CENTER FOR DRUG EVALUATION AND RESEARCH

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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**Division Director**  Cynthia LaCivita, Pharm.D.

**Review Completion Date**  July 20, 2017

**Subject**  Evaluation of need for a REMS

**Established Name**  gemtuzumab ozogamicin

**Trade Name**  Mylotarg

**Name of Applicant**  Pfizer Inc.

**Therapeutic Class**  CD33-directed antibody-drug conjugate (ADC)

**Formulation(s)**  4.5 mg single dose vial administered by intravenous infusion

**Dosing Regimen**  Newly diagnosed acute myeloid leukemia (AML):

- Combination with daunorubicin and cytarabine: 3 mg/m² on days 1, 4, and 7; then 3 mg/m² day 1 for 2 doses
- Single agent: 6 mg/m² day 1, 3 mg/m² day 8; then 2 mg/m² up to 8 doses

Relapsed or refractory AML: 3 mg/m² on days 1, 4, and 7.
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Mylotarg (gemtuzumab ozogamicin) is necessary to ensure the benefits outweigh its risks. Pfizer Inc. (Pfizer) submitted a Biologic Licensing Application (BLA) 761060 for Mylotarg with the proposed indications:

- Combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of adult patients with newly diagnosed, de novo CD33-positive acute myeloid leukemia (AML).
- Treatment of adult patients with CD33-positive AML.

The risks associated with Mylotarg include the followings:

- Heptatotoxicity, including severe or fetal hepatic venoocclusive disease (VOD), also known as sinusoidal obstruction syndrome, has been reported in associate with the use of Mylotarg.
- Severe or fatal hypersensitivity reactions (including anaphylaxis) and other infusion-related reactions, which may include severe pulmonary events have been reported with Mylotarg.
- Hemorrhage, including fatal intracranial hemorrhage, has been reported in association with the use of Mylotarg.

The applicant did not submit a proposed REMS or risk management plan with this application.

If Mylotarg is approved, the risks of hepatotoxicity, including VOD, severe or fetal hypersensitivity reactions, and hemorrhage will be included in labeling. The strategies to mitigate these risks, which include using fractionated dosing and premedication with a corticosteroid, antihistamine, and acetaminophen, will be communicated in the Dosage and Administration section of the label. The safety concerns associated with Mylotarg use are well documented, and healthcare providers who treat AML should be familiar with the risks and the importance of patient monitoring.

Given that AML is a fatal disease, as well as the clinically meaningful activity of Mylotarg, DRISK and the Division of Hematology Products (DHP) agree that a REMS is not necessary for Mylotarg to ensure its benefits outweigh its risks.

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Mylotarg (gemtuzumab ozogamicin) is necessary to ensure the benefits outweigh its risks. Pfizer submitted a Biologic Licensing Application (BLA) 761060 for Mylotarg with the proposed indications:

- Combination therapy with daunorubicin and cytarabine (DA) for the treatment of adult patients with newly-diagnosed, de novo CD33-positive acute myeloid leukemia (AML).
2 Background

2.1 PRODUCT INFORMATION
Mylotarg (gemtuzumab ozogamicin) is a CD33-directed antibody-drug conjugate (ADC) proposed for:

- Combination therapy with daunorubicin and cytarabine (DA) for the treatment of adult patients with newly-diagnosed, de novo CD33-positive acute myeloid leukemia (AML).
- Treatment of adult patients with CD33-positive AML

Mylotarg is proposed as 4.5 mg single dose vial administered by intravenous infusion. Mylotarg is currently approved in Japan.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for BLA 761060 relevant to this review:

- **May 17, 2000**: the FDA granted accelerated approval to Mylotarg (NDA 21174) for the treatment of patients with CD33 positive AML in first relapse and aged 60 and older who were not considered candidates for cytotoxic chemotherapy. The approved dose was 9 mg/m² for 2 doses 14 days apart. Myelosuppression and infusion-related reactions were identified as the major safety concerns at the time of approval. In the postmarketing period, fatal hepatotoxicity and veno-occlusive disease (VOD) were added as a boxed warning, highlighting an especially increased risk of VOD in patients who received Mylotarg either before or after hematopoietic stem cell transplantation (HSCT).

- **June 21, 2010**: Pfizer voluntarily discontinued the commercial marketing of Mylotarg in the United States. This was due to the result of the confirmatory trial (SWOG S0106) that was to fulfill the postmarketing requirement (PMR). S0106 was a randomized trial comparing DA with or without Mylotarg 6 mg/m² (on day 4) to treat patients 60 years or younger with newly-diagnosed AML. The study showed no improvement in complete remission (CR), disease-free survival (DFS) or overall survival (OS) in the Mylotarg arm. There was a higher rate of fatal induction toxicities in the Mylotarg arm (5% versus 1%). The FDA concluded that clinical benefit was not confirmed and that there was a potential safety issue due to the increase in early deaths.

- **October 25, 2010**: Mylotarg was withdrawn from US market. Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) conducted a risk-benefit assessment for Mylotarg as “monotherapy for relapsed or refractory CD33 positive AML patients for whom other re-induction therapies are not indicated”, which is the approved indication in Japan. The PMDA concluded that the efficacy and safety profile of Mylotarg remains unchanged from the time of approval. The drug continues to be marketed in Japan.
• **November 2, 2016**: Pfizer submitted BLA 761060 for the above two indications.

• **April 11, 2017**: FDA mid-cycle meeting, the applicant was told that a REMS is not needed based on the currently available data. The medical reviewers did request a boxed warning for hepatotoxicity, including severe or fatal hepatic VOD, severe or fatal hypersensitivity reactions (including anaphylaxis), and hemorrhage, including fatal intracranial hemorrhage.

• **July 11, 2017**: Oncology Drug Advisory Committee (ODAC) Meeting was convened to vote: Do the results of ALFA-0701 demonstrate a favorable risk:benefit for Mylotarg 3 mg/m² days 1, 4, and 7 added to DA for patient with newly-diagnosed CD33-positive AML?

  The ODAC voted 6 to 1. A REMS proposal was not discussed.

### 3 Therapeutic Context and Treatment Options

#### 3.1 Description of the Medical Condition

Acute Myeloid Leukemia (AML) is the most common type of acute leukemia in adults. The pathophysiology in AML consists of a maturational arrest of bone marrow cells in the earliest stages of development. The mechanism of this arrest is under study, but in many cases, it involves the activation of abnormal genes through chromosomal translocations and other genetic abnormalities. This developmental arrest results in two disease processes. First, the production of normal blood cells markedly decreases, which results in varying degrees of anemia, thrombocytopenia, and neutropenia. Second, the rapid proliferation of these cells, along with a reduction in their ability to undergo programmed cell death, results in their accumulation in the bone marrow, the blood, and the spleen/liver. Estimated new cases and deaths from AML of adults in the United States in 2017 are 21,380 and 10,590.\(^a\) The incidence increases with age, with more than 50% of AML patients being over 60 years old. In adults, treatment results are generally analyzed separately for younger (18-60 years) patients and for older patients (>60 years). With current standard chemotherapy regimens, about 30-35% of younger patients survive longer than 5 years. In older patients, fewer than 10% of survive over 5 years.\(^c\) Patients with AML die from neutropenia-associated infections and/or thrombocytopenia-associated bleeding.

#### 3.2 Description of Current Treatment Options\(^d\)

The treatment of AML is divided into two phases: remission induction and consolidation/maintenance. Remission induction chemotherapy is administered to produce a complete remission (CR) in the bone

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\(^a\) Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

\(^b\) [www.cancer.gov](http://www.cancer.gov), accessed June 16, 2017

\(^c\) Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

marrow. If a CR is achieved and no further therapy given, over 90% of patients will have a recurrence of AML in weeks to months. To prevent recurrence, intensive therapy, called consolidation, is given immediately after recovery from remission induction therapy. The more intensive the chemotherapy and the closer together the courses of therapy are given, the less chance the leukemia returning. Consolidation therapy can be accomplished with multiple courses of chemotherapy or high-dose chemotherapy with autologous or allogeneic stem cell transplantation.

For the past 3 decades, the standard therapy for younger patients with newly diagnosed AML has been the “7+3”remission induction regimen with cytarabine and daunorubicin, followed by high dose cytarabine for remission consolidation. Induction chemotherapy produces complete remission (CR) in most (50-70%) patients with AML, however between 50-80% of patients relapse. Patients with poor prognostic features are recommended to enroll into clinical trials and/or to undergo stem cell transplantation (SCT) following achievement of remission with standard induction chemotherapy.

On April 28, 2017, the FDA approved midostaurin (Rydapt) for the treatment of adult patients with newly diagnosed AML that is FMS-like tyrosine kinase 3 (FLT3) mutation-positive, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Midostaurin is not indicated as a single-agent induction therapy for the treatment of patients with AML. Midostaurin is a kinase inhibitor that works by blocking several enzymes that promote cell growth. It is an oral drug, to be taken by mouth, 50 mg twice daily. There are Warnings and Precautions for embryo-fetal toxicity and pulmonary toxicity in the label; there is no boxed warning for midostaurin.

4 Benefit Assessment

4.1 Combination with daunorubicin plus cytarabine (DA) chemotherapy for newly-diagnosed de novo AML: The pivotal trial (ALFA-0701) supporting this indication consisted of a multi-center (France only), 1:1 randomized, open-label phase 3 study comparing the addition of Mylotarg to a standard chemotherapy induction regimen of daunorubicin and cytarabine (DA) versus DA alone. Eligible patients were between 50 and 70 years of age with newly-diagnosed de novo AML. The primary endpoint was event-free survival (EFS). The secondary endpoints included overall survival (OS), relapse-free survival (RFS), and response rate of complete remission (CR) or complete remission with incomplete platelet recovery (CRp). In total, 271 patients were randomized with 135 patients to induction therapy of 3+7 DA

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6 Rydapt (midostaurin) Prescribing Information, April 2017

7 FMS, first discovered as the oncogene responsible for Feline McDonough Sarcoma, is a type III receptor tyrosine kinase that binds to the macrophage or monocyte colony-stimulating factor.

8 Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

Reference ID: 4127770
plus fractionated 3 mg/m² x3 doses of Mylotarg and 136 patients to 3+7 DA alone. Patients with CR or CRp received consolidation therapy with 2 courses of treatment including DA with or without Mylotarg according to their initial randomization. The trial met its primary objective of demonstrating that Mylotarg added in fractionated doses (3 mg/m² x3) to standard induction chemotherapy for patients with newly-diagnosed de novo AML resulted in a statistically significant and clinically meaningful improvement in EFS. Median EFS was 17.3 months in the Mylotarg arm versus 9.5 months in the control arm. OS was higher but not statistically significant. The median OS for patients in the Mylotarg arm was 27.5 months and 21.8 months for patients in the DA alone arm. RFS was significantly longer for patients in the Mylotarg arm, with a median RFS of 28 months in the Mylotarg arm versus 11.4 months in the DA alone arm. A majority of patients in both treatment arms experienced CR or CRp following induction, and the difference in overall response (81.5% in Mylotarg arm versus 73.5% in DA alone arm) did not reach statistical significance.

4.2 Monotherapy for relapse/refractory AML

The efficacy of Mylotarg as a single agent has been evaluated in 3 single-arm, open-label studies in patients with CD33-positive AML in first relapse. Data from these 3 studies, called first relapse group, were pooled to obtain a larger population (N=277) to provide better estimates for the various efficacy parameters. The treatment course included two 9 mg/m² dose separated by 14 days and a 28-day follow-up after the last dose. The primary endpoint of the 3 clinical studies was the rate of CR, which was defined as

- Leukemic blasts absent from the peripheral blood;
- <=5% blasts in the bone marrow, as measured by morphology studies;
- Hemoglobin >=9 g/dL, platelets>=100,000/mm³, absolute neutrophil count>=1500/mm³
- Red cell and platelets-transfusion independence.

In addition to CR, a second response category, CRp, was defined as patients satisfying the definition of CR, including platelet independence, with the exception of platelet recovery >=100,000/mm³.

Evaluated based on the International Working Group (IWG) guideline, the overall response rate for the 3 pooled monotherapy studies was 35%, consisting of 15% of patients with CR and 20% of patients with CRp. The median RFS for patients experiencing overall remission (OR) was 5 months. The median RFS was 7.4 months for patients who achieved CR and 4.2 months for patients who achieved CRp. The median OS was 4.9 months for all 277 patients. Median OS for OR patients was 11 months; with median OS of 13.1 months for patients achieving CR and median OS of 9.7 months for patients achieving CRp.

Analysis of 3 mg/m²/day dose: MyloFrance 1 (MF1) is a phase 2, single-arm, open-label study (N=57) evaluated Mylotarg in adult patients with CD33-positive AML in first relapse. Study treatment included induction therapy and consolidation therapy. During induction therapy, patients received a single course of Mylotarg administered as monotherapy intravenously of 3 mg/m²/day on days 1, 4, and 7. Consolidation therapy for patients with CR or CRp consisted of high doses of cytarabine intravenously every 12 hours for 3 days. No Mylotarg was given during consolidation therapy. The 57 patients enrolled...
had a median age of 64 years (22-80 years). Thirty-three percent patients experienced an overall response (CR+CRp), including 26% patients with CR and 7% patients with CRp. The OS was 8.4 months.

4.3 Monotherapy for newly-diagnosed AML: AML-19 trial is a randomized, open-label, multi-center, sequential phase 2-3 trial investigating 2 induction Mylotarg regimens in phase 2 and best supporting care (BSC) comparison. Eligible patients were randomized to 3 arms. Arm A received induction of Mylotarg 6 mg/m² on day 1 and 3 mg/m² on day 8. Arm B received Mylotarg 3 mg/m² on days 1, 3, and 5. Arm C received BSC. If patients on Arm A and B did not progress, they received 2 mg/m² for 8 doses every 4 weeks. There were 118 patients in the Mylotarg arm and 119 in the BSC arm. The median age were 77 in both arms. The median OS was 4.9 months in the Mylotarg arm compared to 3.6 months in the BSC arm.

5 Risk Assessment & Safe-Use Conditions

5.1 EARLY MORTALITY
Combination with DA chemotherapy: There were 135 patients in the Mylotarg arm and 136 patients in the control arm. Five patients (3.7%) in the Mylotarg arm versus 3 patients (2.2%) in the control arm died within the first 30 days of treatment. Four deaths of the Mylotarg arm were treatment related: two died of central nervous system hemorrhage, one died of hemorrhagic shock, and one died of VOD. One death of the control arm was treatment related: sepsis in the setting of bone marrow aplasia after reinduction.

Monotherapy for relapse/refractory AML: The safety profile was evaluated by pooled trials of 201, 202, 203 and MyloFrance 1 (MF1). There trials were single arm, open-label, multi-center trials. The treatment plan of 201-203 was Mylotarg 9 mg/m² IV x 2-3 doses 14-28 days apart, while MF1 used Mylotarg 3 mg/m² (capped at 5 mg) IV days 1, 4, and 7. The pooled trials have 277 patients and MF1 has 57 patients.

In first relapse group, the death rate within 28 days was 18% of patients who were given Mylotarg 9mg/m². In MF1 trial, the death rate was 7% of patients who were given 3 mg/m² days 1, 4, and 7.

Monotherapy for newly-diagnosed AML: AML-19 trial is a randomized, open-label, multi-center, sequential phase 2-3 trial investigating 2 induction Mylotarg regimens in phase 2 and best supporting care (BSC) comparison. Eligible patients were randomized to 3 arms. Arm A received induction of Mylotarg 6 mg/m² on day 1 and 3 mg/m² on day 8. Arm B received Mylotarg 3 mg/m² on days 1, 3, and 5. Arm 3 received BSC. If patients on Arm A and B did not progress, they received 2 mg/m² for 8 doses.

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h Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
every 4 weeks. There were 118 patients in the Mylotarg arm and 119 in the BSC arm. The median age were 77 in both arms.

The deaths within 30 days were 11% of patients in the Mylotarg arm and 13% of patients in the BSC arm. The deaths within 60 days were 18% of patients in the Mylotarg arm and 30% in the BSC arm.

5.2 Serious Adverse Reactions

5.2.1 Hepatotoxicity and Veno-occlusive disease (VOD)

- **Combination with DA chemotherapy**: In ALFA-0701 trial (3 mg/m² days 1, 4, and 7), 8 patients developed VOD. Six (4.4%) were in the Mylotarg arm; three cases were fatal and two were determined to be treatment related. The remaining 2 patients were in the control arm but received Mylotarg after relapse and subsequently developed VOD. Grade 3-4 bilirubin elevation were 6.7% of patients in the Mylotarg arm versus 2.9% in the control arm; Grade 3-4 AST elevation were 11.1% of patients in the Mylotarg arm versus 4.4% in the control arm; Grade 3-4 ALT elevation were 9.6% of patients in the Mylotarg arm versus 8.1% in the control arm.

- **Monotherapy for relapse/refractory AML**: Five percent of patients in the first relapse group (9 mg/m² x 2 doses) developed VOD, while no patients developed VOD in MF1 (3 mg/m² days 1, 4, and 7). Hepatotoxicity were seen in 27% of patients in the first relapse group, while no patients in MF1 developed hepatotoxicity.

- **Monotherapy for newly-diagnosed AML**: In AML 19 study (3-6 mg/m² dosing), there were no VOD case in both Mylotarg arm and BSC arm. Seven percent of patients in the Mylotarg arm developed hepatotoxicity and 6% of patients in the BSC arm developed hepatotoxicity.

5.2.2 Infusion related reactions: There were reports of fatal infusion reactions in the postmarketing setting. Severe pulmonary events leading to death occurred with the use of Mylotarg in the postmarketing setting. Infusion reactions may result in severe hypoxia and dyspnea. Other pulmonary events reported with the use of Mylotarg included acute respiratory distress syndrome, pleural effusion, pulmonary edema, lung infiltrates, and respiratory failure. The majority of these events were sequelae of other events, such as infection or sepsis.

- **Combination with DA chemotherapy**: In ALFA-0701 trial (3 mg/m² days 1, 4, and 7), there were no infusion reaction in either arm.

- **Monotherapy for relapse/refractory AML**: Grade 3-4 infusion reactions occurred in 51% of patients in the first relapse group (9 mg/m² x 2 doses), while no patient in MF1 (3 mg/m² days 1, 4, and 7) developed infusion reactions.

- **Monotherapy for newly-diagnosed AML**: There were no data.

5.2.3 Hemorrhage

Reference ID: 4127770
• **Combination with DA chemotherapy:** In ALFA-0701 trial (3 mg/m² days 1, 4, and 7), grade 3 and 4 hemorrhage events occurred in 23% of patients in the Mylotarg arm versus 9% in the control arm during induction therapy. In consolidation therapy, grade 3 and 4 hemorrhage events occurred in 13% of patients in the Mylotarg arm versus 2% in the control arm.

• **Monotherapy for relapse/refractory AML:** Hemorrhage occurred in 27% of patient in the first relapse group (9 mg/m² x 2 doses) versus in 7% of patients in MF1 (3 mg/m² days 1, 4, and 7).

• **Monotherapy for newly-diagnosed AML:** In AML 19 study (3-6 mg/m² dosing), 13% of patients in the Mylotarg arm developed hemorrhage and 12% of patients in the BSC arm developed hemorrhage.

6 **Expected Postmarket Use**

Mylotarg, if approved, will be administered in treatment centers and hospitals and the likely prescribers will be oncologists and hematologists.

7 **Risk Management Activities Proposed by the Applicant**

The Applicant did not propose any risk management activities for Mylotarg beyond routine pharmacovigilance and labeling.

8 **Discussion of Need for a REMS**

The clinical reviewers recommend approval of Mylotarg on the basis of the efficacy and safety information currently available. The clinical review team recommends a boxed warning regarding the risks of hepatotoxicity, including VOD, infusion reactions, and hemorrhage.

DRISK considers factors such as the size of the patient population, the seriousness of the disease, the expected benefit of the drug, the expected duration of treatment, the seriousness of known or potential adverse reactions, and whether the drug is a NME.

Estimated new cases and deaths from AML of adults in the United States in 2017 are 21,380 and 10,590. With the current standard chemotherapy, about 30-35% of younger patients (18-60 years) survive longer than 5 years, fewer than 10% of older patients (>60 years) survive over 5 years.

The medical reviewers concluded that Mylotarg provided clinical meaningful benefit to treat AML patients. In combination with DA for newly diagnosed patients, EFS was improved in the Mylotarg arm (17.3 months versus 9.5 months in the control arm). In monotherapy for relapse/refractory AML, there was a slightly improved CR rate compared to other non-intensive regimens. In monotherapy for newly diagnosed AML, the median OS was 4.9 months in the Mylotarg arm compared to 3.6 months in the BSC arm. The duration of Mylotarg therapy is from 2 cycles to 9 cycles.
Mylotarg has serious adverse reactions (SARs) of hepatotoxicity, including VOD, severe or fatal infusion reactions, and hemorrhage. The risk of severe infusion reactions can be mitigated by giving premedication that will be described in the prescribing information. The risk of hemorrhage is decreased by using fractionated dosing (3 mg/m² given in days 1, 4, and 7 or 6 mg/m² on day 1 and 3 mg/m² on day 8). This dosing regimen is communicated in the Dosage and Administration section of the label.

The most serious safety concern with Mylotarg is VOD. According to the statistics reviewer ⁶, there was a trend towards a decreased incidence of VOD with decrease in the dose of Mylotarg. In the ALFA-0701 trial, Mylotarg was given 3 mg/m² on days 1, 4, and 7. The incidence of VOD was 4.4% of patients in the Mylotarg arm which is lower than 9.1% of patients in the postmarketing registry study 100847 (N=482)⁷. The MF1 trial used the same fractionated dose as ALFA-0701 and there were no VOD cases. The AML 19 trial used fractionated dose 3-6 mg/m² for induction and there were no VOD cases in that trial, either.

VOD is one of the most feared complication of hematopoietic stem cell transplantation (HSCT). VOD is reported to occur in 8-14% of patients after HSCT⁸, although incidence may be as high as 60% in high-risk patients (such as those with underlying liver disease and certain specific drug exposures, including Mylotarg and sirolimus). ALFA-0701 trial demonstrated the incidence of VOD was 4.4% by using fractionated dosing of Mylotarg, the risk is low and acceptable, compared to 9.1% of postmarketing registry study.

The risk of VOD associated with cyclophosphamide, intravenous busulfan, clofarabine, and azathioprine is communicated in Prescribing Information of “Warnings and Precautions” or “Adverse Reaction” sections. There is a boxed warning for dacarbazine concerning hepatic necrosis. None of these drugs have required a REMS to address the VOD risk.

The risk of hepatotoxicity, including VOD, infusion reactions, and hemorrhage will be included in the label. The strategies to mitigate these risks, which includes using a fractionated dose and giving premedications, will be communicated in Dosage and Administration section of the label. The healthcare providers who treat AML should be familiar with the risk of hepatic VOD and the importance of patient selection and monitoring. Given that AML is a fatal disease, as well as the clinically meaningful activity of Mylotarg, DRISK and DHP agree that a REMS is not necessary to ensure the benefits of Mylotarg outweigh its risks.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary for Mylotarg to ensure the benefits outweigh the risks. The safety concerns associated with Mylotarg use are well documented. Healthcare providers who treat AML should be familiar with the risks and the importance of patient monitoring.

Should DHP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.
10 Appendices

10.1 REFERENCES

1 Jen, M. & Ko, C. Clinical and Statistical mid-cycle presentation for Mylotarg BLA 761060, April 11, 2017

2 FDA Briefing Document of Mylotarg (BLA 761060) for ODAC meeting on July 11, 2017.

3 Norsworthy, K. Clinical mid-cycle presentation for Mylotarg BLA 761060, April 11, 2017

4 Proposed Prescribing Information for Mylotarg BLA 761060, updated June 26, 2017

5 same as endnote 1 and 3

6 same as endnote 1 and 2

7 Pfizer Briefing Document of Mylotarg (BLA 761060) for ODAC meeting on July 11, 2017


9 Cyclophosphoamide Prescribing Information, dated November 2013

10 Busulfex (busulfan) for injection Prescribing Information, dated January 2015

11 Clolar (clofarabine) injection Prescribing Information, dated September 2014

12 Azathioprine (Imuran) 50 g tablets Prescribing Information, dated February 2014

13 Dacarbazine for injection Prescribing Information, dated November 2014
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEI-YEAN T CHEN
07/20/2017

CYNTHIA L LACIVITA
07/24/2017
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