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יולי 2023

רופא/ה, רוקח/ת נכבד/ה,

חברת פייזר ישראל בע"מ, מבקשת להודיעכם על על שינוי בהתוויות ומשטרי המינון והוספת מידע בעלון לרופא של התכשיר: **מיילוטארג MYLOTARG**

(POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION)

המרכיב הפעיל:

GEMTUZUMAB OZOGAMICIN 5 MG/VIAL

למידע המלא יש לעיין בעלונים המפורסמים במאגר התרופות של משרד הבריאות,

להלן העדכונים העיקריים בעלון לרופא:

4. INDICATIONS AND USAGE

4.1 Newly-Diagnosed CD33-positive Acute Myeloid Leukemia (AML)

MYLOTARG is indicated for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults and pediatric patients 1 month and older.

4.2 Relapsed or Refractory CD33-positive AML

MYLOTARG is indicated for the treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and pediatric patients 2 years and older.

5. DOSAGE AND ADMINISTRATION

5.1 Premedication and Special Considerations

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- Premedicate pediatric patients 1 month and older with acetaminophen 15 mg/kg (maximum of 650 mg) and diphenhydramine 1 mg/kg (maximum of 50 mg), 1 hour prior to MYLOTARG dosing and 1 mg/kg methylprednisolone orally or intravenously within 30 minutes prior to infusion of MYLOTARG; additional doses of acetaminophen and diphenhydramine may be administered every 4 hours after the initial pretreatment dose. Repeat with the same dose of methylprednisolone or an equivalent corticosteroid for any sign of an infusion reaction, such as fever, chills, hypotension, or dyspnea during the infusion or within 4 hours afterwards.

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5.2 Recommended Dosage

Newly-Diagnosed De Novo CD33-positive AML (Combination Regimen)

Adults

The recommended dose of MYLOTARG in adults is 3 mg/m^2. A treatment course including MYLOTARG in combination therapy for adults with newly-diagnosed de novo CD33-positive AML consists of 1 induction cycle and 2 consolidation cycles *[see Clinical Studies (14.1)]*.

For the induction cycle, the recommended dose of MYLOTARG is 3 mg/m^2 (up to one *5* mg vial) on Days 1, 4 and 7 in combination with daunorubicin and cytarabine. For patients requiring a second induction cycle, do NOT administer MYLOTARG during the second induction cycle.

For the consolidation cycles, the recommended dose of MYLOTARG is 3 mg/m^2 on Day 1 (up to one 5 mg vial) in combination with daunorubicin and cytarabine.

Pediatric Patients 1 Month and Older
The recommended dose of MYLOTARG in pediatric patients 1 month and older is:

- 3 mg/m^2 for patients with body surface area (BSA) greater than or equal to 0.6 m^2
- 0.1 mg/kg for patients with BSA less than 0.6 m^2

For Induction 1, MYLOTARG is given once in combination with standard chemotherapy. No MYLOTARG is given in the second induction cycle.
No MYLOTARG is given in the first or third intensification cycles. For Intensification 2, MYLOTARG is given once in combination with standard chemotherapy. Consider the risks and potential benefits before giving MYLOTARG during Intensification 2.

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5.3 Dosage Modifications for Toxicities

Monitor blood counts frequently through resolution of cytopenias. Monitor blood counts and chemistries at least three times per week through recovery from treatment-related toxicities. Management of some adverse reactions may require dose interruptions or permanent discontinuation of MYLOTARG, Table 1, shows the dose modification guidelines for hematologic and nonhematologic toxicities.

Table 1. Dosage Modifications for Hematologic and Nonhematologic Toxicities

Hematologic and Nonhematologic Toxicities	**Recommended Action**
For patients receiving MYLOTARG in combination therapy	
Persistent thrombocytopenia	• Adults: If platelet count does not recover to greater than or equal to 100 Gi/L within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles). • Pediatrics: Patients should have a platelet count of 75 Gi/L before the next cycle (induction or intensification).
Persistent neutropenia	• Adults: If neutrophil count does not recover to greater than 0.5 Gi/L within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles). • Pediatrics: Patients should have a neutrophil count of 1 Gi/L before the next cycle (induction or intensification).

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8 WARNINGS AND PRECAUTIONS

8.1 Hepatotoxicity, Including Veno-occlusive Liver Disease (VOD)

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In AAML0531, VOD events were reported in 25/520 (5%) pediatric patients in the MYLOTARG arm. VOD was fatal in 2 patients. Among 187 pediatric patients who underwent HSCT in the MYLOTARG arm, VOD occurred within 30 days post-HSCT in 20 (11%) patients.

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8.3 Hemorrhage

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In AAML0531, fatal bleeding occurred in 3/520 (<1%) of the pediatric patients. Grade 3 or 4 bleeding was reported in 66/520 (13%) of the pediatric patients in the MYLOTARG arm.

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9. ADVERSE REACTIONS

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9.1 Clinical Trials Experience

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Combination Therapy in Newly-Diagnosed De Novo CD33-positive AML

The safety of MYLOTARG in first-line combination therapy was evaluated in two prospective clinical trials, Study ALFA-0701 in adults and Study AAML0531 in pediatric patients.

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Study AAML0531

The safety evaluation of MYLOTARG in combination with chemotherapy in pediatric patients is based on data from AAML0531 *[see Clinical Studies (14.1)]* in randomized and treated patients (N = 520 MYLOTARG and chemotherapy and N = 517 chemotherapy alone). In the MYLOTARG arm of this study, 520 patients received Induction 1 and 326 patients received Intensification 2. Safety data collected included only Grade 3 and 4 nonhematologic adverse events, deaths, VOD/SOS, and prolongation of neutropenia and thrombocytopenia.

Table 5 shows the Grade 3 or 4 adverse reactions (≥5%) in the MYLOTARG + chemotherapy or chemotherapy alone arms in patients with newly-diagnosed de novo AML in AAML0531.

In the MYLOTARG + chemotherapy arm, fatal adverse reactions (by grouped terms) were infection (14 [3%]), multi-organ failure (5 [1%]), anemia (1 [<1%]), and hemorrhage (3 [<1%]). In the chemotherapy arm, fatal adverse reactions included infection (7 [1%]), multi-organ failure (6 [1%]), hepatic failure (1 [<1%]), hypotension (3 [<1%]), and hemorrhage (3 [<1%]).

Table 5. Grade 3 and Higher Adverse Reactions (≥5%) in Patients with Newly-Diagnosed De Novo AML in AAML0531 During Treatment Cycles with MYLOTARG

	Induction 1		Intensification 2	
	MYLOTARG + Chemotherapy N = 520 n (%)	Chemotherapy alone N = 517 n (%)	MYLOTARG + Chemotherapy N = 326 n (%)	Chemotherapy alone N = 304 n (%)
Infection[a]	186 (36%)	181 (35%)	220 (67%)	211 (69%)
Febrile neutropenia	167 (32%)	157 (30%)	79 (24%)	68 (22%)
Decreased appetite	78 (15%)	79 (15%)	61 (19%)	36 (12%)
Hyperglycemia	59 (11%)	55 (11%)	36 (11%)	28 (9%)
Mucositis[a]	55 (11%)	64 (12%)	25 (8%)	15 (5%)
Hypoxia	35 (7%)	26 (5%)	19 (6%)	22 (7%)
Hemorrhage[a]	36 (7%)	19 (4%)	19 (6%)	9 (3%)
Transaminase Increased[a]	33 (6%)	24 (5%)	23 (7%)	13 (4%)
Diarrhea	21 (4%)	36 (7%)	15 (5%)	10 (3%)
Nausea	21 (4%)	18 (4%)	23 (7%)	10 (3%)
Hypotension	16 (3%)	26 (5%)	28 (9%)	23 (8%)

[a] Grouped term consisting of multiple preferred terms

The addition of MYLOTARG to chemotherapy was associated with a higher incidence of prolonged thrombocytopenia and neutropenia particularly when used in Intensification 2. During Intensification 2, prolonged thrombocytopenia (platelets <50 Gi/L lasting past cycle Day 42 in the absence of active leukemia) was reported in 64% (190/297) of patients in the MYLOTARG + chemotherapy arm compared with 55% (146/264) in the chemotherapy alone arm. Prolonged neutropenia (neutrophils <0.5 Gi/L lasting past cycle Day 42 in the absence of active leukemia) occurred in 47% (142/300) versus 43% (118/275) of patients, respectively. The prolonged cytopenias were associated with more deaths in remission in the MYLOTARG + chemotherapy arm (29 [5%]) compared to the chemotherapy alone arm (15 [3%]).
VOD events were reported in 25 (5%) patients in the MYLOTARG + chemotherapy arm as well as 25 (5%) of the chemotherapy alone arm. VOD was fatal in 2 (<1%) and 7 (1%) patients in the MYLOTARG + chemotherapy arm and chemotherapy alone arm, respectively.

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10.4 Pediatric Use

The safety and effectiveness of MYLOTARG in combination with standard chemotherapy have been established in pediatric patients 1 month and older with newly-diagnosed de novo AML. The use of MYLOTARG for this indication is supported by evidence of effectiveness from adequate and well-controlled studies in adults with supportive data on safety and effectiveness in Study AAML0531 (NCT00372593) [see Adverse Reactions (9.1), Clinical Studies (14.1)]. AAML0531 included patients in the following age groups: 2 patients less than 27 days old, 94 patients 28 days to less than 2 years old, 225 patients 2 years to less than 12 years old, 175 patients 12 years old to less than 18 years old, and 36 patients 18 years or older in the MYLOTARG plus chemotherapy arm. The safety and effectiveness of MYLOTARG with standard chemotherapy in pediatric patients less than 1 month of age with newly-diagnosed de novo AML have not been established.
The safety and effectiveness of MYLOTARG as a single agent in pediatric patients with newly-diagnosed AML have not been established.

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14. CLINICAL STUDIES

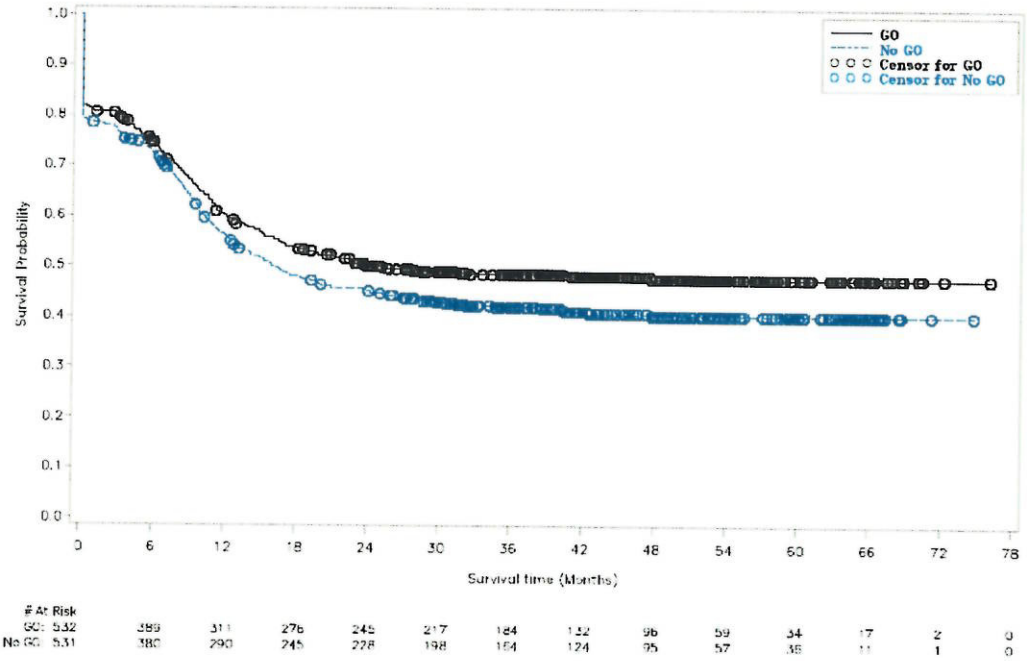
14.1 Newly-Diagnosed CD33-positive AML

Study AAML0531

MYLOTARG in combination with chemotherapy was evaluated in AAML0531 (NCT00372593), a multicenter, randomized study of 1,063 patients with newly-diagnosed AML ages 0 to 29 years. Patients were randomized to 5-cycle chemotherapy alone or with a single dose of MYLOTARG (3 mg/m^2/dose) administered once on Day 6 in Induction 1 and once on Day 7 in Intensification 2. All patients proceeded to Induction 2 regardless of remission status after Induction 1. In the absence of active disease, a neutrophil count (ANC) >1 Gi/L and a platelet count >75 Gi/L was recommended before proceeding with subsequent cycles of therapy. Patients not in remission after Induction 2 discontinued protocol therapy permanently. All other patients proceeded to Intensification 1. Patients with high- and intermediate-risk disease with 5/6 or 6/6 matched family donors (MFD) proceeded to HSCT following Intensification 1. Patients with high-risk disease proceeded to HSCT with an alternative donor if no MFD was available. All patients with low-risk disease and any high- and intermediate-risk patients without appropriate donors proceeded with Intensification 2 with or without MYLOTARG according to their initial randomization, followed by Intensification 3. All patients in remission were to proceed on to Intensification 2 or allogeneic HSCT. In Intensification 2, patients received MYLOTARG according to the initial randomization. Patients in remission after Intensification 2 proceeded to Intensification 3.
There were 532 patients randomized to treatment with MYLOTARG + chemotherapy and 531 to chemotherapy alone. Overall, 94% of patients were <18 years of age, and 6% were adults; median age was 9.0 years (range: 0-29 years). The patients were 49% male, 51% female, 73% White, 11% Black, 5% Asian, 11% other or missing race, and 18% Hispanic. The proportion of patients in each disease risk group: low risk (23% vs 23%), intermediate risk (57% vs 57%), and high risk (15% vs 17%).

Supportive evidence of efficacy was provided by event-free survival (EFS), measured from the date of study entry until induction failure, relapse, or death by any cause. Induction failure was defined as failure to achieve CR by the end of Induction 2 period, and date of induction failure was defined as Day 1 on study. The EFS hazard ratio was 0.84 (95% CI: 0.71-0.99). The estimated percentage of patients free of induction failure, relapse, or death at five years was 48% (95% CI: 43%-52%) in the MYLOTARG + chemotherapy arm versus 40% (95% CI: 36%-45%) in the chemotherapy alone arm. The Kaplan-Meier plot for EFS is shown in Figure 2. No difference between treatment arms in overall survival was demonstrated.

Figure 2. Kaplan-Meier Plot of Event-Free Survival (Full Analysis Set) Study AAML0531 Trial



Abbreviations: GO=gemtuzumab ozogamicin.

כמו כן, בוצעו שינויים נוספים הכוללים תוספת מידע, השמטת מידע ועדכוני נוסח שאינם מהווים החמרה. העלונים המעודכנים זמינים באתר משרד הבריאות.

https://data.health.gov.il/drugs/index.html#!/byDrug

לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פרמצבטיקה ישראל בע"מ, שנקר 9, ת.ד. 12133 הרצליה פיתוח, 46725.

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