

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761060Orig1s000

761060Orig2s000

PRODUCT QUALITY REVIEW(S)

Approval for Acute Myelogenous Leukemia

Recommendation: Approval

BLA 761060 Integrated Quality Assessment Review Date

Drug Name/Dosage Form	Mylotarg lyophilate
Strength/Potency	4.5 mg per vial
Route of Administration	intravenous
Rx/OTC Dispensed	Rx
Indication	Combination therapy with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33 positive acute myeloid leukemia (AML) and patients with CD33-positive AML in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy
Applicant/Sponsor	Pfizer

Product Overview

Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of a humanized IgG4, kappa anti-CD33 mAb manufactured in NS0 cells that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. Gemtuzumab ozogamicin consists of conjugated and unconjugated gemtuzumab; the conjugation range is 0 to 6, with an average of 2 to 3 moles of calicheamicin derivative per mole of gemtuzumab.

The mechanism of action is binding to CD33 expressing tumor cells, followed by internalization 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.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
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(b) (4)/Drug Substance/ Drug Product	Charles Jewell	ONDP/DNDAP1
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Microbiology	Maria Lopez-Barragan/Natalia Pripuzova	OPF/DMA
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Team Lead Microbiology	Reyes Candau-Chacon	OPF/DMA
Team Lead Facilities	Peter Qiu	OPF/DIA
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Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Kris Kolibab	OHOP/DHP
Cross-disciplinary Team Lead	Donna Przepiorka	OHOP/DHP
Medical Officer	Emily Jen/Kelly Norsworthy	OHOP/DHP
Pharm/Tox	Pedro DelValle	OHOP/DHOT
Clinical Pharmacology	Christy John	OCP/DCPV
Statistics	Lei Nie	OB/DBV

a. Names

- i. Proprietary Name: Mylotarg
- ii. Trade Name: Mylotarg
- iii. Non-Proprietary/USAN: gemtuzumab ozogamicin
- iv. CAS name: 220578-59-6
- v. Common name: CMA-676, PF-05208747, CL-555,201
- vi. INN Name: gemtuzumab ozogamicin
- vii. OBP systematic name: CONJ: MAB HUMANAZED (IGG4 S324P) ANTI P20138 (CD33_HUMAN); CALICHEAMICIN [CMA676]

b. Pharmacologic category: A CD33-directed antibody-drug conjugate

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761060.1	11/2/2016 (Original Submission)
761060.3 response to IR #1	11/18/2016 (manufacturing schedule)
761060.7 response to IR #2	12/19/2016 (manufacturing schedule and 356H)
761060.14 response to IR #3	2/22/2017 (DP microbiology)
761060.19 response to IR #4	3/13/2017 (b) (4) DS product quality and microbiology
761060.28 response to IR #5	4/4/2017 (DP microbiology)
761060.37 response to IR #6	6/5/2017 (DP product quality)
761060.44 response to IR #7	7/14/17 (b) (4) DS microbiology)
761060.45 response to IR #8	7/14/17 (DS and DP product quality)
761060. 50 Response to IR #9	7/28/2017 (DP stability)

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	Date Complete	STATUS ²	COMMENTS
(b) (4)	V		(b) (4)	3	N/A	N/A	(b) (4) None
	V		3	N/A	N/A	None	
	V		3	N/A	N/A	None	
	III		3	N/A	N/A	None	
	V		3	N/A	N/A	None	
	III		3	N/A	N/A	None	
	V		3	N/A	N/A	None	
	V		3	N/A	N/A	None	

(b) (4)	(b) (4)				
II		1	4/12/2017	Adequate	None

¹ Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available; 6 – Other (explain under "Comments")

² Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross reference to other Pfizer/Wyeth applications	IND 46635	IND for gemtuzumab ozogamicin
Cross reference to other Pfizer/Wyeth applications	NDA 21-174	Original NDA for Mylotarg

3. CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

- a. Recommendation:
The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761060 for Mylotarg, manufactured by Pfizer pending acceptable compliance checks and response to the microbiology information request dated July 28, 2017. The data submitted in this application are adequate to support the conclusion that the manufacture of Mylotarg is well controlled and leads to a product that is pure and potent. We recommend that Mylotarg be approved for human use under the conditions specified in the package insert.
- b. Summary of Complete Response issues
None
- c. Action letter language
- Manufacturing location:
 - Drug substance
Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., Pearl River, NY 10965-1299
 - Drug product manufacture and filling
Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., Pearl River, NY 10965-1299
 - Drug product labeling and packaging
Pharmacia and Upjohn Company, a subsidiary of Pfizer Inc., Kalamazoo, MI 49001
 -  (b) (4)
 -
 - Fill size and dosage form – 4.5 mg/vial for injection
 - Dating period:
 - Drug product – 60 months; 2-8°C
 - Drug substance –  (b) (4)
 -  (b) (4)
 -
 - Stability option
 - For stability protocols:
Not applicable – data for both  (b) (4)
drug substance and drug product support the requested expiration dating periods with no further extensions
 - Exempt from lot release
 - Yes - specified product per 601.2a
- d. Benefit/Risk Considerations
Mylotarg is intended for the treatment of adult patients with previously untreated, de novo CD33+ acute myeloid leukemia (AML) in combination

with daunorubicin and cytarabine (DA). Mylotarg was granted accelerated approval in 2000 as a single agent for the treatment of patients with CD33+ AML in first relapse who are 60 years of age or older and were not considered candidates for cytotoxic therapy. However, the confirmatory clinical study did not confirm the clinical benefit of Mylotarg and fatal hepatotoxicity and veno-occlusive disease were added as boxed warning in the post-marketing period. Mylotarg was voluntarily withdrawn from the market in 2010. Subsequent studies suggested that lower doses of Mylotarg than the originally approved dose could be used safely in combination with DA. The clinical study supporting the BLA showed a significant difference in event-free survival (EFS) for patients in the Mylotarg + DA arm versus the DA arm alone. The Oncology Drugs Advisory Committee determined that EFS is a reasonable end point for this indication and that a favorable risk: benefit profile was demonstrated

- e. Environmental Assessment or Claim Of Categorical Exclusion
Pfizer requests a categorical exclusion under 21 CFR 25.31 (c). The applicant states at the point of entry into the aquatic environment, the estimated concentration of the substance will be below 1 part per billion. Pfizer states they have no knowledge of any extraordinary circumstances.

The claim of categorical exemption is accepted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. Re-evaluate gemtuzumab ozogamicin drug substance and drug product lot release acceptance criteria for appearance, iCE, CGE and cytotoxicity assays based on ≥ 25 unique combinations of gemtuzumab and ^{(b) (4)}
 lots used to manufacture gemtuzumab ozogamicin drug substance and drug product using the commercial manufacturing process and tested using the commercial specification methods. Pfizer will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
2. To repeat the bioburden and endotoxin test method qualifications using two additional batches of gemtuzumab ozogamicin drug substance and submit the qualification report to the Agency by August 2018.
3. To repeat the sterility and endotoxin drug product release method qualification using two batches of drug product to be manufactured in 2017 and submit the method qualification report by November 2017.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Note that Table 1 describes CQAs intrinsic to the gemtuzumab ozogamicin drug substance. (b) (4)

[Redacted]

[Redacted] (b) (4)

Table 1: API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Total calicheamicin derivative (Potency)	Impact on safety and efficacy			(b) (4)
(b) (4) (Impurity)	Impact on safety and efficacy			
Target Binding (Potency)	Impact on safety and efficacy			
Cytotoxicity (Potency)	Impact on safety and efficacy			NA

		(b) (4)	
Intact IgG (Purity)	Impact on safety and efficacy		NA
Heavy and Light Chain (Purity)	Impact on safety and efficacy		NA
Aggregate (b) (4) (Product Variant)	Impact on biological activity, immunogenicity, PK/PD, and safety		NA
(b) (4) (Product Impurity)	Impact on safety and immunogenicity		(b) (4)

(b) (4)	Impact on safety	(b) (4)	(b) (4) NA
(Product Impurity)			

B. Drug Substance [gemtuzumab ozogamicin] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color and opalescence (General)	Impact on safety and immunogenicity	(b) (4)	(b) (4)	(b) (4)
Protein Quantity (General)	Impact on efficacy			NA
Identity (General)	Impact on safety and efficacy			(b) (4)
pH (General)	Impact on safety			

Endotoxin (Contaminant)	Impact on safety and purity	Raw materials or contamination during the manufacturing process	
Bioburden (Contaminant)	Impact on safety, purity and efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during the manufacturing process	

- a. Description
Gemtuzumab, (b) (4) is a humanized IgG4, kappa anti-CD33 mAb produced in NS0 cells (b) (4)
is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. Gemtuzumab ozogamicin consists of conjugated and unconjugated gemtuzumab ranging from predominantly 0 to 6 calicheamicin per mAb, with an average of 2 to 3 moles of calicheamicin derivative per mole of gemtuzumab.
- b. Mechanism of action
The gemtuzumab mAb (hP67.6) binds to CD33 expressing tumor cells, followed by internalization 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.
- c. Potency Assay
In the cytotoxicity assay, CD33-expressing HL60 cells are incubated with serial dilutions of gemtuzumab ozogamicin reference standard, test samples and controls for three days. Internalization of the ADC-CD33 complex results in inhibition of growth. After three days, the luminescent reagent Cell Titer-Glo is added to the cells, emitting a luminescent signal that is directly proportional to the amount of ATP present in cells. Levels of ATP are directly proportional to the number of viable cells in the culture. Cells incubated with higher levels of gemtuzumab ozogamicin have lower viability and therefore, a lower luminescent signal. Dose response curves are generated by a four-parameter logistic fit and potency of test samples is reported relative to the reference standard.
- d. Reference material(s)
See DP section. (b) (4)
- e. Critical starting materials or intermediates (b) (4)
- f. Manufacturing process summary (b) (4)



(b) (4)

g. Container closure



(b) (4)

h. Dating period and storage conditions



(b) (4)



(b) (4)

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D. Drug Product [Established Name] Quality Summary

Table 5 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 5: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Appearance (Lyophile)	Measure of purity, impact on product safety and immunogenicity	DP manufacture (b) (4)	(b) (4)	(b) (4)
Appearance reconstituted solution; color and clarity, visible particulates	Measure of purity, impact on product safety and immunogenicity	DP manufacture (b) (4)	(b) (4)	
Sub-visible particulates (General)	Impact on product safety and efficacy	DP manufacture (b) (4)	(b) (4)	
Reconstitution time (General)	Impact on product quality	DP manufacture (b) (4)	(b) (4)	(b) (4)

pH (General)	Impact on product stability and conformation	(b) (4)	(b) (4)
Protein Quantity (General)	Impact on efficacy	DP manufacture (b) (4)	(b) (4)
Content Uniformity	Impact on efficacy	DP manufacture (b) (4)	(b) (4)
Moisture Content (General)	Impact on product safety, immunogenicity and therapeutic dose	DP manufacture (b) (4)	(b) (4)
Osmolality (General)	Potential impact on therapeutic dose	(b) (4)	(b) (4)
Identity	Impact on safety and efficacy	Intrinsic to molecule. (b) (4)	(b) (4)
Endotoxin (Contaminant)	Impact on safety and purity	Contamination may be introduced throughout DP	(b) (4)

		manufacturing process.	(b) (4)
Sterility (Contaminant)	Impact on safety, purity and efficacy	Contamination may be introduced throughout DP manufacturing or by container closure integrity failure.	
	(b) (4)		
Container Closure Integrity (Contaminant)	Impact on safety	May be impacted by storage conditions.	

a. Potency and Strength

Mylotarg is supplied as gemtuzumab ozogamicin for injection, 4.5 mg/vial drug product, a white to off-white cake or powder

b. Summary of Product Design

Mylotarg is reconstituted with 5 mL sterile WFI providing a 1 mg/ml solution and a withdrawable volume of 4.5 mL. The Quality Target Product Profile (QTPP) ensures product quality and safety by the following:

- Product meets and maintains quality attribute targets during manufacture, transport, storage shelf-life and use
- DP does not interact with packaging components to compromise safety and efficacy
- DP that is sterile and with low-endotoxin levels
- (b) (4)
- Acceptable appearance, essentially free from visible particles after reconstitution
- DP that is suitable for intravenous administration and meets pharmacopeial requirements for parenteral administration
- Sufficient shelf life at 2-8°C to support commercial use

c. List of Excipients

- Dextran 40 - (b) (4) mg/vial
- Dibasic Sodium Phosphate, Anhydrous - (b) (4) mg/vial
- Monobasic Sodium Phosphate, Monohydrate - (b) (4) mg/vial
- Sodium Chloride - (b) (4) mg/vial
- Sucrose - (b) (4) mg/vial

d. Reference material(s)

(b) (4)

e. Manufacturing Process

(b) (4)

f. Container Closure

(b) (4)

g. Expiration Date & Storage Conditions

The shelf life for drug product is 60 months at 2-8°C, protected from light.

- h. List of co-packaged components, if applicable
Not applicable

E. Novel Approaches/Precedents

No novel approaches. Mylotarg is the first product to be approved initially as an NDA and subsequently as a BLA. The NDA withdrawn from the market in 2010 and due to the change in the definition of a biological product when the Affordable Health Care Act was signed into law in 2010, antibody-drug conjugates are now regulated as biologics under the Public Health Service Act.

F. Any Special Product Quality Labeling Recommendations

Mylotarg will be labeled as 4.5 mg per vial, because the amount of a 1 mg/mL solution upon reconstitution of the lyophilate that can be consistently delivered is 4.5 mg.

G. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE/ DRUG PRODUCT (b) (4)					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Manufacture of drug substance and drug product, release testing, stability testing, storage (b) (4)	Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc. 401 North Middletown Road Pearl River, NY 10965-1c299	054065909/ 2410662	PLI conducted 3/9-17/2017.	7- item 483	Acceptable

(b) (4)

Drug product secondary packaging and labeling	Pharmacia and Upjohn Company (a subsidiary of Pfizer Inc.) 7000 Portage Road Kalamazoo, MI 49001	829076566/ 1810189	No Further Evaluation	NA	NA

(b) (4)

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Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity		X	
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other: Antibody-Drug Conjugate	X		
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (# _____)		X	
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements tem)		X	
18.	SPOTS (Special Products On-line Tracking System		X	

19.	USAN Name Assigned		X		
20.	Other _____				
Quality Considerations					
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements		X		
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____			X	



Marjorie
Shapiro

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Sarah
Kennett

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Reyes
Candau-Chacon

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Charles
Jewell

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