CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761121Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 31, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761121
Product Name and Strength:	Polivy (polatuzumab vedotin-piiq) for Injection, 140 mg per vial
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	April 29, 2019, May 14, 2019 and May 28, 2019
OSE RCM #:	2018-2556-1
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Polivy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Polivy are acceptable from a medication error perspective. We have no further recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Garrison N. Label and Labeling Review for POLIVY (BLA 761121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 23. RCM No.: 2018-2556.

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/s/

NICOLE B GARRISON
05/31/2019 07:11:17 AM

HINA S MEHTA
06/03/2019 08:41:21 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 2, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Wanda Nguyen, RPM
DHP

Subject: QT-IRT Consult to BLA 761121 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 12/20/2018 regarding the sponsor's concentration-QTc report 1089926. The QT-IRT reviewed the following materials:

- Concentration-QTc analysis report: 1089926 (Submission 0001);
- Summary of clinical pharmacology studies (Submission 0001);
- Study reports for DCS4968g and G027834 (Submission 0001);
- Proposed label (Submission 0002);
- Previous QT-IRT review for BLA 125388 / BLA 125399 (link); and
- Previous QT-IRT review(s) for IND 109409 dated 09/04/2014 and 03/22/2017 in DARRTS.

1 QT-IRT Responses

We agree with the sponsor's conclusion that polatuzumab vedotin does not cause large mean increase on QTc interval at the proposed therapeutic dose (i.e., 1.8 mg/kg).

2 Internal Comments to the Division

We agree with the sponsor's proposed label language in Section 12.2, Cardiac Electrophysiology (Submission 0002).

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

We agree with this proposed language. It's consistent with the label for brentuximab vedotin, the other antibody-drug conjugate with the same small molecule component.

3 BACKGROUND

Polatuzumab vedotin (Pola, DCDS4501A) is a CD79b-targeted antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E, or MMAE) to B-cells. Upon binding CD79b, polatuzumab vedotin is rapidly internalized and the linker is cleaved to enable intracellular delivery of MMAE. MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis. After the dosing of polatuzumab vedotin, multiple analytes were measured. The current polatuzumab vedotin assay strategy includes the measurement of three key analytes to assess the overall polatuzumab vedotin PK: antibody-conjugated MMAE (acMMAE), total antibody, and unconjugated MMAE.

Genetech is developing polatuzumab vedotin (b) (4) (b) (4) (b) (4). The proposed therapeutic dose is 1.8 mg/kg IV infusion every 3 weeks.

The molecular size of polatuzumab vedotin (145 g/mol) and acMMAE suggest a very small chance of direct interaction with cardiac ion channels. Unconjugated MMAE (718 g/mol) was found to not inhibit the hERG channel in vitro (i.e. IC50 > 100 μM). With a total Cmax of ~10 nM (~7 ng/mL) at the proposed dose, the IC50-based safety margin is greater than 10000-fold.

Previously the sponsor proposed to use triplicate ECG data and cardiac safety data from Phase I and II studies to assess the QTc prolongation risks for polatuzumab vedotin. In QT-IRT review under IND 109409 dated 03/22/2017, it was concluded that data from the proposed Phase 1 and II studies (i.e. studies DCS4968G and GO27834) were not ideal for characterizing QT effects using concentration-QTc analysis. It was also concluded that no large mean QTc prolongation effect would be expected for polatuzumab vedotin at the proposed therapeutic dose (1.8 mg/kg IV infusion every 3 weeks), because systemic exposure of the unconjugated small molecule component after polatuzumab vedotin treatment is not significantly higher than that with an approved antibody drug conjugate, brentuximab vedotin.

In the current submission, the sponsor submitted a concentration-QTc report of polatuzumab vedotin in patients with B-Cell hematologic malignancies using data from studies DCS4968g and GO27834. Polatuzumab vedotin did not cause significant change in heart rate. The linear mixed-effect concentration-ΔQTcF models were developed for total antibody, acMMAE, and unconjugated MMAE. A total of 996 QTcF data points from 209 patients, and a total of 968 ΔQTcF data points from 197 patients were available for the analysis. The range of doses of available data was from 0.25 to 2.4 mg/kg. The upper bound of 90% CI of ΔQTcF at mean $C_{max,ss}$ was estimated to be less than 10 ms for all three analytes. Concomitant medications

(rituximab or obinutuzumab, both were monoclonal antibodies that are expected to have low likelihood of direct interaction with cardiac ion channels), cycle number, and study ID were not identified as a significant covariate on the concentration-QTc relationship. The results from concentration-QTc analysis was supported by by-timepoint analysis (descriptive statistics) and categorical analyses of QTcF and ΔQTcF. The largest mean increase in ΔQTcF was 10.3 ms (90% CI: 6.9-13.7 ms, n=62) occurring on Cycle 3 Day 1/Day 2 postdose. Only two patients had a QTcF value >500 ms, which all occurred at baseline. No patients had ΔQTcF >60 ms.

Although there are some limitations to the PK/ECG collection times (as described below), the systemic exposure of unconjugated MMAE is not significantly higher than that in brentuximab vedotin and the results from sponsor's analyses are consistent with the projected QTc effect based on experiences with brentuximab vedotin. Therefore, the data are acceptable to exclude large mean increases in the QTc.

1) PK/ECG sampling schedule in the PK/ECG sub-group is too sparse (i.e. one postdose data in each sampling period) to support the evaluation of potential delayed effect which could result in an underprediction of drug effect on QTc; and
2) PK/ECG sampling schedule is not adequate to cover maximum exposure of the unconjugated MMAE. Tmax of unconjugated MMAE is 2-4 days (mean: 3.4 days) after dosing, but PK/ECG data were only available on Day 1, 2, and 8 in the treatment cycle. The observed geometric mean Cmax of MMAE in the PK/ECG population is significantly lower than what was reported based on intensive PK monitoring.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 23, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761121
Product Name and Strength:	Polivy (polatuzumab vedotin-xxxx) for Injection, 140 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	December 19, 2018
OSE RCM #:	2018-2556
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Polivy (polatuzumab vedotin-xxxx) for injection, the Division of Hematology Products (DHP) requested that we review the proposed Polivy Prescribing Information, container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B- N/A
ISMP Newsletters	C- N/A
FDA Adverse Event Reporting System (FAERS)*	D- N/A
Other	E- N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

We performed a risk assessment of the proposed container labels, carton labeling, Prescribing Information for Polivy (polatuzumab vedotin-xxxx) for Injection to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We note that the proposed Prescribing Information (PI) advises that the prepared solution for infusion not be transported because agitation can result in aggregation. Per the PI, if the prepared solution for infusion needs to be transported, air needs to be removed from the infusion bag and transportation be limited to 30 minutes at 9°C to 25°C or (b)(4) hours at 2°C to 8°C. If air is removed, an infusion set with a vented spike is required to ensure accurate dosing during the infusion.

We contacted the Office of Pharmaceutical Quality (OPQ) to determine if the transportation and storage recommendations were necessary for this product. After internal discussions, it was determined that most products advise not to shake or agitate in the labeling, but do not require removal of air from the bag prior to transportation or require transportation temperature. We defer to OPQ on the determination of transportation and storage instructions.

Additionally, we note that the dilution instructions lack clarity. Polivy must be diluted to a final concentration of 0.72 mg/mL – 2.7 mg/mL in an intravenous bag with a minimum volume of 50 mL containing 0.9% Sodium Chloride Injection USP, 0.45% Sodium Chloride USP, or 5% Dextrose Injection USP. However, after determining the volume of the 20 mg/mL reconstituted solution needed based on the required dose the PI instructs users (b) (4) (b) (4) Since Polivy must be diluted to a wide final concentration range of 0.72 mg/mL to 2.7 mg/mL, we sent an Information Request to the Applicant requesting their rationale for withdrawing from the intravenous infusion bag the required volume of reconstituted solution. In a response received on April 15, 2019, the Applicant indicated that the instruction (b) (4) (b) (4) was based on the process done in the clinical trials. However, the Applicant stated it can be removed from the preparation instructions given the entire infusion solution is administered and based on compatibility studies[a].

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Hematology Products (DHP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The Dosage and Administration Section contains negative statements (b) (4)	Post-marketing reports indicate that negative statements (b) (4) may have the opposite of the intended meaning because the word (b) (4) can be overlooked and the warning may be misinterpreted as an affirmative action.	Delete the statement, (b) (4) (b) (4)
2.	The product has complex preparation instructions.	It is important to alert healthcare providers that additional important	Consider adding the statement, "See Full Prescribing Information for instructions on reconstitution

[a] Response to Information Requested received on April 15, 2019.

Table 2. Identified Issues and Recommendations for Division of Hematology Products (DHP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		information is in the Full Prescribing Information.	of lyophilized powder, and preparation and administration of injection. (2.4)."
3.	The dosage information, as presented in the Dosage and Administration section lacks clarity due to the layout in which the information is presented.	Lack of clarity may lead to underdose or overdose medication errors.	We recommend the use of bulleting in order to improve clarity and readability. As an example, consider the following bulleted format: • Administer only as an intravenous infusion. • Recommended dose is 1.8 mg/kg Polivy every 21 days for 6 cycles.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Use of confusing symbols (e.g., ">" and "<")	These symbols may be mistaken as opposite of intended.	Replace the symbols "≤" , "≥","μ" and ">" with their intended meanings to prevent misinterpretation and confusion.
2.	In Section 2.4, *Instructions for Preparation and Administration* of the Prescribing Information, the required diluents 0.9% sodium chloride, 0.45% sodium chloride, and 5% dextrose are not listed using proper nomenclature.	Using improper nomenclature to describe the required diluents may lead to confusion and preparation errors.	Revise the statements to proper nomenclature, "0.9% Sodium Chloride Injection, USP", "0.45% Sodium Chloride Injection, USP", and "5% Dextrose Injection, USP".
3.	The Prescribing Information advises (b) (4)	Inclusion of the statement, (b) (4) (b) (4) is standard practice for intravenous	In Section 2.4, *Instructions for Preparation and Administration* of the Prescribing Information, replace the statement, (b) (4)

Table 2. Identified Issues and Recommendations for Division of Hematology Products (DHP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	preparation and does not need to be restated in the Prescribing Information.	(b) (4) (b) (4) with "Polivy is a cyctotoxic drug. Follow applicable special handling and disposal procedures." (b) (4)
4.	The route of administration is presented using the abbreviation "IV" instead of "intravenous".	The route of administration should be described without abbreviation.	Revise the route of administration from "IV" instead of "intravenous".
5.	The reconstitution instructions lack clarity.	Lack of clarity of the reconstitution instructions may lead to product preparation errors.	• Delete the first bullet, "Reconstitute immediately before dilution." and replace with "Calculate the dose (mg) and number of vials of Polivy required." • Revise the second bullet to, "Reconstitute each vial with 7.2 mL Sterile Water for Injection, USP, to obtain a concentration of 20 mg/mL of Polivy." • Revise the statement (b) (4) (b) (4)

Table 2. Identified Issues and Recommendations for Division of Hematology Products (DHP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			store in a refrigerator at 2°C to 8°C (36°F to 46°F)…" • Delete the last bullet, (b) (4) As this information does not belong in the reconstitution section.
6.	The Dosage and Administration Section contains negative statements (b) (4) in the dilution section of section 2.4 *Instructions for Preparation and Administration* of the Prescribing Information.	Post-marketing reports indicate that negative statements (b) (4) may have the opposite of the intended meaning because the word (b) (4) can be overlooked and the warning may be misinterpreted as an affirmative action.	Delete the statement, (b) (4) (b) (4)

Table 3. Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The Prescribing Information contains conditionally acceptable proprietary name, Polivy. However, the container labels and carton labeling contain a placeholder "Tradename" in the position of the conditionally acceptable proprietary name, Polivy.	The conditionally acceptable proprietary name, Polivy should be prominent on the container labels and carton labeling.	Revise the container labels and carton labeling with the conditionally acceptable proprietary name, Polivy to be consistent with the Prescribing Information.

Table 3. Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The Rx Only statement is prominent.	The Rx Only statement appears prominent on the principal display panel.	Decrease the prominence by debolding the Rx Only statement.
3.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Container Label(s)			
1.	The storage information is not prominent on the side display panel.	Lack of prominence of the storage information may result in product storage errors.	On the side display panel, revise the storage information as follows, “Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.” We recommend this to increase the prominence of this important

Table 3. Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			information and minimize the risk of the storage information being overlooked.
2.	The container label for the Hillsboro packaging site has the numbers, "10207250" located in close proximity of the expiration date.	The close proximity of the numbers, "10207250"may cause them to be mistaken for the expiration date.	If possible, relocate the numbers, "10207250" away from the expiration date to mitigate the risk for confusion with the expiration date.
3.	Polivy has a cytotoxic component; however this information not omitted from on the container labels.	Cytotoxic products require special handling procedures.	Include the statement in bold red font on the side display panel, "CAUTION: Cytotoxic Agent".
Carton Labeling			
1.	The storage information is not prominent on the side display panel.	Lack of prominence of the storage information may result in product storage errors.	On the side display panel, revise the storage information as follows, "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light prior to reconstitution. Reconstitute immediately before dilution. If needed, store unused reconstituted solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 48 hours or at room temperature (9°C to 25°C, 47°F to 77°F) up to a maximum of 12 hours prior to dilution. Discard vials of unused reconstituted solution if cumulative storage time exceeds 48 hours. Do not freeze." We recommend this to increase the prominence of this important information and minimize the risk of the

Table 3. Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			storage information being overlooked.
2.	The side display is cluttered.	Important preparation instructions may be overlooked if the side display panel is cluttered.	Revise the reconstitution and dilution instructions as follows: Reconstitution: Reconstitute each Polivy vial with 7.2 mL of Sterile Water for Injection, USP to obtain a concentration of 20 mg/mL of polatuzumab vedotin-xxxx with a pH of 5.3. Gently swirl. Do not shake." This will allow deletion of "Each mL of reconstituted solution contains 20 mg polatuzumab vedotin. The pH of the reconstituted solution is approximately 5.3." Revise the statement from (b) (4) (b) (4) to read as, "Dosage: See Prescribing Information ."
3.	The storage statement, "Keep Refrigerated" is on the principal display panel and the side display panel.	Having duplicate statements on the label increases visual clutter.	On the principal display, remove the duplicate storage statement, (b) (4) (b) (4).
4.	Polivy has a cytotoxic component; however that information not indicated on the container labels.	Cytotoxic products require special handling procedures.	Include the statement in bold red font on the principal display panel, "CAUTION: Cytotoxic Agent".

4 CONCLUSION

Our evaluation of the proposed Polivy prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Genentech, Inc. so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Polivy that Genentech, Inc. submitted on December 19, 2018.

Table 4. Relevant Product Information for Polivy	
Initial Approval Date	N/A
Active Ingredient	polatuzumab vedotin-xxxx
Indication	(b) (4)
Route of Administration	Intravenous infusion
Dosage Form	for injection
Strength	140 mg per vial
Dose and Frequency	1.8 mg/kg administered as an intravenous infusion every 21 days for 6 cycles in combination with bendamustine and rituximab.
How Supplied	Preservative-free white to grayish-white lyophilized (b) (4) supplied in a single-dose 20 mL vial that delivers 140 mg of polatuzumab vedotin-xxxx vedotin after reconstitution. Each carton contains one single-dose vial.
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not use beyond the expiration date on the carton. Do not freeze. Do not shake.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Polivy labels and labeling submitted by Genentech, Inc..

- Container label(s) received on December 19, 2018
- Carton labeling received on December 19, 2018
- Prescribing Information (Image not shown) received on December 19, 2018

F.2 Label and Labeling Images

Container labels

(b) (4)

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[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 23, 2019

To: Wanda Nguyen, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, Team Leader, OPDP

Subject: OPDP Labeling Comments for POLIVY™ (polatuzumab vedotin-xxxx) for injection, for intravenous use

BLA: 761121

In response to DHP's consult request dated December 3, 2018, OPDP has reviewed the proposed product labeling (PI) for the original BLA submission for POLIVY™ (polatuzumab vedotin-xxxx) for injection, for intravenous use (Polivy).

PI: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on April 19, 2019, and are provided below.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

Product Labeling

Section	Statement from draft	Comment
6 Adverse Reactions, 6.1 Clinical Trial Experience	(b) (4)	
12 Clinical Pharmacology, 12.1 Mechanism of Action		

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/s/

NISHA PATEL
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CLINICAL INSPECTION SUMMARY

Date	April 5, 2019
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Cynthia Kleppinger, M.D., GCPAB *for* Min Lu, M.D., M.P.H. GCPAB Acting Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Yvette Kasamon, M.D., Ph.D., Medical Officer R. Angelo de Claro, Clinical Team Leader Ann Farrell, M.D., Director Wanda D. Nguyen, Regulatory Project Manager Division of Hematology Products
NDA	BLA 761121
Applicant	Genentech, Inc.
Drug	Polatuzumab vedotin
NME	Yes
Therapeutic Classification/Status	Humanized immunoglobulin G1 (IgG1) anti-human CD79b monoclonal antibody
Proposed Indication	(b) (4)
Consultation Request Date	January 7, 2019 (Priority Review)
Summary Goal Date	April 30, 2019 (original)
Action Goal Date	April 30, 2019
PDUFA Date	August 19, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

A single clinical study site (Dr. Matthew Matasar) and the sponsor were selected for inspection in support of BLA 761121. The study appears to have been conducted adequately, and the data from this clinical site, as reported by the sponsor to the NDA as well as sponsor oversight are considered to be reliable in support of the requested indication.

The preliminary regulatory compliance classification of Dr. Matasar's site is No Action Indicated. The preliminary regulatory classification of the sponsor audit is No Action Indicated. A Form FDA 483 (Inspectional Observations) was not issued.

2. BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkins lymphoma (NHL), accounting for approximately about a third of NHL cases. Genetic abnormalities in subsets of patients with DLBCL include the following most common dysregulated genes: BCL6, BCL2 and cMYC genes, in rank order of decreasing frequency. The most common regimen considered to be the standard of care for patients with previously untreated DLBCL deploys up to eight cycles of rituximab combined with six or eight cycles of CHOP or CHOP-like chemotherapy (R-CHOP). R-CHOP consists of R= Rituximab, C= Cyclophosphamide, H= Doxorubicin Hydrochloride (Hydroxydaunomycin), O= Vincristine Sulfate (Oncovin) and P= Prednisone. The proposed indication for the current application is

(b) (4)

CD79b is a cell surface antigen whose expression is restricted to all mature B cells, except plasma cells. It is expressed in a majority of B-cell−derived malignancies, including nearly all NHLs. Polatuzumab vedotin (DCDS4501A [liquid formulation] and DCDS4501S [lyophilized formulation]) is an antibody drug conjugate (ADC) that contains a humanized immunoglobulin G1 (IgG1) anti-human CD79b MAb (MCDS4409A) and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-VC-PABC).

A single study, GO 29365, formed the basis for the regulatory decision-making process for this application. This clinical investigation was Study GO 29365 entitled “A Phase1B/II Study Evaluating the Safety, Tolerability and Anti-tumor Activity of Polatuzumab Vedotin (DCDS4501A) in Combination with Rituximab (R) or Obinutuzumab (G) plus Bendamustine (B) in Relapsed or Refractory Follicular or Diffuse Large B-cell Lymphoma”.

GO 29365

GO 29365 was a Phase 1b/II study evaluating the safety, tolerability and anti-tumor activity of polatuzumab in combination with rituximab, or obinutuzumab plus bendamustine (BR) in relapsed or refractory follicular or diffuse large B-cell lymphoma.

The primary study objective of the Phase II portion of Study GO 29365 was to evaluate the efficacy of the combination of polatuzumab vedotin plus BR compared with BR alone in patients with relapse/refractory follicular lymphoma (R/R FL) or DLBCL as measured by positron emission tomography (PET)-defined complete response (CR) rate using Modified Lugano 2014 Response Criteria (positron emission tomography–computed tomography [PET-CT] criteria) at the time of primary response assessment (6 to 8 weeks after Cycle 6 Day 1 or last dose of study medication) as defined by the Independent Review Committee (IRC). The primary efficacy endpoint of interest is the treatment response of polatuzumab vedotin with bendamustine and rituximab compared with bendamustine and rituximab alone according to the Modified Lugano 2014 Response Criteria (i.e., complete response, partial response and overall treatment response, best objective response, duration of response, overall survival and progression-free survival).

In Protocol Version #5, a new treatment arm was initiated to evaluate a new formulation of polatuzumab vedotin (lyophilized) in combination with bendamustine and rituximab. Note that patients, other than the lyophilized polatuzumab vedotin, were treated with liquid formulation.

For this targeted audit, CDER Division of Hematology Products (DHP) requested evaluation restricted to the DLBCL patients treated on the randomized Phase 2 portion of Study GO 29365. The focus is Arm C and D; that is, these are the DLBCL patients from the randomized phase 2 portion.

For all study arms in GO 29365, a total of 225 patients were enrolled at 65 investigator centers in the US and Canada. The first patient entered on October 15, 2014. For Study Arms A thru F, the last patient entered on September 13, 2016. The study, including cohort Arm G, is ongoing.

For the Phase II randomized DLBCL cohort which is the subject of this inspection, there were a total of 80 screened study subjects: 40 were randomized to the polatuzumab arm with bendamustine and rituximab (Arm C), versus 40 study subjects randomized only to bendamustine and rituximab arm (Arm D).

3. RESULTS (by site):

Name of Clinical Investigator/Address	**Protocol #/ Site #/ # Subjects Enrolled**	**Inspection Dates**	**Classification**
Dr. Matthew Matasar Pharmacy, Room C-1087 Memorial Sloan Kettering Cancer Center NY, NY 10065	GO 29365 Site #272994 9 total enrolled DLBCL	March 18-22, 2019	NAI*
Genentech, Inc. A member of the Roche Group 1 DNA Way MS #355e South San Francisco, CA 94080-4990	GO 29365 80 enrolled patients (78 treated)	March 25-29, 2019	NAI*

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Matthew Matasar, M.D.

A total of nine subjects were screened and nine subjects were enrolled at this site. Seven subjects completed the study. Two subjects discontinued treatment due to disease progression and treatment toxicity, respectively.

The site records reviewed included medical records, regulatory documents, source data worksheets, informed consent forms, follow-up reports, and pharmacy records.

Source documents for the nine study subjects whose records were reviewed were verified against the case report forms and BLA subject line listings for primary efficacy endpoints, adverse events, and serious adverse event reporting. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. There was no under-reporting of adverse events noted during this site audit. There were no limitations during conduct of the clinical site inspection.

Sponsor (Genentech, Inc.)

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocol GO 29365. The inspection included review of organizational charts, vendor list, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures. Interim Site Visiting Monitoring Reports for four clinical study sites were selected and reviewed: Site #272510, Site #272761, Site #272987, and Site #272994. No underreporting of significant adverse events to the Agency was noted. There were no critical deficiencies with oversight and monitoring of the trial.

{See appended electronic signature page}
Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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/s/

ANTHONY J ORENCIA
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CYNTHIA F KLEPPINGER
04/08/2019 09:55:57 AM

KASSA AYALEW
04/08/2019 11:54:14 AM

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	BLA 761121
Applicant	Genentech (Roche)
Proprietary Name **(nonproprietary name)**	POLIVY (polatuzumab vedotin)
Receipt Date	12/19/18
PDUFA Goal Date	08/19/19
Review Classification	Priority
Proposed Indication (or current indication if unchanged)	(b) (4)
Dosing Regimen	1.8 mg/kg administered as an intravenous infusion every 21 days for 6 cycles in combination with bendamustine and rituximab
From	**Virginia Kwitkowski, MS, ACNP-BC** **Associate Director for Labeling, DHP**

Background of Application:

On 12/19/18, the Applicant submitted a new molecular entity BLA for Polivy (polatuzumab vedotin) (b) (4) (b) (4) (b) (4) I have reviewed the USPI for format and content issues.

In this review, I summarize the DHP labeling recommendations and edits in the POLIVY labeling. These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of POLIVY.

The following pages contain a summary of my labeling recommendations followed by the working version of the POLIVY labeling with comments.

Draft Labeling

19 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

VIRGINIA E KWITKOWSKI
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