# Taiwan Food and Drug Administration

# Assessment Report

**Trade Name：滅髓瘤凍晶注射劑 5 毫克 / Mylotarg 5mg Powder for concentrate for solution for infusion**

**Active Ingredient：Gemtuzumab ozogamicin**

**License Number： MOHW-BI 001244**

**Applicant：輝瑞大藥廠股份有限公司**

**Approval Date：2023.10.06**

**Indication：**
**新診斷或首次復發之 CD33 陽性急性骨髓性白血病 (AML)之成人病人。**

**Mylotarg is indicated for the treatment of newly diagnosed or first relapsed CD33 positive Acute Myeloid Leukemia (AML) in adult patients.**

## 1. Background Information

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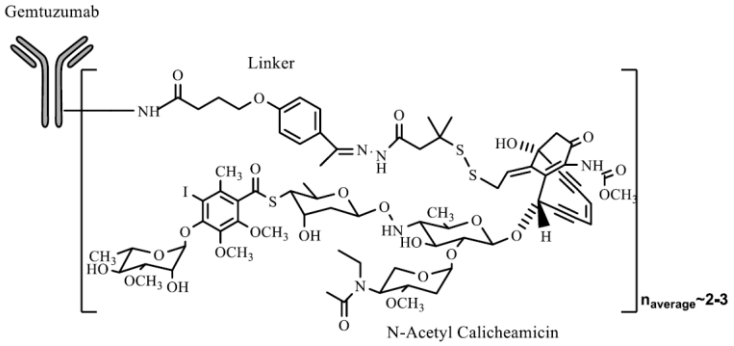
|---|---|
| **Trade Name** | 滅髓瘤凍晶注射劑 5 毫克<br>Mylotarg 5mg Powder for concentrate for solution for infusion |
| **Active Ingredient(s)** | Gemtuzumab ozogamicin |
| **Applicant** | 輝瑞大藥廠股份有限公司 |
| **Dosage Form & Strengths** | 凍晶注射劑 5 毫克 |
| **Indication** | 新診斷或首次復發之 CD33 陽性急性骨髓性白血病 (AML)之成人病人<br>Mylotarg is indicated for the treatment of newly diagnosed or first relapsed CD33 positive Acute Myeloid Leukemia (AML) in adult patients. |
| **Posology** | 詳見仿單 |
| **Pharmacological Category**<br>**ATC Code** | L01FX02 |

## 2. Summary Report

### 2.1 Chemistry, Manufacturing and Controls Evaluation

Gemtuzumab ozogamicin is an antibody drug conjugate composed of a humanized anti-CD33 monoclonal IgG4 antibody covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. The gemtuzumab ozogamicin drug substance consists of a mixture of conjugated and unconjugated gemtuzumab. The number of conjugated calicheamicin derivative molecules per gemtuzumab molecule ranges from 0 to 6, with an average of 2 to 3 moles of calicheamicin derivative per mole of gemtuzumab.

The structure of gemtuzumab ozogamicin is provided in the figure below.




The mechanism of action is binding of gemtuzumab ozogamicin to CD33-expressing tumor cells, followed by internalization of the ADC-CD33 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. The released calicheamicin derivative binds to DNA and induces double-strand DNA breaks,

subsequently inducing cell cycle arrest and apoptotic cell death.

### 2.1.1 Drug Substance Intermediate, Gemtuzumab

Gemtuzumab is produced in NS0 cells. The manufacturing process has been adequately described. The in-process control tests and limits are acceptable.

Sufficient information on raw materials used in the manufacture of gemtuzumab has been provided. An assessment and viral testing were carried out to support the transmissible spongiform encephalopathy/ bovine spongiform encephalopathy and the viral safety of gemtuzumab. Sufficient information on the manufacture and testing of the cell banks has been provided. All results complied with the acceptance criteria confirming the purity, identity and suitability of the cell banks for manufacturing use.

The gemtuzumab manufacturing process has been validated and process validation results demonstrate control, effectiveness and consistency of the gemtuzumab manufacturing process.

The structure and characteristics of gemtuzumab have been adequately described. The analytical results demonstrate that gemtuzumab has the expected primary structure and target binding properties. In addition, the results of amino acid substitution (AAS) characterization studies and the assessment of potential impact of AAS on gemtuzumab/ gemtuzumab ozogamicin quality attributes have been provided. The AASs had no impact on quality attributes, including biological activity of gemtuzumab/ gemtuzumab ozogamicin and did not create new calicheamicin conjugation sites.

The process-related impurities and product-related impurities are adequately controlled in the gemtuzumab manufacturing process.

The specification for gemtuzumab at release and for stability assessment is acceptable.
Information on the reference materials and the container closure system has been adequately provided.

The stability data provided are sufficient to support the proposed shelf life and the storage condition for gemtuzumab.

### 2.1.2 Drug Substance, Gemtuzumab Ozogamicin

The manufacturing process for gemtuzumab ozogamicin and the process controls for each step have been adequately described. The process involves conjugation of two drug substance intermediates, activated calicheamicin derivative and gemtuzumab antibody.

Sufficient information on raw materials used in the manufacturing process of gemtuzumab ozogamicin has been provided.

The gemtuzumab ozogamicin drug substance manufacturing process has been validated. It is concluded that the process consistently produces drug substance batches of acceptable consistent quality.

The structure and characteristics of gemtuzumab ozogamicin have been adequately described. The analytical results demonstrate that gemtuzumab ozogamicin has the expected structure and biological activity (cytotoxicity).

The process-related impurities and product-related impurities are adequately controlled during the gemtuzumab ozogamicin manufacturing process.

The specification for gemtuzumab ozogamicin drug substance at release and for stability assessment is acceptable.

Information on the container closure system has been adequately provided.
The stability data provided are sufficient to support the proposed shelf life and the storage condition for gemtuzumab ozogamicin drug substance.

**2.1.3 Drug Product**

The finished product, Mylotarg, is prepared as a sterile, preservative-free lyophilized dosage form, with a strength of 5 mg gemtuzumab ozogamicin/vial. The product is packaged in a 20 mL amber glass vial sealed with a rubber stopper and aluminum seal. Inactive excipients are sodium chloride, sucrose, dextran 40; monobasic sodium phosphate, monohydrate and dibasic sodium phosphate, anhydrous. Following reconstitution with 5 mL of sterile water for injection, the solution is further diluted with sterile saline and administered to patients by intravenous infusion.

The manufacturing process of gemtuzumab ozogamicin drug product has been adequately described. Sufficient information has been provided on in-process controls include critical process parameters, critical material attributes, and in-process tests used to monitor and control the manufacturing process.

The gemtuzumab ozogamicin drug product manufacturing process has been validated. It is concluded that the process consistently produces drug product lots of acceptable consistent quality.

The compendial excipients and their quality standards have been provided.

The specification for gemtuzumab ozogamicin drug product at release and for the stability assessment is acceptable.

Information on the reference materials and the container closure system has been adequately provided.

Sufficient information on stability studies for gemtuzumab ozogamicin drug product has been provided. Based on the stability data, the shelf life for drug product is 60 months at 2-8°C, protected from light.

**2.2 Preclinical Pharmacology/Toxicology Evaluation**

**2.2.1 Pharmacological Studies**

Gemtuzumab ozogamicin is a CD33-directed antibody-drug conjugate (ADC) which is composed of the hP67.6 antibody, an AcBut linker, and cytotoxic agents (N-Ac-γ-calicheamicin). No significant binding of hP67.6 to monkey CD33-expressed cells was detected. The binding of hP67.6 to soluble CD33, CD33-positive leukemia cells, or normal peripheral blood and bone marrow cells was not significantly altered by the existence of the small molecular moiety. The internalization of antibodies, intracellular release of NAc-γ-calicheamicin DMH, and activation of N-Ac-γ-calicheamicin DMH have been demonstrated in vitro.

The cytotoxic activity of gemtuzumab ozogamicin toward CD33-positive cells was much greater than that of unconjugated forms of calicheamicin or control ADC. Cytotoxic effects of gemtuzumab ozogamicin were demonstrated in primary human leukemic bone marrow samples. The antitumor activity of gemtuzumab ozogamicin was demonstrated in a xenograft mouse model. The in vivo antitumor activity of gemtuzumab ozogamicin in combination with daunorubicin/cytarabine chemotherapy was greater than that of each monotherapy.

An in vitro secondary pharmacological study showed that CD34-positive progenitor cells isolated from healthy donors were highly variable in their sensitivity to gemtuzumab ozogamicin; with low CD33 expression, the earliest progenitor/ stem cells are the most likely to be resistant to gemtuzumab ozogamicin.

Under the experimental condition, no significant changes were noted for safety endpoints regarding cardiovascular, respiratory, or central nervous system. No significant effects were observed on examined parameters for the digestive system and kidney and hepatic function.

### 2.2.2 Toxicological Studies

The primary gemtuzumab ozogamicin-related target organs in rats and monkeys included the liver, hematolymphopoietic system, kidneys, and male/female reproductive organs. An additional target organ identified in the 12-week monkey study included the eyes. The liver findings in monkeys given gemtuzumab ozogamicin and other antibody-calicheamicin conjugates are consistent with a microvascular injury related to primary damage to sinusoidal endothelial cells and recapitulate the spectrum of changes observed in humans with veno-occlusive disease. As gemtuzumab ozogamicin did not bind to the targeted CD33 antigen in rats or monkeys, the liver findings reported above were target-independent effects related to conjugated or unconjugated calicheamicin derivatives in both species.

The unconjugated calicheamicin derivative N-Ac-γ-calicheamicin DMH was positive for mutagenic activity and inducing micronuclei in vitro. Gemtuzumab ozogamicin induced micronuclei in male and female mice at the lowest dose examined. No carcinogenicity studies were conducted with gemtuzumab ozogamicin; however, preneoplastic lesions (oval cell hyperplasia in the liver) have been noted in general toxicity studies in rats.

Gemtuzumab ozogamicin damaged male/female reproductive organs, impaired male/female fertility, and resulted in malformations and embryonic lethality in rats. No hemolysis potential, unexpected tissue cross-reactivity, or phototoxicity were noted in in vitro studies. The safety of unconjugated calicheamicin derivatives (N-Ac-γ-calicheamicin DMH, N-Ac-γ-calicheamicin DMH AcBut, N-Ac-ε-calicheamicin) was evaluated, and no additional toxicity was found.

## 2.3 Clinical Pharmacology Evaluation

### 2.3.1 General Pharmacodynamics and Pharmacokinetics

Gemtuzumab ozogamicin (GO) is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (hP67.6) covalently linked to the cytotoxic agent N-Ac-γ-calicheamicin. When GO is administered at 9 mg/m$^2$ (2 doses, 14 days apart), $C_{max}$ of hP67.6 following the first dose for patients who received 9 mg/m$^2$ GO was 3.0 mg/L; $C_{max}$ increased to 3.6 mg/L after the second dose. N-Ac-γ-calicheamicin dimethyl hydrazide (DMH) is the hydrazide derivative of calicheamicin. Plasma protein binding of N-Ac-γ-calicheamicin dimethyl hydrazide (DMH) was high in mouse, rat, rabbit monkey, and human plasma (≧97%).

In vitro metabolism studies indicated that N-Ac-γ-calicheamicin DMH is primarily metabolized via non-enzymatic reduction. Based on noncompartmental analysis, CL of hP67.6 from plasma was 0.35 L/h after the first dose and 0.15 L/h after the second dose.

Moreover, $t_{1/2}$ for hP67.6 was 62 hours after the first dose and 90 hours after the second dose.

### 2.3.2 Interaction Studies

No formal drug interaction studies have been performed with GO. Coadministration of GO with inhibitors or inducers of CYP450 or UGT drug metabolizing enzymes is unlikely to alter exposure to N-Ac-γ-calicheamicin DMH.

Nonclinical in vitro assessments indicated a low potential for GO to inhibit the activities of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 at clinically relevant concentrations.

In vitro, N-Ac-γ-calicheamicin DMH had a low potential to inhibit the activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 at clinically relevant concentrations.

### 2.3.3 Special Populations

Age, race, sex had no clinically significant effect on the pharmacokinetics of GO. The PopPK results showed that the clearance of hP67.6 in patients with mild renal impairment and with moderate renal impairment was similar to the clearance of hP67.6 in patients with normal renal function. Severe renal impairment could not be assessed due to lack of information. Besides, mild hepatic impairment had no clinically significant effect on the pharmacokinetics of GO. The pharmacokinetics of GO in patients with moderate and severe hepatic impairment is unknown.

## 2.4 Clinical Efficacy and Safety Evaluation

### 2.4.1 Efficacy Results

In this submission, four studies have been provided to support the efficacy of Mylotarg for the claimed indications. Of these, Studies [ALFA-0701] and [AAML-0531] are pivotal studies, whereas Studies [AML-19] and [Mylofrance 1] are supportive studies. The key efficacy results of these studies are summarized below.

- ***Pivotal Study [ALFA-0701]***

This was a Phase III, randomized, open-label, multi-center, placebo-controlled study designed to evaluate the efficacy of GO plus DNR/AraC vs. DNR/AraC alone in patients 50-70 years old with untreated, de novo AML. The primary endpoint was investigator-assessed event-free survival (EFS), defined as the time from randomization to induction failure, relapse, or death, whichever occurred first.

The investigator-assessed EFS was significantly longer in the GO + DNR/AraC arm (HR = 0.562; 95% CI: [0.415, 0.762]; p-value = 0.0002). The IRC-assessed EFS confirmed the investigator-assessed EFS results (HR = 0.661; 95% CI: [0.491, 0.891]; p-value = 0.0059). The OS results although favored the GO + DNR/AraC arm, but the difference was not significant (HR = 0.807; 95% CI: [0.596, 1.093]; p-value= 0.1646).

- ***Pivotal Study [AAML-0531]***

This was a Phase III, randomized, open-label, multi-center, placebo-controlled study to evaluate the efficacy of GO plus chemotherapy versus chemotherapy alone in children, adolescents, and young adults aged 1 month to 29 years with newly diagnosed AML. The primary efficacy endpoints were EFS and OS.

Treatment of GO plus chemotherapy significantly improved EFS (HR = 0.838; 95% CI: [0.706, 0.995]; p-value = 0.0431), but not OS (HR = 0.904; 95% CI: [0.721, 1.133]; p-value = 0.3799). As there was no pre-specified testing strategy for the two primary endpoints (EFS and OS), no firm conclusion could be drawn from statistical perspective.

- ***Study [AML-19]***

This was a Phase III, randomized, open-label, multi-center, placebo-controlled study to evaluate the GO monotherapy versus best supportive care (BSC) in 237 adults with aged ≧ 61 years previously untreated primary or secondary AML. The primary endpoint was OS. At the data cutoff (July 31, 2014), 227 patients had died (113 patients [95.8%] in the GO arm and 115 [96.6%] in the BSC arm). Patients in the GO arm had a significantly longer OS compared to the BSC (median OS was 4.9 months and 3.6 months, respectively; HR = 0.69; 95% CI: [0.53, 0.90]; p = 0.005). The benefit of OS was observed in most subgroups.

- ***Study [Mylofrance 1]***

This was a Phase II, single-arm study to evaluate the fractionated does of GO monotherapy in adult patients with AML in first relapse. The primary endpoint was complete response rate (CR and CRp) within 43 days. Of the 57 patients enrolled, 19 patients reached CR (n = 15) or CRp (n = 4), with the complete response rate of 33.33% (95% CI: 21.4%, 47.06%). This study objective was achieved because the lower bound of the 95% CI was greater than the pre-specified threshold of 15%.

**2.4.2 Safety Results**

Major safety concerns include myelosuppression, infections, hemorrhage, veno-occlusive disease (VOD), hypophosphatemia, hypokalemia, elevated liver enzymes, increased bilirubin, nausea, vomiting, constipation, mucositis and headache.

### 2.5 Bridging Study Evaluation

The $C_{max}$ and $AUC_{inf}$ of hP67.6 following initial various doses were compared between U.S. (Study 101) and Japanese patients (Study 103). The results showed that the exposures were comparable at 6 mg/m$^2$. Besides, the $C_{max}$ and $AUC_{inf}$ in Western (Studies 101, 201, 202, 203) and Japanese patients (Study 103) following a single 9 mg/m$^2$ dose were compared. Although the PK parameter distributions varied widely, regardless of region, the GO exposure in Japanese patients was within the range of values observed in Western patients. Taken together, no obvious difference in GO exposure following an initial dose range over 6 to 9 mg/m$^2$ was observed between Western and Japanese patients.

The comparison of GO PK in Western and East-Asian patients in regard to the data following the first dose, second dose, and at the steady state (e.g. $C_{max,ss}$, $C_{trough,ss}$, and $AUC_{ss}$) are the information of interest to evaluate the ethnic sensitivity of GO. The adult popPK model indicated no significant race effect on the PK of hP67.6 or unconjugated calicheamicin. Moreover, the adult popPK model indicated race (including Asian) was not a significant covariate in the exposure-response relationship for efficacy and safety endpoints within the adult population. In addition, based on the exposure-response relationship curve for efficacy or safety, there was no steep curve within the recommended dosing range. In conclusion, no adjustment of dose nor a PK bridging study is warranted for Asian patients.

There were few East Asian subjects in global clinical trials.

Study 103 was conducted in Japanese subjects with relapsed/refractory AML, 20 subjects were assigned to 6.0, 7.5 and 9.0 mg/m$^2$ of gemtuzumab ozogamicin given twice 14 days apart. The complete remission rate (CR+CRp) was 30%.

### 2.6 Conclusion

Approval of Mylotarg is recommended for the following indications.
(1) Newly diagnosed CD33 positive AML (combination therapy) in adults
(2) Newly diagnosed CD33 positive AML (monotherapy) in adults
(3) First relapsed CD33-positive AML as single-agent regimen

## 3. Post-Marketing Requirements

(1) Submit PBRER every year for periodic review, the PBRER should include analysis and discussion of the major identified risks, e.g. liver toxicity and VOD.
(2) Post marketing requirements in approval letter issued by USFDA dated on Sep. 11, 2017: PMR 3266-1 and PMR 3266-2.