ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MYLOTARG 5 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder for concentrate for solution for infusion contains 5 mg gemtuzumab ozogamicin.

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

Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (hP67.6; recombinant humanised 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MYLOTARG is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients aged 15 years and above with previously untreated, *de novo* CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL) (see sections 4.4 and 5.1).

4.2 Posology 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.

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

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

Appropriate measures to help prevent the development of tumour lysis-related hyperuricaemia, such as hydration, administration of antihyperuricemic or other agents for treatment of hyperuricaemia should be taken (see section 4.4).

Posology

Induction

The recommended dose of MYLOTARG is 3 mg/m^2/dose (up to a maximum of one 5 mg vial) infused over a 2-hour period on Days 1, 4, and 7 in combination with DNR 60 mg/m^2/day infused over 30 minutes on Day 1 to Day 3, and AraC 200 mg/m^2/day by continuous infusion on Day 1 to Day 7.

If a second induction is required, MYLOTARG should not be administered during second induction therapy. Only DNR and AraC should be administered during the second induction cycle, at the following recommended dosing: DNR 35 mg/m^2/day on Days 1 and 2, and AraC 1 g/m^2 every 12 hours, on Day 1 to Day 3.

Consolidation

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

Table 1. Dosing regimens for MYLOTARG in combination with chemotherapy

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

[a.] See Table 3 and Table 4 for dose modification information.
[b.] For patients experiencing a complete remission (CR) following induction.

Dose and schedule modifications

Schedule modification for hyperleukocytosis

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

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

Table 2. Schedule modification for the treatment of hyperleukocytosis with cytarabine

Treatment course	MYLOTARG	daunorubicin	cytarabine	hydroxyurea
Induction[a]	3 mg/m^2/dose (up to a maximum of one 5 mg vial) on Days 3, 6, and 9	60 mg/m^2/day on Day 3 to Day 5	200 mg/m^2/day on Day 1 to Day 7	Day 1 (as per standard medical practice)

See Table 1 for dose recommendations for consolidation course.

[a.] See Table 3 and Table 4 for additional dose modification information.

Dose modification for adverse drug reactions

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

Tables 3 and 4 show the dose modification guidelines for haematological and non-haematological toxicities, respectively.

Table 3. Dose modifications for haematological toxicities

Haematological toxicities	Dose modifications
Persistent thrombocytopenia (Platelets < 100 000/mm^3 at the planned start date of the consolidation course)	• Postpone start of consolidation course. • If platelet count recovers to ≥ 100 000/mm^3 within 14 days following the planned start date of the consolidation course: initiate consolidation therapy (see as described in Table 1). • If platelet count recovers to < 100 000/mm^3 and ≥ 50 000/mm^3 within 14 days following the planned start date of the consolidation course: MYLOTARG should not be re-introduced and consolidation therapy should consist of DNR and AraC only. • If platelet count recovery remains < 50 000/mm^3 for greater than 14 days consolidation therapy should be re-evaluated and a BMA should be performed to re-assess the patients' status.
Persistent neutropenia	• If neutrophil count does not recover to greater than 500/mm^3 within 14 days following the planned start date of the consolidation cycle (14 days after 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, DNR=daunorubicin.

Table 4. Dose modifications for non-haematological toxicities

Non-haematological toxicities	Dose modifications
VOD/SOS	Discontinue MYLOTARG (see section 4.4).
Total bilirubin > 2 × ULN and AST and/or 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. Consider omitting 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).
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

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 4, sections 4.4 and 5.2).

Renal impairment

No dose adjustment 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).

Elderly

No dose adjustment is required in elderly patients (≥ 65 years) (see section 5.2).

Paediatric population

The safety and efficacy of MYLOTARG in patients less than 15 years of age has not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

Method of administration

MYLOTARG is for intravenous use and must be reconstituted and diluted before administration (see section 6.6). When reconstituted to a 1 mg/mL concentration, the extractable content of one vial is 4.5 mg (4.5 mL). The reconstituted and diluted solution should be administered intravenously by infusion over a 2-hour period under close clinical monitoring, including pulse, blood pressure, and temperature. MYLOTARG should not be administered as an intravenous push or bolus (see section 6.6).

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

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

Hepatotoxicity, including life-threatening, and sometimes fatal hepatic failure and VOD/SOS have been reported in patients treated with MYLOTARG (see section 4.8).

Based on an analysis of potential risk factors, adult patients who received MYLOTARG as monotherapy, either before or after an haematopoietic stem cell transplant (HSCT), and patients with moderate or severe hepatic impairment are at increased risk for developing VOD (see section 4.8).

Due to the risk of VOD/SOS, signs and symptoms of VOD/SOS should be closely monitored; these may include elevations in ALT, 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 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). In patients who experience VOD/SOS, MYLOTARG should be discontinued and patients treated according to standard medical practice.

Infusion related reactions (including anaphylaxis)

In clinical studies infusion related reactions, including anaphylaxis were reported (see section 4.8). There have been reports of fatal infusion reactions in the post-marketing 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. Infusion of MYLOTARG should be performed 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). Infusion should be interrupted immediately for patients who develop evidence of severe reactions, especially dyspnoea, bronchospasm, or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of treatment should be strongly considered for patients who develop signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension (see section 4.2).

Myelosuppression

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

Complete blood counts should be monitored prior to each dose of MYLOTARG. During treatment, patients should be monitored for signs and symptoms of infection, bleeding/haemorrhage, or other effects of myelosuppression. Routine clinical and laboratory surveillance testing during and after treatment 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).

Tumour lysis syndrome (TLS)

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

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

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 size of the effect in patients with adverse cytogenetics (see section 5.1). For patients being treated with MYLOTARG in combination with daunorubicin and cytarabine for newly diagnosed *de novo* AML, when cytogenetics testing results become available it should be considered whether the potential benefit of continuing treatment with MYLOTARG outweighs the risks for the individual patient (see section 5.1).

Contraception

Women of childbearing potential, or partners of females of childbearing potential should be advised to use 2 methods of effective contraception during treatment with MYLOTARG for at least 7 months (females) or 4 months (males) after the last dose (see section 4.6).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

This medicinal product may be further prepared for administration with sodium-containing solutions (see sections 4.2 and 6.6), and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies have been conducted with MYLOTARG. See section 5.2 for available data from *in vitro* studies.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

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

Women of childbearing potential, or partners of females of childbearing potential should be advised to use 2 methods of effective contraception during treatment with MYLOTARG for at least 7 months (females) or 4 months (males) after the last dose.

Pregnancy

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

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

Breast-feeding

There is no information regarding the presence of gemtuzumab ozogamicin or its metabolites in human milk, the effects on the breast-fed child, or the effects on milk production. Because of the potential for adverse drug reactions in breast-fed children, women should not breast-feed during treatment with MYLOTARG and for at least 1 month after the final dose (see section 5.3).

Fertility

There is no information on fertility in patients. Based on non-clinical findings, male and female fertility may be compromised by treatment with gemtuzumab ozogamicin (see section 5.3). Both men and women should seek advice on fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

MYLOTARG has moderate influence on the ability to drive and use machines. Patients should be advised they may experience fatigue, dizziness and headache during treatment with MYLOTARG (see section 4.8). Therefore, caution should be exercised when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of MYLOTARG is based on data from patients with 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 5. Information about adverse drug reactions from monotherapy studies using the non-fractionated regimen (Studies 201/202/203) and post-marketing experience is presented in Table 6 and the monotherapy study B1761031 using the fractionated regimen is presented in the section below in order to provide full characterisation of adverse drug reactions.

In the combination therapy study ALFA-0701, clinically relevant serious adverse drug reactions were hepatotoxicity, including VOD/SOS (3.8%), haemorrhage (9.9%), severe infection (41.2%), and tumour lysis syndrome (1.5%). In monotherapy studies (Studies 201/202/203), clinically relevant serious adverse drug reactions also included infusion related reactions (2.5%), thrombocytopenia (21.7%), and neutropenia (34.3%). In the monotherapy study B1761031, clinically relevant serious adverse drug reactions included infection (30.0%), febrile neutropenia (22.0%), pyrexia (6.0%), haemorrhage (4.0%), thrombocytopenia (4.0%), anaemia (2.0%), and tachycardia (2.0%).

The most common adverse drug reactions (> 30%) in the combination therapy study were haemorrhage and infection. In monotherapy studies (Studies 201/202/203) the most common adverse drug reactions (> 30%) included pyrexia, nausea, infection, chills, haemorrhage, vomiting, thrombocytopenia, fatigue, headache, stomatitis, diarrhoea, abdominal pain, and neutropenia. In the monotherapy study B1761031 the most frequent adverse drug reactions (> 30%) included infection (50.0%), febrile neutropenia (40.0%) and haemorrhage (32.0%).

The most frequent (≥ 1%) adverse drug reactions that led to permanent discontinuation in the combination therapy study were thrombocytopenia, VOD, haemorrhage and infection. The most frequent (≥ 1%) adverse drug reactions that led to permanent discontinuation in monotherapy studies (Studies 201/202/203) were infection, haemorrhage, multi-organ failure, and VOD. The adverse drug reactions that led to permanent discontinuation in monotherapy study B1761031 were infection and pyrexia.

Tabulated list of adverse drug reactions

The adverse drug reactions are presented by system organ class (SOC) and frequency categories, defined using the following convention: very common (³ 1/10), common (³ 1/100 to < 1/10), uncommon (³ 1/1 000 to < 1/100), rare (³ 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 drug reactions are presented in order of decreasing seriousness.

Table 5. Selected[**] adverse drug reactions in patients who received MYLOTARG in combination therapy study (ALFA-0701)

System organ class *Frequency* Preferred term	MYLOTARG + daunorubicin + cytarabine (N=131)		daunorubicin + cytarabine (N=137)	
	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 6. Adverse drug 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 drug reactions in the post-marketing setting.
[***]MYLOTARG in the treatment of relapsed AML (9 mg/m^2) (Studies 201/202/203).
[#]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 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 5). 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.

In the monotherapy study B1761031, no VOD events were reported for any patient. However, 1 (2.0%) patient had fatal capillary leak syndrome with symptoms consistent with VOD (ascites and hyperbilirubinemia). The Grade 3 hepatotoxicity events included gamma-glutamyltransferase increased (4.0%), alanine aminotransferase increased (2.0%), aspartate aminotransferase increased (2.0%), hypoalbuminemia (2.0%) and transaminases increased (2.0%). No patients had Grade 4 or Grade 5 hepatotoxicity.

Based on an analysis of potential risk factors, adult patients who received non-fractionated MYLOTARG as monotherapy, patients who had received an HSCT prior to gemtuzumab ozogamicin exposure were 2.6 times more likely (95% confidence interval [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. Management of signs or symptoms of hepatic toxicity may require a dose interruption, or discontinuation of MYLOTARG (see section 4.2).

Myelosuppression

In the combination therapy study in patients with previously untreated *de novo* AML treated with fractionated doses of 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).

In the monotherapy study B1761031 (N=50), Grade 3/4 infections were reported in 10 (20%) patients. The most frequent (≥ 5.0%) reported Grade 3/4 infections were sepsis and pneumonia in 3 (6.0%) patients, each. Six (6) (12.0%) patients had Grade 5 infection (sepsis in 4 [8.0%], atypical pneumonia, and COVID-19 pneumonia in 1 [2.0%] patient, each). All grade bleeding/haemorrhagic events were reported in 16 (32.0%) patients. Grade 3/4 haemorrhagic events occurred in 2 (4.0%) patients (gastric haemorrhage Grade 3 and traumatic intracranial haemorrhage Grade 4 in 1 patient, each). No fatal bleeding/haemorrhagic events were reported.

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

Immunogenicity

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

The anti-drug antibody (ADA) against MYLOTARG was evaluated using electrochemiluminescence (ECL) method. For patients whose ADA samples were tested positive, a cell-based assay was developed to measure neutralizing antibody (NAb) against MYLOTARG.

In the monotherapy study B1761031 in 50 treated adult patients with relapsed or refractory CD33-positive AML, the incidence of ADA and NAb was 12.0% (6/50) and 2.0% (1/50), respectively. The presence of ADA had no statistically significant or clinically relevant effects on PK of total hP67.6 antibody or conjugated calicheamicin. None of the patients experienced anaphylaxis, hypersensitivity or other clinical sequelae related to ADA. There was no evidence that the presence of ADA had a direct association with any potential safety issues.

In the dose finding part of MyeChild 01 study in 54 treated paediatric patients ≥12 months of age with newly diagnosed AML, the overall ADA incidence across cohorts was 2% (1/49). No AESI-infusion-related reactions were reported for the ADA positive patient.

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.

Paediatric population

Previously untreated AML

The safety and efficacy of MYLOTARG in children and adolescents with previously untreated AML below the age of 15 years has not been established (see section 4.2).

In the completed randomised paediatric Phase 3 Study AAML0531 (see section 5.1) 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%).

In the dose finding part of the paediatric study MyeChild 01 (see section 5.1) of gemtuzumab ozogamicin combined with induction therapy (cytarabine plus either mitoxantrone or liposomal daunorubicin) in 54 children ≥12 months of age with newly diagnosed AML, the safety profile was similar with that observed in the other studies of gemtuzumab ozogamicin combined with intensive chemotherapy in adult and paediatric patients with *de novo* AML. The rate of infection for all grades was 57.4%. The most frequently reported ADRs ≥Grade 3 for all cohorts were febrile neutropenia (92.6%), thrombocytopenia (90.7%), neutropenia (87.0%) and anaemia (83.3%). The most frequently reported serious ADRs for all cohorts were febrile neutropenia (29.6%) and infection (14.8%). Serious febrile neutropenia was experienced by 13.3%, 15.0% and 57.9% of patients in cohorts 1, 2 and 3, respectively. By day 45 post Course 1 or 2, 27.8% of patients did not recover neutrophil count to 1 000/mm^3 and 11.1% of patients did not recover a non-transfusion dependent platelet count to 80 000/mm^3 due to documented bone marrow aplasia/hypoplasia. VOD occurred during the post-transplant period in 13% of patients. Fatal VOD was observed in 1.9% of patients.

Relapsed or refractory AML

The safety and efficacy of MYLOTARG in paediatric patients with relapsed or refractory AML has not been established (see sections 4.1 and 4.2).

Safety results observed in a systematic literature review of studies evaluating MYLOTARG in paediatric patients (see section 5.1), are presented in Table 7.

Table 7. Safety results from a systematic literature review in paediatric patients with relapsed or refractory AML who received MYLOTARG

	Monotherapy						**Combination[a]**					
	Fractionated[b] MYLOTARG			**Non-fractionated[b] MYLOTARG**			**Fractionated[b] MYLOTARG**			**Non-fractionated[b] MYLOTARG**		
	Number of studies	N per study (range)	Rate[c] (%)	Number of studies	N per study (range)	Rate (%)	Number of studies	N per study (range)	Rate (%)	Number of studies	N per study (range)	Rate (%)
VOD	1	6	0	10	5, 30	6.8	2	3, 17	0	5	5, 84	4.4
VOD post HSCT	Not reported			5	4, 14	19.1	2	3, 8	0	2	12, 28	14.7
Death[d]	1	6	0	4	6, 29	10.8	Not reported			3	5, 45	6.5
Infection	5 studies; N per study (range) 12-30; 28.4%						4 studies; N per study (range) 12-84; 42.2%					
Myelosuppression[e]	Almost all patients (> 90 %) experienced myelosuppression across studies											

a: When MYLOTARG was given in combination, cytarabine was part of the combination studied in 8 out of the 9 studies.
b: Fractionated dosing refers to MYLOTARG dose of 3 mg/m^2 on days 1, 4, 7. Non-fractionated dosing refers to MYLOTARG (total dose ranging 1.8 mg/m^2 – 9 mg/m^2) 2 times during a cycle at least 14 days apart.
c: Rates across studies were estimated using inverse variance weighting with fixed effects. Proportions were transformed using Freeman-Tukey double arcsine transformation prior to combining studies, and the estimated combined rate was back-transformed using the harmonic mean of study sample sizes.
d: Within 30 days from the last dose of MYLOTARG.
e: Where analysed, median recovery (defined as 20 x 10^9/L or 50 x 10^9/L for platelets and 0.5 x 10^9/L for neutrophils) ranged from 42-48 days for platelets and 30-37 days for neutrophils.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX02

Mechanism of action

Gemtuzumab ozogamicin is a CD33-directed ADC. Gemtuzumab is a humanised immunoglobulin class G subtype 4 (IgG4) antibody which specifically recognises human CD33. The antibody portion 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. Non-clinical data suggest that the anticancer activity of gemtuzumab ozogamicin is due to the binding of the ADC to CD33-expressing cancer cells, followed by internalisation of the ADC-CD33 complex, and the intracellular release of N-acetyl gamma calicheamicin dimethyl hydrazide via hydrolytic

cleavage of the linker. Activation of N-acetyl gamma calicheamicin dimethyl hydrazide induces double-stranded DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

Saturation of a high percentage of CD33 antigenic sites is presumed to be required for maximum delivery of calicheamicin to leukaemic blast cells. Several single agent studies measured 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 efficacy and safety

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

The efficacy and safety of MYLOTARG were evaluated in a multicentre, randomised, 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 (Study ALFA-0701). Patients with acute promyelocytic leukaemia (APL, AML3) and patients with AML arising from myelodysplastic syndrome (MDS) or secondary AML were excluded from the study.

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

In total, 271 patients were randomised in this study with 135 to induction treatment of 3+7 DA plus fractionated 3 mg/m^2 × 3 doses of MYLOTARG and 136 to 3+7 DA alone (see section 4.2). A second course of induction therapy with DA but without MYLOTARG, regardless of the 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.

Overall, the median age of patients was 62 years (range 50 to 70 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 LeukaemiaNet (ELN) 2010 risk classifications, respectively. CD33 expression on AML blasts by flow cytometry harmonised 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 study met its primary objective of demonstrating that MYLOTARG added in fractionated doses (3 mg/m^2 × 3 doses) to standard induction chemotherapy for patients with previously untreated *de novo* AML resulted in a statistically significant and clinically meaningful improvement in EFS. Median EFS was 17.3 months (95% CI: 13.4, 30.0) in the MYLOTARG arm versus 9.5 months (95% CI: 8.1, 12.0) in the DA alone arm; hazard ratio (HR) 0.562 (95% CI: 0.415, 0.762); 2-sided p=0.0002 by log-rank test. Efficacy data from ALFA-0701 study are summarised in Table 8, and the Kaplan-Meier plot for EFS is shown in Figure 1.

Table 8. Efficacy results from study ALFA-0701 (mITT population)

	MYLOTARG + daunorubicin + cytarabine	**daunorubicin + cytarabine**
Event-free survival (by Investigator)	**N=135**	**N=136**

Number of events, n (%)	73 (54.1)	102 (75.0)
Median EFS in months [95% CI][a,]	17.3 [13.4, 30.0]	9.5 [8.1, 12.0]
2-year EFS probability[95% CI][b]	42.1 [32.9, 51.0]	18.2 [11.1, 26.7]
3-year EFS probability [95% CI][b]	39.8 [30.2, 49.3]	13.6 [5.8, 24.8]
Hazard ratio [95% CI][c]	0.562 [0.415, 0.762]	
p-value[d]	0.0002	
Relapse-free survival (by Investigator)	**N=110**	**N=100**
Number of events, n (%)	49 (44.5)	66 (66.0)
Median RFS in months [95% CI][a]	28.0 [16.3, NE]	11.4 [10.0, 14.4]
Hazard ratio [95% CI] [c]	0.526 [0.362, 0.764]	
p-value[d]	0.0006	
Overall survival	**N=135**	**N=136**
Number of deaths, n (%)	80 (59.3)	88 (64.7)
Median OS in months [95% CI][a]	27.5 [21.4, 45.6]	21.8 [15.5, 27.4]
Hazard ratio [95% CI][c]	0.807 [0.596, 1.093]	
p-value[d]	0.1646	
Response rate (by Investigator)	**N=135**	**N=136**
Overall response % [95% CI][e]	81.5 [73.89, 87.64]	73.5 [65.28, 80.72]
CR	70.4	69.9
CRp	11.1	3.7
Risk difference [95% CI][f]	7.95[-3.79, 19.85]	
p-value[g]	0.1457	

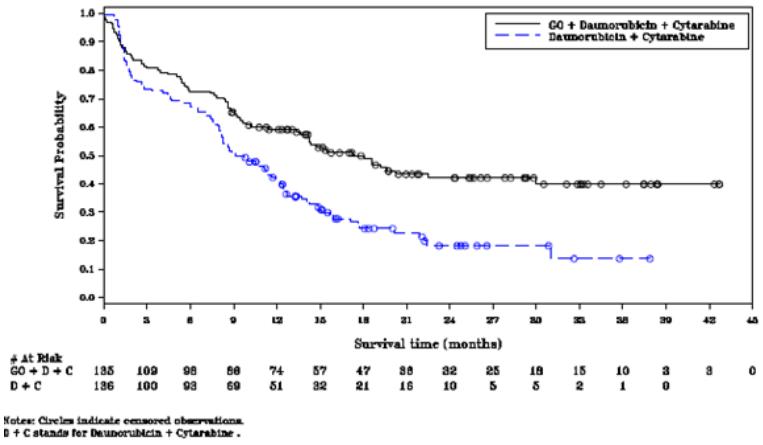
Based on the primary definition of EFS: event dates (induction failure, relapse, or death) determined by investigator assessment.

The mITT population included all patients who were 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 by investigator assessment from study ALFA-0701 (mITT population)



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

Use in AML with adverse-risk cytogenetics

In subgroup analyses in ALFA-0701, the addition of MYLOTARG to standard combination chemotherapy did not improve EFS in the subgroup of patients having adverse-risk cytogenetics (HR 1.11; 95% CI: 0.63, 1.95). EFS and OS analysed by cytogenetic risk classification and cytogenetic/molecular risk classification are presented in Table 9 and Table 10 below.

Table 9. Event-free survival by investigator assessment by AML risk classifications from study ALFA-0701 (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]	22.5 [15.5, NE]	11.6 [8.3, 13.7]
Hazard ratio [95% CI][b]	0.460 [0.313, 0.676]	
p-value[c]	< 0.0001	
Cytogenetics (unfavourable), N	**27**	**30**
Number of events, n (%)	23 (85.2)	26 (86.7)
Median EFS in months [95% CI][a]	4.5 [1.1, 7.4]	2.8 [1.6, 8.7]
Hazard ratio [95% CI][b]	1.111 [0.633, 1.949]	
p-value[c]	0.7151	
ELN (favourable/intermediate), N	**86**	**91**
Number of events, n (%)	40 (46.5)	63 (69.2)
Median EFS in months [95% CI][a]	22.5 [15.5, NE]	12.2 [8.5, 14.3]
Hazard ratio [95% CI][b]	0.485 [0.325, 0.724]	
p-value[c]	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]	7.4 [3.7, 14.3]	4.0 [1.7, 8.6]
Hazard ratio [95% CI][b]	0.720 [0.430, 1.205]	
p-value[c]	0.2091	

The ALFA-0701 study was not designed to prospectively evaluate the benefit of MYLOTARG in subgroups; analysis are presented for descriptive purposes only.

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

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.

Table 10. 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][b]	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][b]	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][b]	0.730 [0.489, 1.089]	
p-value[c]	0.1216	
ELN (poor/adverse), N	**37**	**36**
Number of deaths, n (%)	31 (83.8)	29 (80.6)
Median OS in months [95% CI][a]	13.2 [7.0, 18.5]	13.5 [10.8, 19.8]
Hazard ratio [95% CI][b]	1.124 [0.677, 1.867]	
p-value[c]	0.6487	

The ALFA-0701 study was not designed to prospectively evaluate the benefit of MYLOTARG in subgroups; analysis 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 LeukaemiaNet; 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

Previously untreated AML

COG AAML0531

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 sections 4.2 and 4.8). 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).

MyeChild 01

The major dose finding part of the paediatric study MyeChild 01 investigated the number of doses of MYLOTARG 3 mg/m^2 (up to a maximum of 3 doses; each dose was capped at one 5 mg vial/dose) which can be combined safely with cytarabine plus either mitoxantrone or liposomal daunorubicin in induction therapy. Key inclusion criteria included patients ≥12 months and <18 years of age at trial entry and diagnosis of AML/high risk MDS (>10% blasts in the bone marrow)/isolated myeloid sarcoma with no prior therapy. There were 3 cohorts that varied by the number of MYLOTARG infusions during the induction phase: Cohort 1 (n=15): Patients received a single dose of MYLOTARG (3 mg/m^2) on day 4 of Course 1 of induction chemotherapy. Cohort 2 (n=20): Patients received a single dose of MYLOTARG (3 mg/m^2) on days 4 and 7 of Course 1 of induction chemotherapy. Cohort 3 (n=19): Patients received a single dose of MYLOTARG (3 mg/m^2) on days 4, 7 and 10 of Course 1 of induction chemotherapy. Among 55 enrolled patients, 30 (54.5%) patients were 2 years to <12 years of age, 32 (58.2%) patients were male and the median age of all patients was 7.0 (range: 1, 17) years. Though efficacy was a secondary endpoint, best overall response (CR+CRi) among patients treated (n=54) was achieved in 49 (90.7%; 95% CI: 79.7%, 96.9%) patients (cohort 1, 80.0%, cohort 2, 95.0%, cohort 3, 94.7%). MRD negativity was reported in 35 (71.4%) patients after Course 2 of treatment (cohort 1, 58.3%, cohort 2, 78.9%, cohort 3, 72.2%). The MyeChild 01 study is ongoing. The optimal dose of gemtuzumab ozogamicin for paediatric patients is not yet established (see section 4.2).

Relapsed or refractory AML

A systematic literature review of studies was conducted to evaluate MYLOTARG in paediatric patients with relapsed or refractory AML, which included 454 patients receiving MYLOTARG either as a monotherapy (single or fractionated dosing) or combination therapy from 16 published papers plus the US Expanded Access Study (see section 4.8). The median study size was 15 patients, with a range of 5-105 patients. The overall minimum and maximum ages range from 0 years to 22.3 years, with an overall median age of 8.7 years at the time of treatment.

Most studies were in the compassionate use setting (70.6%). MYLOTARG was given as monotherapy in 47.1%, part of a combination in 23.5%, and in both settings in 29.4% of the studies. Total dosing of MYLOTARG ranged from 1.8 mg/m^2 to 9 mg/m^2. When MYLOTARG was given in combination, a cytarabine based regimen was used in 8 of the 9 studies. In 23.5% of the studies the majority of patients received fractionated (3 mg/m^2 on Day 1, 4, 7) doses of MYLOTARG, while in 35.3% of the studies doses higher than 3 mg/m^2 were given. MYLOTARG was given as induction treatment in most studies (82.4%).

With MYLOTARG monotherapy, the response rate (CR/CRp/CRi; weighted average across studies) was 33.3% with fractionated dosing (1 study) and 24.3% with non-fractionated dosing (9 studies). In the combination setting, the response rate was 49.0% with non-fractionated MYLOTARG (3 studies) and 38.8% with fractionated MYLOTARG (2 studies).

Safety information on myelosuppression, infections, VOD overall and VOD post-HSCT, and death, which are known adverse events for MYLOTARG (see section 4.8 and Table 7), was obtained from literature.

Limitations of this analysis include the small sample size of some studies, heterogeneity of the studies, and the lack of control data in this setting.

Cardiac electrophysiology

The effect of MYLOTARG on corrected QT interval was evaluated in monotherapy study B1761031, in 50 adult patients with relapsed or refractory CD33-positive AML. At therapeutic plasma concentrations, the largest mean QTcF interval change from baseline was 5.10 msec (90% CI: 2.15, 8.06 msec). There were no patients with a maximum QTcF increase from baseline of > 60 msec and no patients had a QTcF > 480 msec. One (1) event each of atrial fibrillation (Grade 3) and supraventricular tachycardia (Grade 3) occurred in the same patient. No Grade 4 or Grade 5 cardiac conduction adverse events were reported.

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

5.2 Pharmacokinetic properties

Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of CD33-directed monoclonal antibody (hP67.6) that is covalently linked to the cytotoxic agent N-acetyl-gamma calicheamicin. The pharmacokinetics (PK) of gemtuzumab ozogamicin is described by measuring PK characteristics of the antibody (hP67.6) as well as conjugated and unconjugated calicheamicin derivatives.

Clinical PK data were collected following a monotherapy dosing regimen (3 mg/m^2 up to one 5 mg vial on Days 1, 4, 7) of MYLOTARG in adult patients with relapsed/refractory AML. Exposures as measured by geometric mean AUC_{336} and C_{max} following multiple doses for conjugated calicheamicin and total hP67.6 antibody were 461 500 pg·hr/mL and 11 740 pg/mL; 26 820 ng·hr/mL and 585.6 ng/mL, respectively. The PK data for unconjugated calicheamicin are not presented due to instability issues in plasma.

Distribution

In vitro, the binding 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). In patients, the total volume of distribution of hP67.6 antibody (sum of V_1 [13.0 L] and V_2 [6.91 L]) was found to be approximately 20 L.

Biotransformation

The primary metabolic pathway of gemtuzumab ozogamicin is anticipated to be hydrolytic release of N acetyl gamma calicheamicin dimethyl hydrazide. In vitro studies demonstrated that N-acetyl gamma calicheamicin dimethyl hydrazide is extensively metabolised, primarily via nonenzymatic reduction of the disulphide moiety. The activity (cytotoxicity) of the resultant metabolites is expected to be significantly attenuated.

Interactions with other medicinal products

Effect of other medicinal products on gemtuzumab ozogamicin

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

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

Effect of gemtuzumab ozogamicin on other medicinal products

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 OCT2, and organic anion transporting polypeptide (OATP)1B1 and OATP1B3 at clinically relevant concentrations.

Effect on co-administered chemotherapeutic agents

Based on population pharmacokinetic (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.

Elimination

Gemtuzumab ozogamicin PK was well characterised by a 2-compartment model with linear and time-dependent clearance components. In 50 patients with relapsed or refractory AML following a monotherapy dosing regimen (3 mg/m^2 up to one 5 mg vial on Days 1, 4, 7) of MYLOTARG, the clearance of total hP67.6 antibody was 0.288 L/h, and the terminal elimination half-life ($t_{½}$) was estimated to be 96.6 h.

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 gemtuzumab ozogamicin disposition.

Hepatic impairment

No formal PK studies of gemtuzumab ozogamicin 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).

Renal impairment

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

Based on a 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 ($CL_{cr} \geq 90$ mL/min; n=209). The PK of gemtuzumab ozogamicin has not been studied in patients with severe renal impairment.

Paediatric population

Clinical PK data were collected following a dosing regimen (3 mg/m^2 up to one 5 mg vial on Days 4, 7 and 10) of MYLOTARG with induction therapy in pediatric patients ≥12 months of age with newly diagnosed AML. Exposures as measured by geometric mean AUC_{tau} and C_{max} following the third dose for conjugated calicheamicin and total hP67.6 antibody were 777 300 pg.hr/mL and 24 340 pg/mL; 46 500 ng.hr/mL and 1 336 ng/mL, respectively.

5.3 Preclinical safety data

Repeat-dose toxicity

The main toxicities occurred in the liver, bone marrow and lymphoid organs, haematology parameters (decreased RBC mass and WBC counts, mainly lymphocytes), kidney, eye and male and female reproductive organs. Effects on liver, kidney and male reproductive organs in rats, and on lymphoid tissues in monkeys (approximately 18 times for rats, and 36 times for monkeys, the human clinical exposure after the third human dose of 3 mg/m^2 based on AUC_{168}) were not reversible. Effects on female reproductive organs and the eye in monkeys were adverse in the 12-week study (approximately 193 and 322 times, respectively, the human clinical exposure after the third human dose of 3 mg/m^2 based on AUC_{168}). The relevance of the irreversible animal findings to humans is uncertain. Nervous system effects have not been observed in animals after administration of MYLOTARG. Nervous system alterations were identified in rats with other antibody-calicheamicin conjugates.

Genotoxicity

Gemtuzumab ozogamicin was found to be clastogenic. This is consistent with the known induction of DNA breaks by calicheamicin and other enediyne antitumour antibiotics. N-acetyl gamma calicheamicin DMH (the released cytotoxin) was found to be mutagenic and clastogenic.

Carcinogenicity

Formal carcinogenicity studies have not been conducted with gemtuzumab ozogamicin. In toxicity studies, rats developed preneoplastic lesions (minimal to slight oval cell hyperplasia) in the liver approximately 54 times the human clinical exposure after the third human dose of 3 mg/m^2 based on AUC_{168}. There were no preneoplastic or neoplastic lesions observed in monkeys up to approximately 115 times the human clinical exposure after the third human dose of 3 mg/m^2 based on AUC_{168}. The relevance of these animal findings to humans is uncertain.

Reproductive toxicity

In a female rat fertility study slightly lower numbers of corpora lutea and increased embryolethality were observed in the presence of maternal toxicity (approximately 9.7 times the human clinical exposure after the third human dose of 3 mg/m^2 based on AUC_{168}). Effects on the reproductive tract of female monkeys were observed in the 12-week study (atrophy of the ovary, oviduct, uterus, and cervix; approximately 193 times the human clinical exposure after the third dose of 3 mg/m^2).

In a male fertility study, effects on male reproduction included lower spermatogonia and spermatocytes, decreases in testicular spermatids and epididymal sperm, vacuolation of the nucleus in spermatids, and/or appearance of giant cells. Additional findings included effects on the testes, epididymides and mammary gland as well as fertility. When male rats were mated again after a 9-week non-dosing period, effects on sperm and fertility were worse but there was partial recovery of the lower spermatogonia and spermatocytes in the testes. Effects on male rat reproductive organs were partially reversible or not reversible (see section 4.6). Male reproductive effects (testes, epididymides, seminal vesicles) in monkeys were observed at approximately 66 times the human clinical exposure after the third dose of 3 mg/m^2.

In an embryo-foetal toxicity study lower foetal body weight, higher incidence of foetal wavy ribs, and lower incidence of foetal skeletal ossification were observed. Increased embryolethality and foetal morphological anomalies included digital malformations, absence of the aortic arch, anomalies in the long bones in the forelimbs, misshapen scapula, absence of a vertebral centrum, and fused sternebrae. Increased embryolethality was also observed in the presence of maternal toxicity. The lowest dose with embryo-foetal effects correlated with 9.7 times the human clinical exposure after the third human dose of 3 mg/m^2, based on AUC_{168} (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

5 years

Reconstituted and diluted solution

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

If the product cannot be used immediately:

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

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store the vial in the original carton to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

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

Reconstitution

- Calculate the dose (mg) of MYLOTARG required.
- Prior to reconstitution, allow the vial to reach room temperature (below 30°C) for approximately 5 minutes. Reconstitute each 5 mg vial with 5 mL of water for injections to obtain a single-use solution of 1 mg/mL of gemtuzumab ozogamicin.
- Gently swirl the vial to aid dissolution. Do not shake.
- Inspect the reconstituted solution for particulates and 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 16 hours in a refrigerator (2°C–8°C) or up to 3 hours at room temperature (below 30°C). Protect from light and do not freeze.

Dilution

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

Administration

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

- Infusion lines made of PVC (DEHP- or non DEHP-containing), polyurethane or polyethylene are recommended.

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

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

Disposal

Toxic waste disposal procedures prescribed for anticancer medicinal products must be used.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1277/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 April 2018
Date of latest renewal: 15 November 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Wyeth Pharmaceutical Division of Wyeth Holdings LLC
401 North Middletown Road
Pearl River, New York 10965
United States

Name and address of the manufacturer responsible for batch release

Pfizer Service Company BV
Hermeslaan 11
1932 Zaventem
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

MYLOTARG 5 mg powder for concentrate for solution for infusion
gemtuzumab ozogamicin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 5 mg of gemtuzumab ozogamicin.
After reconstitution each vial contains 1 mg/mL gemtuzumab ozogamicin.

3. LIST OF EXCIPIENTS

Dextran 40, sucrose, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1277/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MYLOTARG 5 mg powder for concentrate
gemtuzumab ozogamicin
For IV infusion after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

MYLOTARG 5 mg powder for concentrate for solution for infusion
gemtuzumab ozogamicin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What MYLOTARG is and what it is used for

MYLOTARG contains the active substance gemtuzumab ozogamicin, an anticancer medicine, which is made up of a monoclonal antibody linked to a substance intended to kill cancer cells. This substance is delivered to cancer cells by the monoclonal antibody. A monoclonal antibody is a protein which recognises certain cancer cells.

MYLOTARG is used to treat a certain type of blood cancer called acute myeloid leukaemia (AML) in which the bone marrow makes abnormal white blood cells. MYLOTARG is intended for the treatment of AML for patients aged 15 years and above who have not tried other treatments. MYLOTARG is not for use in patients with a type of cancer called acute promyelocytic leukaemia (APL).

2. What you need to know before you are given MYLOTARG

MYLOTARG should not be given if you:
- are allergic to gemtuzumab ozogamicin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
When you first receive this medicine and during the course of treatment, tell your doctor or nurse if you:
- **have or ever had liver problems:** MYLOTARG may cause, during or after treatment, a potentially life-threatening condition called hepatic venoocclusive disease, in which the blood vessels in the liver become damaged and obstructed by blood clots which may lead to fluid retention, rapid weight gain, increased liver size (which may be painful), and ascites (excessive accumulation of fluid in the abdominal cavity).
- **allergic reaction:** experience a high-pitched whistling sound during breathing (wheezing), difficult breathing, shortness of breath or cough with or without mucous, hives, itching, swelling, or feeling fever and chills (signs of an infusion related reaction) during or shortly after the MYLOTARG infusion.
- **infection:** have or think you have, an infection, develop chills or shivering, or feel warm, or have fever. Some infections may be serious and may be life-threatening.
- **bleeding:** have unusual bleeding, bleeding from your gums, bruising easily or getting nose bleeds on a regular basis.

- **anaemia:** have headaches, feel tired, experience dizziness, or look pale .
- **infusion reaction**: experience during or shortly after MYLOTARG infusion symptoms such as dizziness, decreased urination, confusion, vomiting, nausea, swelling, shortness of breath, or heart rhythm disturbances (this may be a potentially life-threatening complication known as tumour lysis syndrome).

Children and adolescents
MYLOTARG must not to be used in children and adolescents under 15 years of age because limited data are available in this population.

Other medicines and MYLOTARG
Tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or nurse for advice before you are given this medicine.

You must avoid becoming pregnant or fathering a child because of potential adverse effects on the child. Women must use 2 methods of effective contraception during treatment and for at least 7 months after the last dose of treatment. Men must use 2 methods of effective contraception during treatment and for at least 4 months after the last dose of treatment. Contact your doctor immediately if you or your partner becomes pregnant while taking this medicine.

Seek advice regarding fertility preservation before treatment.

If you need treatment with MYLOTARG, you must stop breast-feeding during treatment and for at least 1 month after treatment. Talk to your doctor.

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

MYLOTARG contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially ‘sodium-free’.

3. How MYLOTARG will be given

- A doctor or nurse will give you MYLOTARG through a drip in your vein (intravenous infusion) gradually over 2 hours.
- Your doctor will decide on the correct dose.
- Your doctor or nurse may change your dose, interrupt, or completely stop treatment with MYLOTARG if you have certain side effects.
- Your doctor may lower your dose based on your response to treatment.
- Your doctor will do blood tests during the treatment to check for side effects and for response to treatment.
- Before you receive MYLOTARG, you will be given some medicines to help reduce symptoms such as fever and chills, known as infusion reactions, during or shortly after the MYLOTARG infusion.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

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

Some of the side effects could be serious and may occur during or after treatment with MYLOTARG. Immediately contact your doctor or nurse if you experience any of the following serious side effects (see also section 2 “What you need to know before you are given MYLOTARG”):

- **Liver problems**
  Tell your doctor right away if you have rapid weight gain, feel pain in the upper right side of your abdomen, have accumulation of fluid causing abdominal swelling. Your doctor may do blood tests and find abnormalities in liver blood tests, which might be signs of a potentially life-threatening condition called venoocclusive liver disease.

- **Bleeding (signs of a low number of blood cells known as platelets)**
  Tell your doctor right away if you bruise easily or get nose bleeds on a regular basis, or have black tarry stools, coughing up of blood, bloody sputum, feeling dizzy, fainting, or confusion.

- **Infections (signs of a low number of white blood cells known as neutrophils)**
  Some infections may be serious and can be due to viruses, bacteria, or other causes that may be life-threatening.

- **Complication known as tumour lysis syndrome**
  Tell your doctor right away if you experience dizziness, decreased urination, confusion, vomiting, nausea, swelling, shortness of breath, or heart rhythm disturbances.

- **Infusion reactions**
  Medicines of this type (monoclonal antibodies) can cause infusion reactions such as a rash, shortness of breath, difficulty breathing, a tight chest, chills or fever, back pain.

Side effects include:

Very common (may affect more than 1 in 10 people):
- Infections (including serious infections)
- Reduced number of blood platelets (cells that help blood to clot)
- Reduced number of white blood cells which may result in general weakness and a tendency to develop infections
- Reduced number of red blood cells (anaemia) which may result in fatigue and shortness of breath
- High blood sugar
- Decreased appetite
- Headache
- Rapid heartbeat
- Bleeding
- Low blood pressure
- High blood pressure
- Shortness of breath
- Vomiting
- Diarrhoea
- Pain in the abdomen
- Feeling sick (nausea)
- Mouth inflammation
- Constipation
- Abnormalities in liver blood tests (which can be indicators of liver injury)
- Skin rash
- Fever

- Oedema (excess fluid in body tissue, causing swelling of the hands and feet)
- Fatigue
- Chills
- Changes in the levels of different enzymes in the blood (may show in your blood tests)
- Prolonged clotting time (which may result in prolonged bleeding)
- High level of uric acid in the blood

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

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

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

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store MYLOTARG

MYLOTARG will be stored by the health professionals at the hospital or clinic.

Keep this medicine out of the sight and reach of children.

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

Unopened vial: Store in a refrigerator (2°C–8°C). Do not freeze. Store the vial in the original carton to protect from light.

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

If not used immediately:

- Following reconstitution, the original vial may be stored up to 16 hours in a refrigerator (2°C–8°C) or up to 3 hours at room temperature (below 30°C).

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

Do not use this medicine if you notice any particulate matter or discolouration prior to administration.

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

6. Contents of the pack and other information

What MYLOTARG contains

- The active substance is gemtuzumab ozogamicin.
- One vial contains 5 mg gemtuzumab ozogamicin.
- After reconstitution, each ml of the concentrated solution contains 1 mg gemtuzumab ozogamicin.
- The other ingredients are dextran 40, sucrose, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous. See section 2, “MYLOTARG contains sodium”.

What MYLOTARG looks like and contents of the pack

MYLOTARG is a powder for concentrate for solution for infusion. It is supplied as white to off-white cake or powder.

Each carton contains 1 amber glass vial, with rubber stopper and crimp seal with flip-off cap.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

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

Reconstitution

- Calculate the dose (mg) of MYLOTARG required.
- Prior to reconstitution, allow the vial to reach room temperature (below 30°C) for approximately 5 minutes. Reconstitute each 5 mg vial with 5 mL of water for injections to obtain a single-use solution of 1 mg/mL of gemtuzumab ozogamicin.
- Gently swirl the vial to aid dissolution. Do not shake.
- Inspect the reconstituted solution for particulates and 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 16 hours in a refrigerator (2°C–8°C) or up to 3 hours at room temperature (below 30°C). Protect from light and do not freeze.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial using a syringe. Mylotarg vials contain 5 mg of medicinal product with no overfill. When reconstituted to a 1 mg/mL concentration as directed, the extractable content of the vial is 4.5 mg (4.5 mL). Protect from light. Discard any unused reconstituted solution left in the vial.
- Doses must be mixed to a concentration between 0.075 mg/mL to 0.234 mg/mL according to the following instructions:
    - Doses less than 3.9 mg must be prepared for administration by syringe. Add the reconstituted MYLOTARG solution to a syringe with sodium chloride 9 mg/mL (0.9%) solution for injection to a final concentration between 0.075 mg/mL to 0.234 mg/mL. Protect from light.
    - Doses greater than or equal to 3.9 mg are to be diluted in a syringe or an intravenous bag in an appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection to ensure a final concentration between 0.075 mg/mL to 0.234 mg/mL. Protect from light.
- Gently invert the infusion container to mix the diluted solution. Do not shake.

- Following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, MYLOTARG solution should be infused immediately. If not used immediately, the diluted solution may be stored up to 18 hours in a refrigerator (2°C–8°C) and up to 6 hours at room temperature (below 30°C). The allowed time at room temperature (below 30°C) includes the time required for preparation of the diluted solution, equilibration, if needed, and administration to the patient. The maximum time from preparation of the diluted solution through administration should not exceed 24 hours. Protect from light and do not freeze.
- It is recommended that the infusion container be made of polyvinyl chloride (PVC) with DEHP, ethylene vinyl acetate (EVA) or polyolefin (polypropylene and/or polyethylene).

Administration

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

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

Disposal

- Toxic waste disposal procedures prescribed for anticancer medicinal products must be used.