Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Gemtuzumab ozogamicin

Proprietary Product Name: Mylotarg

Sponsor: Pfizer Australia Pty Ltd

October 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
AraC	Cytarabine
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
CD33	Cluster of differentiation 33
CMI	Consumer Medicines Information
CNS	Central nervous system
CPD	Certified product details
CR	Complete remission
CRp	Complete remission with incomplete platelet recovery
CYP	Cytochrome P450
DLP	Data lock point
DMH	Dimethylhydrazide
DNR	Daunorubicin
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
EMA	European Medicines Agency
EU-RMP	European Union-risk management plan
FDA	Food and Drug Administration
GLP	Good laboratory practice
GO	Gemtuzumab ozogamicin
GOELAMS	Le Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang
HSCT	Haematopoietic stem cell transplant

Abbreviation	Meaning
Ida	Idarubicin
IgG4	Immunoglobulin G4
IPD	Individual patient data
IV	Intravenous
KM	Kaplan-Meier
NOAEL	No observed adverse event level
PI	Product information
PK	Pharmacokinetic(s)
PSUR	Periodic Safety Update Report
RMP	Risk management plan
SOS	Sinusoidal obstruction syndrome
TEAE	Treatment emergent adverse event
VOD	Veno-occlusive disease

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Active ingredient:	Gemtuzumab ozogamicin
Product name:	Mylotarg
Decision:	Approved
Date of decision:	8 April 2020
Date of entry onto ARTG:	9 April 2020
ARTG numbers:	316671
, *Black Triangle Scheme:* [1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Pfizer Australia Pty Ltd Level 17, 151 Clarence Street Sydney NSW 2000
Dose form:	Powder for injection
Strength:	5 mg
Container:	Vial
Pack size:	1
Approved therapeutic use:	*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).*
Route of administration:	Intravenous infusion

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Dosage:	Mylotarg must be reconstituted and diluted before administration. **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 x 10^9 cells/L with a platelet count of 100 x 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. For further information regarding dosage, refer to the Product Information.
Pregnancy category	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Pfizer Australia (the sponsor) to register Mylotarg (gemtuzumab ozogamicin) 5 mg powder for injection for the following proposed indication:

> *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).*

Acute myeloid leukaemia (AML) is a life-threatening illness that usually occurs in the elderly, with the average age at diagnosis being 67 years. The majority of cases (75%) occur *de novo* (cases that arise anew and are not due to other diseases or prior cancer therapy), but a significant minority (25%) are secondary to prior cytotoxic therapy.

The fundamental approach to AML treatment has changed little during the last 40 years. Standard treatment for AML is chemotherapy with a regimen including cytarabine (AraC) and an anthracycline for example, daunorubicin (DNR) or idarubicin (Ida). This is used with the intention of inducing complete remission, for which allogenic haematopoietic stem cell transplant (HSCT) can be considered. For patients who are not eligible for intensive chemotherapy (due to performance status, age and/or comorbidities), treatment options include less intensive chemotherapy, best supportive care and enrolment in clinical trials. Prognosis depends on heterogeneous genetic characteristics of AML itself, as well as age and co-morbidities. However, long term survival is 40% in the best case, and relapse often occurs within 3 years of treatment.

Gemtuzumab ozogamicin is an antibody-drug conjugate directed against cluster of differentiation 33 (CD33), comprising an immunoglobulin G4 (IgG4) binding region linked to the cytotoxin, calicheamicin. CD33 is expressed on progenitor myeloid cells and neoplastic myeloid cells present in AML. In the submission described in this AusPAR, the sponsor proposes that gemtuzumab ozogamicin meets an unmet medical need for new therapeutic options that could improve survival of patients and prevent or delay relapse of the disease in patients with previously untreated *de novo* AML.

The approved European Union (EU) indication is:

> *Mylotarg is indicated for combination therapy with daunorubicin (DNR) and cytaribine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukemia, except acute promyelocytic leukemia (APL).*

The sponsor has proposed the EU indication for Australia, except that it is 'agnostic' as to which anthracycline is to be used (that is, it does not specify DNR). The sponsor has indicated that the reason for this is that DNR is not currently publicly funded in Australia, and Ida is the more commonly used anthracycline. Hence the intention is to prevent the registered indication from precluding use with Ida for publicly-funded treatment.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

The regulatory history of gemtuzumab ozogamicin is complex. An application to the EMA for use of Mylotarg as a re-induction treatment of CD33-positive AML adult patients in first relapse was refused in 2008.[2] Mylotarg had been approved by the Food and Drug Administration (FDA) in 2000 under accelerated approval as monotherapy in patients > 60 years of age who were unsuitable candidates for chemotherapy.[3] It was subsequently

[2] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Refusal Assessment Report for Mylotarg, International Nonproprietary Name: gemtuzumab ozogamicin, Document Reference: EMEA/CHMP/5130/2008, 24 January 2008. Available from the EMA website.
[3] United States (US) Food and Drug Administration (FDA), Center for Drug Evaluation and Research, Application number: NDA 21174, Mylotarg - gemtuzumab ozogamicin, Approval letter, 17 May 2000. Available from the FDA website.

withdrawn from the market worldwide (except Japan) in 2010 when confirmatory trials submitted to the US FDA failed to demonstrate therapeutic benefit.[4,5]

At the time the TGA considered this application, similar applications (with reduced dosage and usage compared to the previous applications) had been approved in the US (1 September 2017) and EU (19 April 2018). Similar applications were also under consideration in Canada (subsequently approved on 28 November 2019), Switzerland (subsequently approved on 5 December 2019) and Hong Kong (subsequently approved 19 December 2019) during the review period.

Table 1: International regulatory status of Mylotarg (as of March 2020)

Region	Submission date	Status	Approved indications
United States	2 November 2016	Approved on 1 September 2017	*Mylotarg is a CD33-directed antibody-drug conjugate indicated for:* *treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults.* *treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older.*
European Union – Centralised Procedure	1 December 2016	Approved on 19 April 2018	*Mylotarg is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33 positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).*
Switzerland	1 June 2018	Approved on 5 December 2019	*Mylotarg 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 (APL) (see "Warnings and precautions" and "Clinical efficacy".*
Canada	14 December 2018	Approved on 28 November 2019	*Mylotarg is indicated for combination therapy with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia, except acute promyelocytic leukemia.*
Hong Kong	30 April 2019	Approved on 19 December 2019	*Mylotarg is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).*

[4] Withdrawal of Mylotarg is discussed in the background of the following FDA report. FDA, Center for Drug Evaluation and Research, Application numbers: 761060Orig1s000 and 761060Orig2s000, Mylotarg - gemtuzumab ozogamicin, Summary Review, 31 August 2017. Available from the FDA website.
[5] Subsequently published as: Petersdorf el al (2013). A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia, *Blood*; 121(24): 4854–4860.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-01426-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	13 June 2019
First round evaluation completed	29 November 2019
Sponsor provides responses on questions raised in first round evaluation	24 December 2019
Second round evaluation completed	3 February 2020
Delegate's Overall benefit-risk assessment	17 March 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	8 April 2020
Completion of administrative activities and registration on the ARTG	9 April 2020
Number of working days from submission dossier acceptance to registration decision*	175

*Statutory timeframe for standard applications is 255 working days

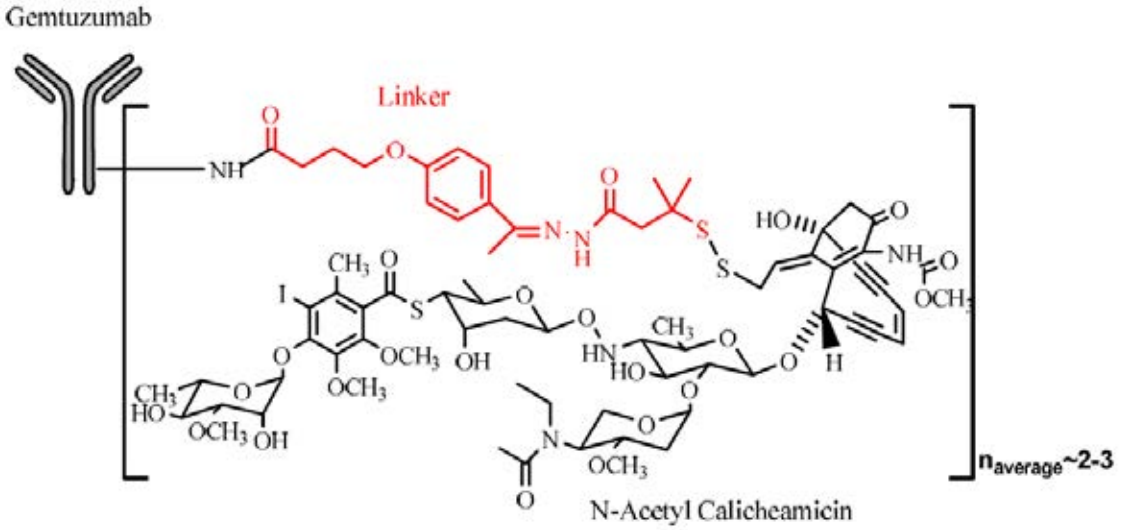
III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

The gemtuzumab ozogamicin drug substance consists of a mixture of conjugated and unconjugated gemtuzumab. The conjugated molecules differ in the number of activated calicheamicin derivative moieties attached to gemtuzumab. A schematic representation of the gemtuzumab ozogamicin structure is shown in Figure 1.

Figure 1: Two dimensional structural depiction of gemtuzumab ozogamicin



Gemtuzumab ozogamicin drug product is packaged in amber, Type 1 glass vials, with butyl rubber stoppers and crimp seals with flip-off caps.

There were no objections to approval of this application raised by the quality assessor.

Nonclinical

Gemtuzumab ozogamicin is a humanised monoclonal antibody (IgG4) against CD33 that is covalently linked (via an acid labile linker) to *N*-acetyl gamma calicheamicin dimethylhydrazide (*N*-Ac-γ-calicheamicin DMH), a cytotoxic agent.

The nonclinical evaluator noted that:

- The nonclinical dossier was of good overall quality and adequate in scope according to relevant TGA-adopted guidelines.[6,7]All pivotal toxicity studies were Good Laboratory Practice (GLP)-compliant;[8] but safety pharmacology studies were non-GLP. This is not considered to be a significant deficiency.
- *In vitro* studies established that gemtuzumab ozogamicin binds to human CD33 with high affinity, is internalised after binding to CD33-positive cells, and routed to the lysosome where the cytotoxic payload is released following cleavage of the linker in the acidic environment. Activation of the cytotoxin (mediated non-enzymatically), binding to DNA, induction of double-strand breaks, and apoptotic cell death follow. Gemtuzumab ozogamicin showed potent cytotoxic activity against CD33-positive cells, acting with a high degree of specificity (from comparison of potency against CD33-negative cells) and with much greater potency compared to unconjugated calicheamicin derivatives. *In vivo,* anti-tumour was demonstrated with gemtuzumab ozogamicin in immunodeficient mice bearing human AML xenografts. A strong

[6] European Medicines Agency (EMA), Committee for medicinal products for human use (CHMP), ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals, EMA/CHMP/ICH/731268/1998, June 2011.
[7] European Medicines Agency (EMA), Committee for medicinal products for human use (CHMP), ICH S9 Non-clinical evaluation for anticancer pharmaceuticals, EMA/CHMP/ICH/646107/2008, May 2010.
[8] **Good Laboratory Practice (GLP)** is an international quality system of management controls for the experimental (nonclinical) research arena, research laboratories and organisations to ensure the uniformity, consistency, reliability, reproducibility, quality, and integrity of products in development for human or animal health (including pharmaceuticals) through non-clinical safety tests; from physio-chemical properties through acute to chronic toxicity tests.

synergistic effect was seen with gemtuzumab ozogamicin in combination with daunorubicin and cytarabine. While noting that efficacy in combination with anthracycline was not investigated, these studies offer support for the utility of gemtuzumab ozogamicin in the treatment of CD33-positive AML.

- Gemtuzumab ozogamicin does not recognise rat or cynomolgus monkey CD33, and is not expected to recognise CD33 from other routine laboratory animal species. The antibody is not seen to be cytotoxic in its own right.
- Immunohistochemistry experiments with human tissues revealed no off-target binding for gemtuzumab ozogamicin, with the staining pattern consistent with the known expression of CD33 (confined mainly to cells of the macrophage/monocyte lineage (macrophages, monocytes, histiocytes and Kupffer cells) and mast cells).
- Safety pharmacology assessment revealed no clinically relevant effects on central nervous system (CNS), cardiovascular, respiratory and renal function, nor on gastrointestinal motility.
- The pharmacokinetic (PK) profile of gemtuzumab ozogamicin in laboratory animal species was typical for an antibody, featuring a long plasma half-life, low systemic clearance and a limited volume of distribution. Gemtuzumab ozogamicin is largely stable in plasma. Tissue distribution of gemtuzumab ozogamicin was limited in rats. Due to the species specificity of the antibody component, the nonclinical species do not model target-mediated drug disposition for gemtuzumab ozogamicin.
- *N*-Ac-γ-calicheamicin DMH displayed a high degree of plasma protein binding in humans and laboratory animal species. Extensive metabolism of *N*-Ac-γ-calicheamicin DMH was shown in the rat.
- No clinically meaningful drug interactions are anticipated based on the results of *in vitro* experiments with cytochromes P450 (CYPs),[9] uridine 5'-diphospho-glucuronosyltransferase and transporters.
- Gemtuzumab ozogamicin showed a high to moderately high order of acute toxicity following intravenous (IV) administration in mice, rats and cynomolgus monkeys.
- Repeat-dose toxicity studies of 6 weeks duration were conducted in rats and up to 12 weeks duration in cynomolgus monkeys. A 13-day study in rabbits was also submitted, but was limited in scope. The major target organs for toxicity by gemtuzumab ozogamicin identified were the liver, kidney, bone marrow, lymphoid tissues, the male and female reproductive tract, and eye. The toxicity observed is seen to be driven by the calicheamicin component, and related to the non-CD33-target-mediated disposition of gemtuzumab ozogamicin.
- The pivotal repeat dose toxicity study, involving weekly administration to cynomolgus monkeys for 12 weeks, has established no observed adverse event level (NOAEL) for toxicity to the liver, bone marrow, lymphoid tissues and the male reproductive tract, and clinical relevance is seen. Animal: human exposure ratios at the NOAELs for

[9] CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

toxicity to the kidney, female reproductive tract and eye are high, however, suggesting limited clinical relevance.

- Positive results for genotoxicity were obtained, as expected. Gemtuzumab ozogamicin was shown to be clastogenic *in vivo* in mice, and *N*-Ac-γ-calicheamicin DMH was shown to be mutagenic in bacteria and clastogenic *in vitro* (in a human lymphoblast cell line).
- No carcinogenicity studies were submitted; this is acceptable for a medicine indicated for the treatment of advanced cancer and not warranted given gemtuzumab ozogamicin is presumed to be a trans-species carcinogen due to its genotoxic activity. In the general repeat-dose toxicity program, pre-neoplastic lesions were observed in the liver of rats treated with gemtuzumab ozogamicin for 6 weeks.
- Marked impairment of male fertility was observed in rats at all dose levels tested. In female rats, gemtuzumab ozogamicin inhibited ovulation (without affecting the incidence of pregnancy), caused embryofetal lethality, malformations (affecting digits, the aortic arch, skull, forelimb long bones, scapula, vertebral centrum and sternebrae), and reduced fetal weight. Relative exposure at the NOAEL for effects on embryofetal development in the rat is low (approximately 4), supporting strong concern for embryofetal harm in patients. Pregnancy Category D,[10] as the sponsor proposes, is considered to be appropriate.
- *N*-Ac-γ-calicheamicin DMH was demonstrated to be non-phototoxic *in vitro*.

There are no nonclinical objections to the registration of Mylotarg for the proposed indication.

Clinical

The clinical dossier consisted of the following:

- One pivotal efficacy/safety study (Study ALFA-0701).
- One supportive individual patient data (IPD) meta-analysis of 5 studies in untreated AML (Study ALFA-0701, Study SWOG 0106, Study MRC AML 15, Study NCRI AML 16 and GOELAMS;[11] Study 2006IR).[12]
- Numerous other studies involving different indications or doses compared to current application, use of gemtuzumab ozogamicin as monotherapy, or paediatric population.

Pharmacology

Previous studies on single-agent gemtuzumab ozogamicin at 9 mg/m^2 indicated that it was efficacious in treating AML but associated with haematological and hepatic toxicity, as well as veno-occlusive disease (VOD). A regimen of gemtuzumab ozogamicin 3 mg/m^2 x 3 was chosen for investigation in place of the higher dose based on dose-ranging conducted in the original drug development process (initial Phase I Study 0903A1-101-US). 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-gemtuzumab ozogamicin dose in patients with relapsed and

[10] Australian Pregnancy Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[11] **GOELAMS**; Le Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang (Tours, France)
[12] Clinical study reports were not available in the dossier for 4 studies: Study SWOG 0106, Study MRC AML 15, Study NCRI AML 16, and GOELAMS Study 2006IR. Publications of these studies were submitted in the clinical dossier.

refractory AML. Across all studies, near maximal peripheral CD33 saturation was observed post-gemtuzumab ozogamicin dose at all dose levels of 2 mg/m^2 and above, suggesting that a low dose of gemtuzumab ozogamicin is sufficient to bind all available CD33 sites. *In vitro* studies indicated that AML cells internalise CD33 after gemtuzumab ozogamicin binding and re-expression of these receptors occurred every 72 hours to near pre-treatment levels at a dose of 3 mg/m^2.

There were no specific PK studies at the recommended dosing regimen included in this application. Gemtuzumab ozogamicin is 100% bioavailable, and it would be expected that its distribution and clearance would be determined by CD33.

Efficacy

The efficacy analysis was based on a single pivotal study, Study ALFA-0701.[13] This was a randomised Phase III study that compared gemtuzumab ozogamicin + AraC + DNR with AraC + DNR treatment for first line treatment of AML in 271 patients randomised to the two treatment arms.

The main inclusion criteria were:

- Previously untreated primary AML,
- Age ≥ 50 and ≤ 70 years,
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3,[14]
- Cardiac function within normal on scintigraphy or echocardiography.

The main exclusion criteria were:

- Patients with acute promyelocytic leukaemia,
- AML secondary to known myelodysplastic disease or cytotoxic therapy,
- CNS involvement in AML.

[13] Study ALFA-0701; title 'A Randomized Study of Gemtuzumab Ozogamicin (GO) With Daunorubicine and Cytarabine in Untreated Acute Myeloid Leukemia (AML) Aged of 50-70 Years Old'. ClinicalTrials.gov Identifier: NCT00927498; EudraCT Number: 2007-002933-36.

[14] **ECOG Performance Status:** The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work

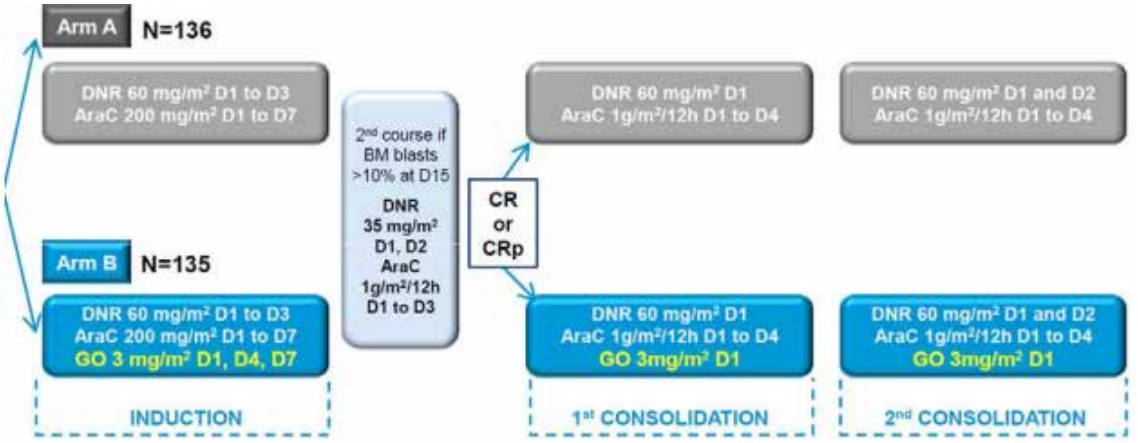
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 – Dead

Figure 2: Study ALFA-0701 Schema and study plan



GO = gemtuzumab ozogamicin; CR = complete remission; CRp = complete remission with incomplete platelet recovery.

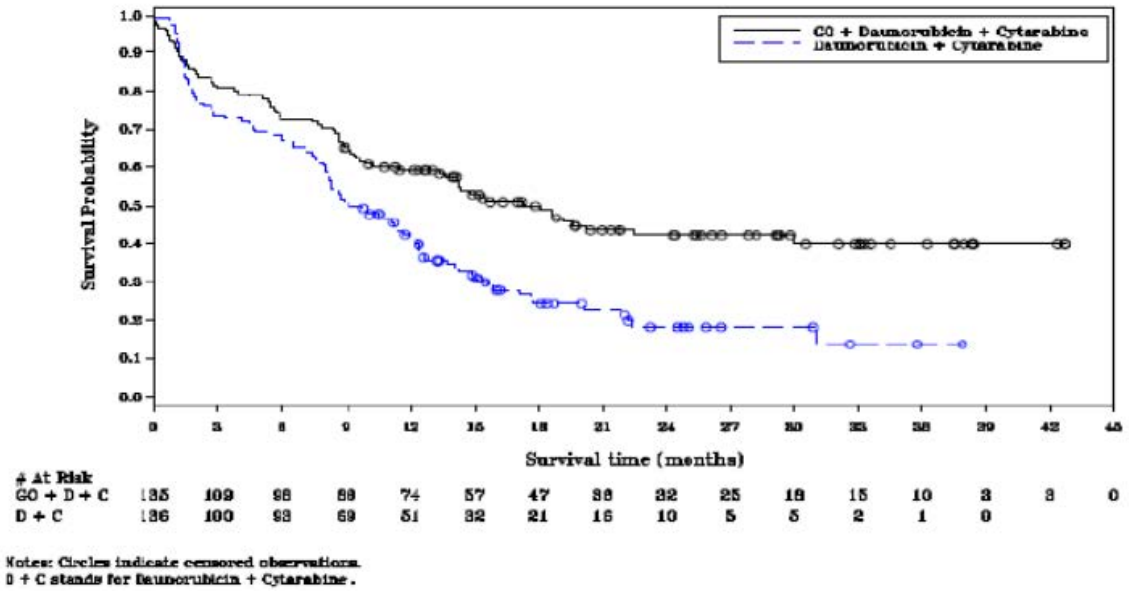
The primary endpoint was the time event free survival (EFS), defined as the failure of a composite endpoint of induction failure, relapse or death from any cause to occur.

Rate of CR and complete remission with incomplete platelet recovery (CRp) rates in each arm of treatment were examined.

CR was defined as the absence of blast cells in blood and disappearance of all tumours, a percentage of marrow blast cells < 5%, haemoglobin (Hb) > 9 g/dL, platelets > 100 000/mm^3 and neutrophils > 1000/mm^3 without transfusion.

CRp was defined as the same criteria as CR, except that platelets could be ≤ 100 000/mm^3.

Figure 3: Study ALFA-0701 Kaplan-Meier plot of event free survival



The clinical evaluator has noted that the efficacy results were generally supportive of a positive effect of the gemtuzumab ozogamicin combination treatment versus comparator. There was a statistically significant improvement in EFS of a median of 17.3 months in the gemtuzumab ozogamicin arm compared to 9.5 months in the control arm. This corresponds to a 44% reduction in the risk of EFS in the gemtuzumab ozogamicin arm compared to the control arm over the period of observation. There was no statistically significant difference in overall survival between the two arms, being a median of 27.5 months in the gemtuzumab ozogamicin arm and 21.8 months in the control arm (p = 0.16).

There is also no statistically significant difference in the proportion of patients achieving CR or CRp between the gemtuzumab ozogamicin and control arms.

A meta-analysis of IPD from all randomised gemtuzumab ozogamicin trials was performed. The evaluator has commented that the results of this analysis generally support those of the pivotal trial. The Delegate concurs with this conclusion.

Safety

The safety data for gemtuzumab ozogamicin is drawn from the pivotal efficacy study and the IPD meta-analysis.

Table 3: Study ALFA-0701 Summary of statistical analysis of comparative event free survival

	GO + Daunorubicin + Cytarabine (N=135)	Daunorubicin + Cytarabine (N=136)
Number of events, n (%)	73 (54.1)	102 (75.0)
Induction failure	17 (12.6)	29 (21.3)
Relapse	44 (32.6)	58 (42.6)
Death	12 (8.9)	15 (11.0)
Number of censored patients, n (%)	62 (45.9)	34 (25.0)
Reason for censoring, n (%)		
Event-free at reference date	62 (45.9)	34 (25.0)
Event-free at last assessment prior to reference date	0	0
No on-study disease assessment	0	0
Patient withdrew consent	0	0
Lost to follow-up	0	0
KM estimate of median time to event (months) [95% CI][a]	17.3 [13.4, 30.0]	9.5 [8.1, 12.0]
Probability of being event-free at 2 years [95% CI][b,c]	42.1 [32.9, 51.0]	18.2 [11.1, 26.7]
Probability of being event-free at 3 years [95% CI][b,c]	39.8 [30.2, 49.3]	13.6 [5.8, 24.8]
Versus daunorubicin + cytarabine – unstratified		
Hazard ratio[d] [95% CI]	0.562 [0.415, 0.762]	
p-Value[e]	0.0002	
Versus daunorubicin + cytarabine – stratified by risk (NCCN guideline)		
Hazard ratio[d] [95% CI]	0.575 [0.418, 0.790]	
p-Value[e]	0.0006	
Versus daunorubicin + cytarabine – stratified by risk (ELN guideline)		
Hazard ratio[d] [95% CI]	0.559 [0.408, 0.767]	
p-Value[e]	0.0003	

Source: Table 14.2.1.1

Based on the primary definition of EFS: event dates (induction failure, relapse, or death) determined by investigator assessment and censoring date being the reference date of 01 Aug 2011 or the last disease assessment date before the reference date where patient was event-free (no induction failure, relapse, or death). If data existed after reference date confirming the patient was event-free, patient was considered event-free at reference date; otherwise, patient was event-free at the last assessment prior to reference date.

Abbreviations: CI=confidence interval; EFS=event-free survival; ELN=European LeukemiaNet; GO=gemtuzumab ozogamicin; KM=Kaplan-Meier; mITT=modified intent-to-treat; n=number of patients; N=number of patients; NCCN=National Comprehensive Cancer Network.

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

b. Estimated from the KM curve.

c. Calculated from the product-limit method/Calculated from the log[-log(x-<year,month> survival probability)] using a normal approximation and back transformation.

d. Based on the Cox Proportional Hazards Model.

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

In Study ALFA-0701, the median duration of therapy was 12.1 weeks in the gemtuzumab ozogamicin arm.

The clinical evaluator has noted that the safety profile observed in the submitted data was consistent with known adverse events of gemtuzumab ozogamicin, for which there is post-market experience prior to 2010 and since the FDA/EMA approvals for the current indication in the past three years.

Table 4: Study ALFA-0701 Duration of exposure

Duration (weeks)		GO + Daunorubicin + Cytarabine (N=131)	Daunorubicin + Cytarabine (N=137)
All patients			
Overall duration[a]	N	131	137
	Median (range)	12.14 (0.6, 22.1)	11.71 (0.3, 19.0)
Induction duration[b]	N	131	137
	Median (range)	6.00 (0.6, 13.9)	5.86 (0.3, 15.1)
Consolidation duration[c]	N	97	97
	Median (range)	6.57 (0.6, 13.6)	6.43 (0.6, 10.1)
CR/CRp patients (per investigator)			
Overall duration[a]	N	108	101
	Median (range)	12.71 (1.0, 22.1)	12.43 (0.7, 19.0)
Induction duration[b]	N	108	101
	Median (range)	6.29 (1.0, 13.9)	6.14 (0.7, 15.1)
Consolidation duration[c]	N	97	94
	Median (range)	6.57 (0.6, 13.6)	6.50 (0.7, 10.1)
NonCR/CRp patients (per investigator)			
Induction duration[b]	N	23	36
	Median (range)	1.14 (0.6, 6.6)	2.57 (0.3, 9.7)

Abbreviations: CR=complete remission; CRp=complete remission with incomplete platelet recovery; GO=gemtuzumab ozogamicin; HSCT=hematopoietic stem cell transplant; N=number of patients.
a. Overall duration defined as duration from first dose to last dose of any study treatment (excluding HSCT).
b. Induction duration defined as duration from first dose of induction to the start of consolidation or to last dose of induction +1 if there was no consolidation treatment, including any re-induction or salvage treatment.
c. Consolidation duration defined as duration from first dose of consolidation 1 to the last dose of consolidation 2.

The main adverse effects with gemtuzumab ozogamicin relate to myelosuppression including neutropaenia and thrombocytopaenia and its sequelae (infections/bleeding), and VOD.

Table 5: Study ALFA-0701 Percentage of adverse events leading to treatment discontinuation

System Organ Class Preferred Term	GO + Daunorubicin + Cytarabine (N=131) n (%)	Daunorubicin+ Cytarabine (N=137) n (%)	Total (N=268) n (%)
Permanent drug discontinuation in patients with AEs	**41 (31.3)**	**10 (7.3)**	**51 (19.0)**
Blood and lymphatic system disorders	20 (15.3)	0	20 (7.5)
Thrombocytopenia	20 (15.3)	0	20 (7.5)
Cardiac disorders	2 (1.5)	1 (0.7)	3 (1.1)
Acute coronary syndrome	1 (0.8)	0	1 (0.4)
Left ventricular failure	0	1 (0.7)	1 (0.4)
Ventricular hypokinesia	1 (0.8)	0	1 (0.4)
Gastrointestinal disorders	0	1 (0.7)	1 (0.4)
Gastrointestinal haemorrhage	0	1 (0.7)	1 (0.4)
General disorders and administration site conditions	1 (0.8)	0	1 (0.4)
Death	1 (0.8)	0	1 (0.4)
Hepatobiliary disorders	8 (6.1)	1 (0.7)	9 (3.4)
Hepatic cirrhosis	1 (0.8)	0	1 (0.4)
Hepatitis cholestatic	1 (0.8)	0	1 (0.4)
Hepatocellular injury	1 (0.8)	1 (0.7)	2 (0.7)
Hepatotoxicity	1 (0.8)	0	1 (0.4)
Veno-occlusive liver disease	4 (3.1)	0	4 (1.5)
Infections and infestations	3 (2.3)	2 (1.5)	5 (1.9)
Septic shock	3 (2.3)	2 (1.5)	5 (1.9)
Injury, poisoning and procedural complications	1 (0.8)	0	1 (0.4)
Subdural haematoma	1 (0.8)	0	1 (0.4)
Investigations	2 (1.5)	2 (1.5)	4 (1.5)
Ejection fraction	1 (0.8)	0	1 (0.4)
Ejection fraction decreased	0	1 (0.7)	1 (0.4)
Liver function test abnormal	1 (0.8)	0	1 (0.4)
Oxygen saturation decreased	0	1 (0.7)	1 (0.4)
Nervous system disorders	3 (2.3)	2 (1.5)	5 (1.9)
Cerebral haematoma	1 (0.8)	0	1 (0.4)
Cerebral haemorrhage	0	1 (0.7)	1 (0.4)
Cerebrovascular accident	0	1 (0.7)	1 (0.4)
Intracranial haematoma	1 (0.8)	0	1 (0.4)
Neuropathy peripheral	1 (0.8)	0	1 (0.4)
Renal and urinary disorders	1 (0.8)	0	1 (0.4)
Acute kidney injury	1 (0.8)	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0	1 (0.7)	1 (0.4)
Acute respiratory distress syndrome	0	1 (0.7)	1 (0.4)

Abbreviations: AE=adverse event; GO=gemtuzumab ozogamicin; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients; TEAE=treatment-emergent adverse event; v=version.

Table 6: Study ALFA-0701 Incidence of significant treatment emergent adverse events

	GO + Daunorubicin + Cytarabine N n (%)	Daunorubicin + Cytarabine N n (%)
Retrospective Data Collection		
All Patients	131	137
Infections and infestations Severe (Grade ≥3)	102 (77.9)	106 (77.4)
Grade 3/4	100 (76.3)	102 (74.4)
Grade 5	2 (1.5)	4 (2.9)
HAEMORRHAGE All Grades (Grade ≥1) Cluster TEAEs, Total	118 (90.1)	107 (78.1)
Grade 3	23 (17.6)	12 (8.8)
Grade 4	4 (3.1)	0
Grade 5	3 (2.3)	1 (0.7)
VOD All Grades (Grade ≥1) Cluster TEAEs, Total	6 (4.6)	2 (1.5)
Grade 3	2 (1.5)	1 (0.7)
Grade 4	1 (0.8)	1 (0.7)
Grade 5	2 (1.5)	0
Responder Patients (Patients in CR/CRp)	108	101
Infections and infestations Severe (Grade ≥3)	88 (81.5)	85 (84.2)
Grade 3/4	88 (81.5)	83 (82.2)
Grade 5	0	2 (2)
HAEMORRHAGE All Grades (Grade ≥1) Cluster TEAEs, Total	98 (90.7)	82 (81.2)
Grade 3	21 (19.4)	10 (9.9)
Grade 4	4 (3.7)	0
Grade 5	1 (0.9)	0
VOD All Grades (Grade ≥1) Cluster TEAEs, Total	5 (4.6)	2 (2)
Grade 3	2 (1.8)	1 (1)
Grade 4	1 (0.9)	1 (1)
Grade 5	1 (0.9)	0
Responder patients refers to Patients in CR/CRp		

TEAE = treatment emergent adverse event.

The incidence of VOD was higher overall in the gemtuzumab ozogamicin treatment arm than in the control arm, being 4.6% versus 1.5% respectively.

Risk management plan

The sponsor has submitted European Union-risk management plan (EU-RMP) version 1.2 (9 January 2018; data lock point (DLP) 23 May 2016) and Australian specific Annex (ASA) version 1.1 (11 December 2019) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7.[15]

[15] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 7: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	**Additional**	**Routine**	**Additional**
Important identified risks	Severe (Grade ≥ 3) and/or serious hepatotoxicity including all VOD/ sinusoidal obstruction syndrome (SOS)	ü	–	ü	-
	Myelosuppression - Severe (Grade "ð) and/or serious infection - Haemorrhage	ü	–	ü	–
	Tumour lysis syndrome	ü	–	ü	–
	Infusion-related reactions (including anaphylaxis) from start of infusion to within 24 hours of end of infusion	ü	–	ü	–
Important potential risks	Renal toxicity	ü	–	ü	–
	Reproductive and developmental toxicity (post exposure during pregnancy, including breastfeeding)	ü	–	ü	–
	Neurotoxicity	ü	–	ü	–
	Second primary malignancy	ü	–	ü	–
	Immunogenicity	ü	*	ü	–
	Off label use in paediatric patients	ü	†	ü	–
Missing information	Use in patients with severe hepatic impairment	ü	–	ü	–
	Use in patients with severe renal impairment	ü	–	ü	–
	Effect on cardiac conduction	ü	*	ü	–
	Use in Aboriginal and Torres Strait Islander peoples≠	ü	–	ü	–

*Ongoing US FDA post marketing requirements study to evaluate further the effect of fractionated dosing regimen of gemtuzumab ozogamicin on QTc;[16] PK, safety and immunogenicity.[17]

† MyeChild study ongoing to establish the optimum tolerated number of 3 mg/m^2 doses of gemtuzumab ozogamicin (up to a maximum of 3 doses) that can be safely delivered in combination with induction chemotherapy.

≠ Missing Information specific to ASA only and does not apply to the EU-RMP.

The risk management plan (RMP) evaluator has noted a number of potential adverse effects of therapy. These will be managed through routine pharmacovigilance and risk minimisation programs.

The RMP evaluator has noted that the US Prescribing Information for Mylotarg has a black boxed warning regarding the incidence of VOD, and recommended that the Delegate consider whether this should be included in the Australian PI. The RMP evaluator has quoted the sponsor as having responded that:

- Mylotarg has been available to patients commercially and/or through clinical trials for nearly 20 years, and its effects, including hepatic effects are well characterised and clearly described in literature and in labelling documents.
- The risk of VOD was higher in adult patients who received the higher doses of Mylotarg as monotherapy. In the US, Mylotarg is indicated as monotherapy and in combination therapy. In the EU (and proposed for Australia), the indication for Mylotarg is for combination therapy only and does not include monotherapy.[18]
- Furthermore, in Australia, consumer access to medicine information in the prescription medicine landscape differs markedly from the US. The US is one of only two countries that allow direct-to-consumer drug advertising that includes product claims. Australia does not permit such advertising directly to patients. In Australia, important information on the safety and efficacy of the use of Mylotarg in AML is provided to patients by highly specialised haematologists and administration of therapy generally occurs in the inpatient setting. The sponsor proposes to include additional safety information in the Australian Consumer Medicines Information (CMI) to support patient awareness on the risks of VOD and hepatotoxicity.

[16] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The **corrected QT interval (QTc)** estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

[17] Sponsor clarification: ongoing Study B1761031 is a single arm, open label, Phase IV study evaluating the effect of gemtuzumab ozogamicin on the QTc, pharmacokinetics (PK), safety, and immunogenicity of GO as a single agent monotherapy in adult and paediatric patients with relapsed or refractory CD33-positive AML. During the review of the BLA, the FDA issued PMRs that requested additional assessment of the impact of the fractionated dosing regimen of GO on the risk of veno-occlusive disease or sinusoidal obstruction syndrome (VOD/SOS) in patients with previous or subsequent hematopoietic stem cell transplantation (HSCT), hemorrhage, unexpected serious risk of QT interval prolongation and unexpected serious risk of anti-drug antibodies.

[18] Sponsor clarification - the following additional information was also provided by the sponsor:
- The EU Summary of Product Characteristics (SmPC) does not have a boxed warning and presents equivalent safety information in section 4.4 and considerably more detailed safety information in section 4.8. The proposed Australian PI presents equivalent language regarding warning and precautions and adverse effects relating to hepatotoxicity compared to the SmPC.
- Mylotarg is intended to be used only by highly specialised haematologists who are experienced in the treatment of patients with AML, including the management of toxicities associated with the disease and treatment.
- Mylotarg is administered in the hospital setting under specialised care for induction and consolidation therapy and is not typically intended for outpatient treatment.

Risk-benefit analysis

Delegate's considerations

The gemtuzumab ozogamicin combination appears to provide a benefit in EFS over the comparator chemotherapy. This does not seem to derive from an improved rate of complete response or overall survival. The Delegate concludes that the combination improves disease control without necessarily adding to the potential for curative therapy. This is potentially an important consideration in patients would be expected to have a reasonable chance of achieving remission on standard therapy, since gemtuzumab ozogamicin adds toxicity without necessarily conferring benefit in those patients.

The pivotal combination therapy study, Study ALFA-0701, enrolled patients between 50 and 70 years of age, which means that the proposed indication extrapolates efficacy to younger patients. While the Delegate feels this is acceptable, as have other regulators, this extrapolation should be qualified. The Delegate feels that while it is reasonable to extrapolate the effect of gemtuzumab ozogamicin itself to other age groups, the comparative benefit of gemtuzumab ozogamicin versus chemotherapy is more difficult to extrapolate because it involves the rate of response to chemotherapy. This is higher in younger patients, and this confounds the broad analysis of gemtuzumab ozogamicin's optimal place in therapy.

The 'Clinical Trials' section of the draft PI is lengthy, and the Delegate feels this has the potential to lose important conclusions among the detail. The sponsor is requested to include as the first paragraph in this section, separate from the following paragraphs, the following:

> In a Phase III trial (Study ALFA-0701) the combination of Mylotarg + Cytarabine + Daunorubicin was compared to Cytarabine + Daunorubicin. Combination therapy with Mylotarg + chemotherapy resulted in a statistically significant improvement in progression free survival compared to the chemotherapy combination alone. There was no significant improvement in rates of Overall Survival or Complete Response demonstrated in Mylotarg combination therapy compared to the chemotherapy combination alone.

The sponsor may refer to the tabulated results at the end of this paragraph, but is advised not to include numerical results in this paragraph.

The Delegate does not feel that additional labelling of the risk of VOD is required for the reasons outlined by the sponsor in their response to the RMP evaluator. This is medication which is managed in an intensive environment and has many potential adverse effects which require close monitoring of specialist staff.

The main regulatory issue in Australia is the sponsor's proposal to register an indication which does not specify which anthracycline is to be used in the treatment regimen. The Delegate concedes that current usage of anthracyclines favours Ida because of funding arrangements, but notes that this is not a matter which can be considered under Section 25 of the *Therapeutic Goods Act* (1989). This is therefore immaterial to the current approval decision.

The Delegate notes that following issues regarding a proposed non-specific indication are considered material:

- There is no evidence in the pivotal study for the efficacy of gemtuzumab ozogamicin plus AraC plus Ida.
- There is no evidence in the pivotal study for the safety of gemtuzumab ozogamicin plus AraC plus Ida.

- The pivotal data is already imputing safety and efficacy from the 50 to 70 year old age group to a broader adult population, and extrapolating further with regard to a different combination in this population is not possible with any certainty.

It is noted that the EU specifies DNR in the indication for gemtuzumab ozogamicin, and the US Prescribing Information specifies it in the dosing instructions for the drug.

The Delegate therefore does not currently support approval of the sponsor-proposed indication.

Proposed action

The Delegate intends to register gemtuzumab ozogamicin with the indication:

> *Mylotarg is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukemia, except acute promyelocytic leukemia (APL).*

The Delegate requests the sponsor to provide prior to resolution of this application:

- A summary no longer than 5 pages in length of the comparative efficacy and safety of DNR and Ida, citing (but not necessarily providing) peer reviewed studies.[19]
- A draft PI amended as outlined in the 'Delegate's Considerations' (above) and annotated to indicate where amendments in line the nonclinical evaluation have been included.

Advisory Committee considerations[20]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Mylotarg (gemtuzumab ozogamicin) 5 mg powder for injection vial, indicated for:

> *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).*

[19] Inclusion of this response is beyond the scope of this AusPAR.

[20] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific conditions of registration applying to these goods

- Mylotarg (gemtuzumab ozogamicin) is to be indicated in the Black Triangle Scheme. The PI and CMI for Mylotarg must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Mylotarg EU-RMP (version 1.2, dated 09 January 2018; DLP 23 May 2016), with ASA (version 1.1, dated 11 December 2019), included with submission PM-2019-01426-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- Batch release testing and compliance with Certified Product Details (CPD)
  - It is a condition of registration that all batches of Mylotarg (gemtuzumab ozogamicin) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - It is a condition of registration that up to 5 initial batches of Mylotarg (gemtuzumab ozogamicin) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.
  - The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

  This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.
- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.
- For all injectable products the PI must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Mylotarg approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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