However, slightly lower numbers of corpora lutea were observed at 1.08 mg/m^2/day and embryolethality occurred at ≥ 0.36 mg/m^2/day (99 and 32 times the exposure of patients after the third 3 mg /m^2 dose, based on plasma AUC) in the presence of maternotoxicity. Adverse effects on the female reproductive tract (atrophy in the ovary, oviduct, uterus and cervix) with the potential to disrupt normal menstrual cycling were observed in monkeys treated at ≥6.6 mg/m^2/week for 12 weeks. Dosing at 2.2 mg/m^2/week (67 times the exposure in patients) did not adversely affect reproductive tissues in female monkeys.

Use in pregnancy – Pregnancy Category D

There are no or very limited data for the use of gemtuzumab ozogamicin in pregnant women.

Gemtuzumab ozogamicin caused embryofetal lethality (increased post-implantation loss and decreased live litter size) and malformations (missing or shortened digits, absent aortic arch, misshapen or shortened forelimb long bones, misshapen scapula, absent vertebral centrum and fused sternebrae) with daily intravenous administration at 0.36 mg/m^2/day in pregnant rats. At 0.15 mg/m^2/day fetal weight was reduced, the incidence of wavy ribs was increased and ossification was impaired. The findings occurred at maternotoxic doses but may reflect direct toxicity to the embryo/fetus. No adverse effects on embryofetal development were observed in the rat at 0.06 mg/m^2/day (approximately 4 times the exposure in patients after the third 3 mg/m^2 dose, based on plasma AUC.)

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

Women of childbearing potential, or partners of females of childbearing potential should be advised to use effective contraception during treatment with MYLOTARG for at least 7 months (females) or 4 months (males) after the last dose.

Use in lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Summary of the safety profile

The overall safety profile of MYLOTARG is based on data from patients with acute myeloid leukaemia 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 consisted of all grades haemorrhages, all grades VOD, and severe infections. All of these TEAEs were determined to be adverse drug reactions. Because of this limited data collection, laboratory data from the combination therapy study are included in Table 4. Information about adverse drug reactions from monotherapy studies and post-marketing experience is presented Table 5 in order to provide full characterisation of adverse reactions.

In the combination therapy study ALFA-0701, clinically relevant serious adverse reactions were hepatotoxicity, including VOD/SOS (3.8%), haemorrhage (9.9%), severe infection (41.2%), and TLS (1.5%). In monotherapy studies, clinically relevant serious adverse reactions also included infusion related reactions (2.5%), thrombocytopenia (21.7%), and neutropenia (34.3%).

The most common adverse reactions (>30%) in the combination therapy study were haemorrhage and infection. 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 the combination therapy study were thrombocytopenia, VOD, haemorrhage and infection. The most frequent (≥1%) adverse reactions that led to permanent discontinuation in monotherapy studies were infection, haemorrhage, multi-organ failure, and VOD.

Tabulated list of adverse reactions

Tables 4 and 5 show the adverse reactions reported in patients with previously untreated *de novo* AML who received MYLOTARG in a combination study and in patients with AML who received MYLOTARG in monotherapy studies, respectively.

The adverse reactions are presented by system organ class (SOC) and frequency categories, defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4. Selected[**] adverse reactions in patients who received MYLOTARG incombination therapy study (ALFA-0701)

System organ class ***Frequency***	**MYLOTARG + daunorubicin + cytarabine (N=131)**		**daunorubicin + cytarabine (N=137)**	
Preferred term	**All grades %**	**Grade 3/4 %**	**All grades %**	**Grade 3/4 %**
Infections and infestations				
Very common				
Infection[*a]	77.9	76.3	77.4	74.4
Vascular disorders				
Very common				
Haemorrhage[*b]	90.1	20.6	78.1	8.8
Hepatobiliary disorders				
Common				
Venoocclusive liver disease[*c]	4.6	2.3	1.5	1.5
Investigations [***]				
Very common				
Haemoglobin decreased	100	86.2	100	89.7
Platelets decreased	100	100	100	100
White blood cells decreased	100	100	99.3	99.3
Lymphocytes (absolute) decreased	98.5	90.7	97.8	89.6
Neutrophils decreased	97.7	96.1	98.5	97.0
Hyperglycaemia	92.0	19.2	91.1	17.8
Aspartate aminotransferase (AST) increased	89.2	14.0	73.9	9.0
Prothrombin time increased	84.8	3.3	89.1	0
Activated partial thromboplastin time prolonged	80.0	6.4	57.5	5.5
Alkaline phosphatase increased	79.7	13.3	68.9	5.3

Alanine aminotransferase (ALT) increased	78.3	10.9	81.3	15.7
Blood bilirubin increased	51.6	7.1	50.8	3.8
Hyperuricaemia	32.5	2.6	28.5	0

Abbreviations: N=number of patients; PT=preferred term.

* Including fatal outcome.

** Only selected safety data were collected in this study of newly diagnosed AML.

*** Frequency is based on laboratory values (Grade per NCI CTCAE v4.03).

a. 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 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*.

Table 5. Adverse reactions in patients who received MYLOTARG in monotherapy*** studies and post-marketing

System organ class ***Frequency*** **Preferred term**	**All grades** **%**	**Grade 3/4** **%**
Infections and infestations		
Very common		
Infection*[a]	68.2	32.8
Blood and lymphatic system disorders		
Very common		
Febrile neutropenia	19.1	11.6
Thrombocytopenia[b]	48.4	48.0
Neutropenia[c]	30.3	29.2
Anaemia[d]	27.1	24.2
Leukopenia[e]	26.7	26.7
Common		
Pancytopenia[f]	5.0	4.3
Lymphopenia[g]	3.6	3.2
Immune system disorders		
Common		
Infusion related reaction[h]	7.6	3.6
Metabolism and nutrition disorders		
Very common		
Hyperglycaemia[i]	11.2	6.9
Decreased appetite	27.1	6.1
Common		
Tumour lysis syndrome**	2.5	1.8
Nervous system disorders		
Very common		
Headache	38.3	12.3
Cardiac disorders		
Very common		

Tachycardia[j]	13.0	4.3
Vascular disorders		
Very common		
Haemorrhage[*k]	67.1	23.8
Hypotension[l]	20.2	14.8
Hypertension[m]	17.3	10.5
Respiratory, thoracic and mediastinal disorders		
Very common		
Dyspnoea[n]	27.4	12.6
Unknown		
Interstitial pneumonia[*]		
Gastrointestinal disorders		
Very common		
Vomiting	60.6	33.6
Diarrhoea	33.9	14.8
Abdominal pain[o]	33.2	7.2
Nausea	71.1	39.3
Stomatitis[p]	36.1	12.3
Constipation	25.3	5.0
Common		
Ascites	2.9	0.4
Dyspepsia	8.7	1.1
Oesophagitis	1.8	0.7
Unknown		
Neutropenic colitis[*]		
Hepatobiliary disorders		
Very common		
Transaminases increased[q]	24.5	18.8
Hyperbilirubinaemia[r]	13.0	10.5
Common		
Venoocclusive liver disease[*s]	2.9	1.1
Hepatomegaly	2.5	0.7
Jaundice	2.2	1.1
Hepatic function abnormal[t]	2.5	1.4
Gamma-glutamyltransferase increased	1.8	0.7
Uncommon		
Hepatic failure[*#]	0.4	0.4
Budd-Chiari syndrome[#]	0.4	0.4
Skin and subcutaneous tissue disorders		
Very common		
Rash[u]	19.9	5.8
Common		
Erythema[v]	9.4	2.2
Pruritus	5.4	0.4
Renal and urinary disorders		
Unknown		
Haemorrhagic cystitis[*]		

General disorders and administration site conditions		
Very common		
Pyrexia[w]	82.7	52.3
Oedema[x]	21.3	3.2
Fatigue[y]	41.2	11.2
Chills	67.9	17.3
Common		
Multi-organ failure[*]	2.2	0.7
Investigations		
Very common		
Blood lactate dehydrogenase increased	16.6	7.2
Common		
Blood alkaline phosphate increased	8.7	6.1

[*] Including fatal outcome.

[**] Including fatal adverse reactions in the post-marketing setting.

[***] MYLOTARG in the treatment of relapsed AML (9 mg/m^2).

Singular cases.

Abbreviation: PT=preferred term.

a. Infection includes Sepsis and Bacteraemia (25.6%), Fungal infection (10.5%), Lower respiratory tract infection (13.0%), Upper respiratory tract infection (4.3%), Bacterial infection (3.6%), Viral infection (24.2%), Gastrointestinal infection (3.3%), Skin infection (7.9%), and Other infections (19.5%). Post-marketing (frequency category unknown) fungal lung infections including Pulmonary mycosis and Pneumocystis jirovecii pneumonia*; and bacterial infections including Stenotrophomonas infection were also reported.

b. Thrombocytopenia includes the following reported PTs: Platelet count decreased and Thrombocytopenia*.

c. Neutropenia includes the following reported PTs: Neutropenia, Granulocytopenia and Neutrophil count decreased.

d. Anaemia includes the following reported PTs: Anaemia and Haemoglobin decreased.

e. Leukopenia includes the following reported PTs: Leukopenia and White blood cell count decreased.

f. Pancytopenia includes the following reported PTs: Pancytopenia and Bone marrow failure.

g. Lymphopenia includes the following reported PTs: Lymphopenia and Lymphocyte count decreased.

h. Infusion related reaction includes the following reported PTs: Infusion related reaction, Urticaria, Hypersensitivity, Bronchospasm, Drug hypersensitivity, and Injection site urticaria#.

i. Hyperglycaemia includes the following reported PTs: Hyperglycaemia and Blood glucose increased#.

j. Tachycardia includes the following reported PTs: Tachycardia, Sinus tachycardia, Heart rate increased#, and Supraventricular tachycardia#.

k. Haemorrhages include Central nervous system haemorrhage (5.1%), Upper gastrointestinal haemorrhage (21.3%), Lower gastrointestinal haemorrhage (15.2%), Subcutaneous haemorrhage (28.5%), Other haemorrhage (32.9%), and Epistaxis (28.5%).

l. Hypotension includes the following reported PTs: Hypotension and Blood pressure decreased.

m. Hypertension includes the following reported PTs: Hypertension and Blood pressure increased.

n. Dyspnoea includes the following reported PTs: Dyspnoea and Dyspnoea exertional.

o. Abdominal pain includes the following reported PTs: Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal discomfort, and Abdominal tenderness.

p. Stomatitis includes the following reported PTs: Mucosal inflammation, Oropharyngeal pain, Stomatitis, Mouth ulceration, Oral pain, Oral mucosal blistering, Aphthous stomatitis, Tongue ulceration, Glossodynia, Oral mucosal erythema, Glossitis#, and Oropharyngeal blistering#.

q. Transaminases increased includes the following reported PTs: Transaminases increased, Hepatocellular injury, Alanine aminotransferase increased, Aspartate aminotransferase increased, and Hepatic enzyme increased.

r. Hyperbilirubinaemia includes the following reported PTs: Blood bilirubin increased and Hyperbilirubinaemia.

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

t. Hepatic function abnormal includes the following reported PTs: Liver function test abnormal and Hepatic function abnormal.

u. Rash includes the following reported PTs: Rash, Dermatitis#, Dermatitis allergic#, Dermatitis bullous, Dermatitis contact, Dermatitis exfoliative#, Drug eruption, Pruritus allergic# and Rash erythematous#, Rash macular#, Rash maculo papular, Rash papular, Rash pruritic, Rash vesicular#.

v. Erythema includes the following reported PTs: Catheter site erythema, Erythema and Infusion site erythema#.

w. Pyrexia includes the following reported PTs: Pyrexia, Body temperature increased, and Hyperthermia.

x. Oedema includes the following reported PTs: Oedema, Face oedema, Oedema peripheral, Swelling face, Generalised oedema, and Periorbital oedema.

y. Fatigue includes the following reported PTs: Fatigue, Asthenia, Lethargy, and Malaise.

Description of selected adverse drug reactions

Hepatotoxicity, including hepatic VOD/SOS

In the combination therapy study, VOD and hepatic laboratory abnormalities were collected. Additional characterisation of hepatotoxicity adverse reactions is provided from the monotherapy studies.

In the combination therapy study (N=131), VOD was reported in 6 (4.6%) patients during or following treatment, 2 (1.5%) of these reactions were fatal (see Table 4). Five (3.8%) of these VOD reactions occurred within 28 days of any dose of gemtuzumab ozogamicin. One VOD event occurred more than 28 days of last dose of gemtuzumab ozogamicin; with 1 of these events occurring a few days after having started an HSCT conditioning regimen. The median time from the last gemtuzumab ozogamicin 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 gemtuzumab ozogamicin. One of these patients experienced VOD 25 days after the subsequent HSCT.

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 as recommended in Section 4.4 Special warnings and precautions for use. Management of signs or symptoms of hepatic toxicity may require a dose interruption, or discontinuation of MYLOTARG (see Section 4.2 Dose and method of administration).

Myelosuppression

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

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

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

During the induction phase, 121 (92.4%) and 118 (90.1%) patients had a documented neutrophil recovery to ANC of 500/mm^3 and 1,000/mm^3, respectively. The median time to neutrophil recovery to ANC of 500/mm^3 and 1,000/mm^3 was 25 days. In the consolidation 1 phase of therapy, 94 (96.9%) patients had neutrophil recovery to counts of 500/mm^3, and 91 (94%) patients recovered to counts of 1,000/mm^3. The median times to neutrophil recovery to ANC of 500/mm^3 and 1,000/mm^3 were 21 and 25 days, respectively. In the consolidation 2 phase of therapy, 80 (97.6%) patients had neutrophil recovery to counts of 500/mm^3, and 79 (96.3%) patients recovered to counts of 1,000/mm^3. The median times to neutrophil recovery to ANC of 500/mm^3 and 1,000/mm^3 were 22 and 27 days, respectively.

In the combination therapy study, in patients with *de novo* AML treated with fractionated doses of gemtuzumab ozogamicin in combination with chemotherapy (N=131), 102 (77.9%) patients experienced all causality severe (Grade ≥ 3) infections. Treatment-related death due to septic shock was reported in 1 (0.8%) patients. Fatal severe infection was reported in 2 (1.53%) patients in the MYLOTARG arm and 4 (2.92%) patients in the control arm.

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

Management of patients with severe infection, bleeding/haemorrhage, or other effects of myelosuppression, including severe neutropenia or persistent thrombocytopenia, may require

a dose delay or permanent discontinuation of MYLOTARG (see Section 4.2 Dose and method of administration, and Section 4.4 Special warnings and precautions for use).

Immunogenicity

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 ADAs.

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 gemtuzumab ozogamicin concentrations, sample handling, timing of sample collection, concomitant treatments, and underlying disease. For these reasons, comparison of incidence of antibodies to gemtuzumab ozogamicin with the incidence of antibodies to other products may be misleading.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Paediatric population

The safety and efficacy of MYLOTARG in children and adolescents below the age of 15 years has not been established (see Section 4.2 Dose and method of administration).

In the completed randomised paediatric Phase 3 Children's Oncology Group (COG) Study AAML0531 (see Section 5.1 Pharmacodynamic properties) of gemtuzumab ozogamicin combined with intensive first-line therapy in 1,063 newly diagnosed children (93.7% of patients < 18 years of age), and young adults (6.3% of patients) with *de novo* AML aged 0 to 29 years, the safety profile was similar with that observed in the other studies of gemtuzumab ozogamicin combined with intensive chemotherapy in adult patients with *de novo* AML. However, the optimal dose of gemtuzumab ozogamicin for paediatric patients was not established, since in Study AAML0531 during the second intensification period after the second dose of gemtuzumab ozogamicin, a larger proportion of patients in the gemtuzumab ozogamicin arm experienced prolonged neutrophil recovery time (> 59 days) as compared with the comparator arm (21.0% versus 11.5%), and more patients died during remission (5.5% versus 2.8%).

4.9 Overdose

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Gemtuzumab ozogamicin is a CD33-directed ADC. Gemtuzumab is a humanised immunoglobulin class G subtype 4 (IgG4) antibody which specifically recognizes human CD33. The antibody portion (hP67.6) binds specifically to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of myeloid leukaemic blasts and immature normal cells of myelomonocytic lineage, but not on normal haematopoietic stem cells. The small molecule, N-acetyl gamma calicheamicin, is a cytotoxic semisynthetic natural product. N-acetyl gamma calicheamicin is covalently attached to the antibody via an AcBut (4-(4'-acetylphenoxy) butanoic acid linker. Nonclinical data suggest that the anticancer activity of gemtuzumab ozogamicin is due to the binding of the ADC to CD33-expressing tumour 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.

Pharmacodynamic (PD) effects

In vitro cytotoxicity assays showed that gemtuzumab ozogamicin was effective at selectively killing CD33-positive human leukaemia cell line (HL-60) target cells. In nonclinical murine models, gemtuzumab ozogamicin demonstrates antitumour effects in the HL-60 human promyelocytic leukaemia xenograft tumour in athymic mice. Combining DNR and AraC chemotherapy with gemtuzumab ozogamicin was effective in eliminating disease and prolonging survival in nonclinical AML models, with synergistic activity evident.

Saturation of a high percentage of CD33 antigenic sites is presumed to be required for maximum delivery of calicheamicin to leukaemic blast cells. Several single agent studies measured target (CD33) saturation post-MYLOTARG dose in patients with relapsed and refractory AML. Across all studies, near maximal peripheral CD33 saturation was observed post-MYLOTARG dose at all dose levels of 2 mg/m² and above, suggesting that a low dose of gemtuzumab ozogamicin is sufficient to bind all available CD33 sites.

Clinical trials

In a Phase 3 trial (ALFA-0701) the combination of MYLOTARG + AraC + DNR was compared to AraC + DNR. Combination therapy with MYLOTARG + chemotherapy resulted in a statistically significant improvement in Event-Free Survival (EFS) compared to the chemotherapy combination alone. There was no significant improvement in rates of Overall Survival (OS) or CR demonstrated in MYLOTARG combination therapy compared to the chemotherapy combination alone.

ALFA-0701 study of previously untreated patients with de novo AML

The efficacy and safety of MYLOTARG were evaluated in a multicenter, randomized, open-label, Phase 3 study comparing the addition of MYLOTARG to a standard chemotherapy induction regimen of daunorubicin and cytarabine (DA) versus DA alone. Eligible patients were between 50 and 70 years of age with previously untreated *de novo* AML. Patients with acute promyelocytic leukaemia (APL, AML3) and patients with AML arising from myelodysplastic syndrome (MDS) or secondary AML were excluded from the study.

Patients were randomized (1:1) to receive induction therapy consisting of DNR (60 mg/m^2 on Days 1 to 3) and AraC (200 mg/m^2 on Days 1 to 7) (DA) with (N=135) or without (N=136) MYLOTARG 3 mg/m^2 (up to maximum of one vial) on Days 1, 4, and 7. Patients who did not achieve a response after first induction could receive a second induction with DNR and AraC alone, consisting of 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 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 randomisation. 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 EFS. The secondary endpoints included CR and CRp rates, Relapse-Free Survival (RFS), OS, and safety of the combination DA with or without MYLOTARG.

EFS was measured from randomisation to induction failure, relapse, or death due to any cause. Per protocol, induction failure was defined as failure to achieve CR or CRp in induction, and date of induction failure was defined as date of marrow evaluation after the last course of induction. Remission was assessed by the investigators and classified as CR defined as fewer than 5% blasts in a normocellular marrow and an ANC of more than 1×10^9 /L with a platelet count of more than 100×10^9 /L in the peripheral blood in the absence of transfusion; and CRp, defined as CR with residual thrombocytopenia (platelets ≤100 x 10^9/L).

In total, 271 patients were randomized in this study with 135 to induction treatment of 3+7 DA plus fractionated 3 mg/m^2 × 3 doses of MYLOTARG and 136 to 3+7 DA alone (see Section 4.2 Dose and method of administration). A second course of induction therapy with DA but without MYLOTARG, regardless of the randomisation arm, was allowed. Patients in either arm who did not receive the second course of induction therapy and did not achieve a

CR after induction could receive a salvage course comprised of idarubicin, AraC and granulocyte colony-stimulating factor (G-CSF).

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

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

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

The trial met its primary objective of demonstrating that MYLOTARG added in fractionated doses (3 mg/m^2 × 3) to standard induction chemotherapy for patients with previously untreated *de novo* AML resulted in a statistically significant and clinically meaningful improvement in EFS. Median EFS was 17.3 months (95% confidence interval [CI]: 13.4-30.0) in the MYLOTARG arm versus 9.5 months (95% CI: 8.1-12.0) in the DA alone arm; hazard ratio (HR) 0.562 (95% CI: 0.415-0.762); 2-sided p=0.0002 by log-rank test. EFS results derived from investigator assessment are summarized in Table 6, and the Kaplan-Meier plot is shown in Figure 1.

Table 6. Efficacy results from study ALFA-0701 (mITT population)

	MYLOTARG + Daunorubicin + Cytarabine	**Daunorubicin + Cytarabine**
Event-Free Survival (by Investigator)	**(N=135)**	**(N=136)**
Number of events, n (%)	73 (54.1)	102 (75.0)
Median EFS in months [95% CI][a]	17.3 [13.4, 30.0]	9.5 [8.1, 12.0]
2-year EFS probability [95% CI][b]	42.1 [32.9, 51.0]	18.2 [11.1, 26.7]
3-year EFS probability [95% CI][b]	39.8 [30.2, 49.3]	13.6 [5.8, 24.8]
Hazard ratio [95% CI][c]	0.562 [0.415, 0.762]	
p-value[d]	0.0002	

Table 6. Efficacy results from study ALFA-0701 (mITT population)

	MYLOTARG + Daunorubicin + Cytarabine	**Daunorubicin + Cytarabine**
Relapse-free survival (by Investigator)	**N=110**	**N=100**
Number of events, n (%)	49 (44.5)	66 (66.0)
Median RFS in months [95% CI][a]	28.0 [16.3, NE]	11.4 [10.0, 14.4]
Hazard ratio [95% CI][c]	0.526 [0.362, 0.764]	
p-value[d]	0.0006	
Overall survival	**N=135**	**N=136**
Number of deaths, n (%)	80 (59.3)	88 (64.7)
Median OS in months [95% CI][a]	27.5 [21.4, 45.6]	21.8 [15.5, 27.4]
Hazard ratio [95% CI][c]	0.807 [0.596, 1.093]	
p-value[d]	0.1646	
Response rate (by Investigator)	**N=135**	**N=136**
Overall response % [95% CI][e]	81.5 [73.89, 87.64]	73.5 [65.28, 80.72]
CR	70.4	69.9
CRp	11.1	3.7
Risk difference [95% CI][f]	7.95[-3.79, 19.85]	
p-value[g]	0.1457	

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

The mITT population included all patients who were randomised, unless withdrawal of consent prior to start of treatment and were analysed according to initial randomisation arm.

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

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

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

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

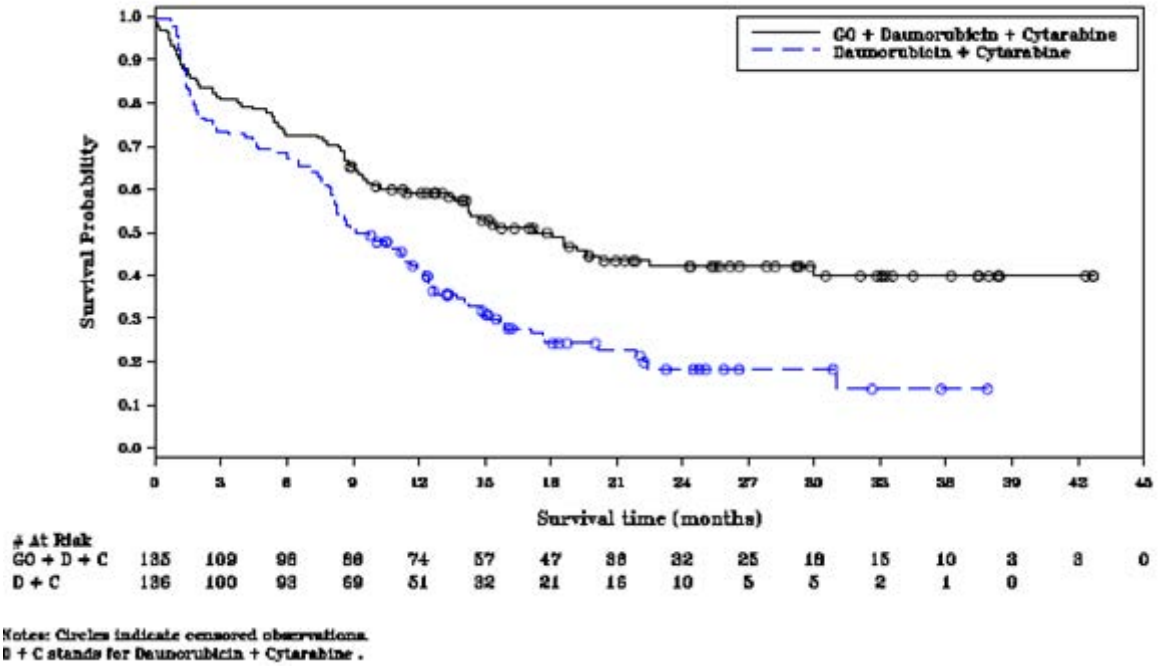
d. 2-sided p-value from the log-rank test.

e. Response defined as CR+CRp.

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

g. Based on Fisher's exact test.

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



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

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

Use in AML with adverse-risk cytogenetics

In subgroup analyses in ALFA-0701, the addition of MYLOTARG to standard combination chemotherapy did not improve EFS in the subgroup of patients having adverse-risk cytogenetics (HR 1.11; 95% CI: 0.63, 1.95). EFS and OS analyzed by cytogenetic risk classification and cytogenetic/molecular risk classification are presented in Table 7 and Table 8.

Table 7. Event-Free Survival by AML Risk Classifications (mITT Population)

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

Table 7. Event-Free Survival by AML Risk Classifications (mITT Population)

	MYLOTARG + Daunorubicin + Cytarabine	**Daunorubicin + Cytarabine**
ELN (Favourable/Intermediate), n	**86**	**91**
Number of events, n (%)	40 (46.5)	63 (69.2)
Median EFS in months [95% CI][a,b]	22.5 [15.5, NE]	12.2 [8.5, 14.3]
Hazard ratio[c] [95% CI]	0.485 [0.325, 0.724]	
p-value[d]	0.0003	
ELN (Poor/Adverse), n	**37**	**36**
Number of events, n (%)	27 (73.0)	32 (88.9)
Median EFS in months [95% CI][a,b]	7.4 [3.7, 14.3]	4.0 [1.7, 8.6]
Hazard ratio[c] [95% CI]	0.720 [0.430, 1.205]	
p-value[d]	0.2091	

Method (A1): Event date determined by investigator assessment

The modified intent-to-treat (mITT) population included all patients who were randomized, unless withdrawal of consent prior to start of treatment and were analysed according to initial randomisation arm;

Abbreviations: AML=acute myeloid leukaemia; CI=confidence interval; EFS=event-free survival; ELN=European LeukemiaNet; KM=Kaplan-Meier; mITT=modified intent-to-treat; n=number; N=number; NE=not estimable.

a. Based on the Brookmeyer and Crowley Method with log-log transformation.

b. Estimated from the KM curve.

c. Based on the Cox Proportional Hazards Model.

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

Table 8. Overall Survival by AML Risk Classifications from Study ALFA-0701 (mITT Population)

	MYLOTARG + Daunorubicin + Cytarabine	Daunorubicin + Cytarabine
Cytogenetics (favourable/intermediate), N	**94**	**95**
Number of deaths, n (%)	51 (54.3)	57 (60.0)
Median OS in months [95% CI][a]	38.6 [24.4, NE]	26.0 [18.9, 39.7]
Hazard ratio [95% CI]	0.747 [0.511, 1.091]	
p-value[c]	0.1288	
Cytogenetics (unfavourable), N	**27**	**30**
Number of deaths, n (%)	24 (88.9)	24 (80.0)
Median OS in months [95% CI][a]	12.0 [4.2, 14.2]	13.5 [9.4, 27.3]
Hazard ratio [95% CI]	1.553 [0.878, 2.748]	
p-value[c]	0.1267	
ELN (favourable/intermediate), N	**86**	**91**
Number of deaths, n (%)	44 (51.2)	53 (58.2)
Median OS in months [95% CI][a]	45.6 [25.5, NE]	26.9 [19.3, 46.5]
Hazard ratio [95% CI]	0.730 [0.489, 1.089]	
p-value[c]	0.1216	
ELN (poor/adverse), N	**37**	**36**
Number of deaths, n (%)	31 (83.8)	29 (80.6)
Median OS in months [95% CI][a]	13.2 [7.0, 18.5]	13.5 [10.8, 19.8]
Hazard ratio [95% CI]	1.124 [0.677, 1.867]	
p-value[c]	0.6487	

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

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

Paediatric population

Paediatric study

In a randomised study (COG AAML0531) that evaluated standard chemotherapy alone or combined with MYLOTARG in 1,063 newly diagnosed children with AML (93.7% of patients < 18 years of age), and young adults (6.3% of patients); mean age was 8.9 years (range: 0-29 years), patients with *de novo* AML were randomly assigned to either standard 5-course chemotherapy alone or to the same chemotherapy with 2 doses of MYLOTARG (3 mg/m^2 /dose) administered once in induction Course 1 and once in intensification Course 2. The study showed that addition of MYLOTARG to intensive chemotherapy improved EFS (3 years: 50.6% versus 44.0%; HR 0.838; 95% CI: 0.706, 0.995; p=0.0431) in *de novo* AML owing to a reduced relapse risk, with a trend towards longer OS in the MYLOTARG arm which was not statistically significant (3 years: 72.4% versus 67.6%; HR 0.904; 95% CI: 0.721, 1.133; p=0.3799). However, it was also found that increased toxicity (post-remission toxic mortality) was observed in patients with low-risk AML which was attributed to the

prolonged neutropenia that occurred after receiving gemtuzumab ozogamicin during intensification Course 2 (see Section 4.2 Dose and method of administration, and Section 4.8 Adverse effects (undesirable effects)). Overall, 29 (5.5%) of patients in the MYLOTARG arm and 15 (2.8%) patients in the comparator arm died during remission. Thus, the optimal dose of gemtuzumab ozogamicin for paediatric patients was not established (see Section 4.2 Dose and method of administration).

Cardiac electrophysiology

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

5.2 Pharmacokinetic properties

Gemtuzumab ozogamicin is an ADC composed of CD33-directed monoclonal antibody (hP67.6) that is covalently linked to the cytotoxic agent N-acetyl-gamma calicheamicin. The pharmacokinetics (PK) of gemtuzumab ozogamicin is described by measuring PK characteristics of the antibody (hP67.6) as well as total and unconjugated calicheamicin derivatives. Given that the hP67.6 portion renders target selectivity on the intact molecule, and that MYLOTARG dosages are reported in terms of milligrams of protein (hP67.6), the hP67.6 concentration results are reported as the primary PK measures. After gemtuzumab ozogamicin binds to CD-33 it is internalised and N-acetyl calicheamicin is released by hydrolytic cleavage. Determination of PK parameters for unconjugated calicheamicin was limited due to the low systemic concentration levels.

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

Distribution

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

Excretion

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

Pharmacokinetics in specific groups of subjects or patients

Age, race, and gender

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

Hepatic impairment

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

Based on a population PK analysis, the clearance of gemtuzumab ozogamicin (hP67.6 antibody and unconjugated calicheamicin) is not expected to be affected by mild 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) (see Section 4.2 Dose and method of administration). The PK of gemtuzumab ozogamicin has not been studied in patients with severe hepatic impairment (see Section 4.2 Dose and method of administration).

Renal impairment

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

Based on population PK analysis in 406 patients, the clearance of gemtuzumab ozogamicin in patients with mild renal impairment (creatinine clearance [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 (CLcr 15-29 mL/min; n=1).

Geriatric use

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

Paediatric use

The results of the population modelling showed that the PK behaviour of gemtuzumab ozogamicin (hP67.6 antibody and unconjugated calicheamicin) is similar between adult and paediatric AML patients following the 9 mg/m^2 dosing regimen.

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

Formal carcinogenicity studies have not been conducted with gemtuzumab ozogamicin. After 6 weeks of administration of gemtuzumab ozogamicin to rats, preneoplastic lesions (minimal to slight oval cell hyperplasia) were observed in the liver at 7.2 mg/m^2/week (approximately 54 times the exposure in patientsafter the third 3 mg/m^2 dose based on plasma AUC_{168}). Preneoplastic and neoplastic lesions have been observed in the livers of rats with other antibody-calicheamicin conjugates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextran 40
Dibasic sodium phosphate
Monobasic sodium phosphate monohydrate
Sodium chloride
Sucrose

6.2 Incompatibilities

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

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Unopened vials

Store at 2°C to 8°C (Refrigerate. Do not freeze). Store in the original carton and protect from light.

Reconstituted and diluted solution

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) from the time of initial vial puncture with not more than 6 hours at room temperature (below 25°C). This includes the time required for reconstitution, dilution, and administration.

6.5 Nature and contents of container

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

Each carton contains 1 single-dose vial containing sterile, preservative-free, white to off-white lyophilized cake or powder.

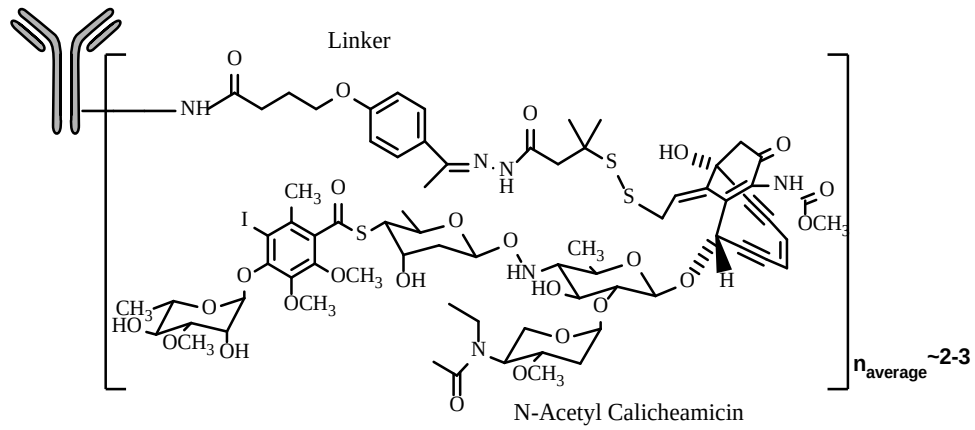
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

Gemtuzumab



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.

CAS number

220578-59-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

9 April 2020

10. DATE OF REVISION

Not applicable.

Summary Table of Changes

Section changed	Summary of new information
NA	NA