CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761121Orig1s008

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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:	April 18, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761121/S-008
Product Name, Dosage Form, and Strength:	Polivy (polatuzumab vedotin-piiq) for Injection, 30 mg/vial, 140 mg/vial
Applicant/Sponsor Name:	Genentech, Inc.
TTT ID #:	2022-1098-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 17, 2023 for Polivy. We reviewed the revised container labels and carton labeling for Polivy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to the proposed changes in the Prescribing Information, which include revising the handling precautions from, "Cytotoxic Agent" to "Hazardous Agent".

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

NICOLE F IVERSON
04/18/2023 11:29:26 AM

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04/19/2023 10:03:44 AM

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

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

Memorandum

Date: April 4, 2023

To: Laura Wall, Regulatory Project Manager,
Division of Hematologic Malignancies II (DHM2)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

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

BLA: 761121, S-008

Background:

In response to DHM2's consult request dated June 2, 2022, OPDP has reviewed the proposed Prescribing Information (PI) for supplement 008 for POLIVY® (polatuzumab vedotin-piiq) for injection, for intravenous use. This supplement provides for addition of data from Study GO39942 (POLARIX), and verification of the clinical benefit of POLIVY® for the treatment of adult patients with R/R DLBCL, fulfilling accelerated approval requirements.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 30, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

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JENNIFER W CHEN
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Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

BLA	761121
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Polatuzumab vedotin (Pola-v)
Indication	Diffuse large B-cell lymphoma (DLBCL)
Applicant	Genentech
Requesting Division	Division of Hematological Malignancies 2 (DHM2)
Primary Reviewer	Ling Lan, MD, PhD, Clinical Analyst, DILI Team, DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Other Reviewers	Edwige Chiogo Vouffo, PharmD, PhD Non-clinical analyst, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Frank A. Anania, MD, Acting Director, OND/DHN
Assessment Date	February 21, 2023

Context: Polatuzumab vedotin (Pola-v) is an antibody-drug conjugate (ADC) that delivers monomethyl auristatin E (MMAE), a small molecule, which inhibits mitosis by binding microtubules. The proposed indication for this conjugate is diffuse large B-cell lymphoma (DLBCL). The monoclonal antibody portion of the drug targets CD79b, a signal receptor on B-cells. In this NDA, Pola-v is given in combination with rituximab targeting DLBCL. Several subjects exposed to study drug met liver biochemistry criteria for Hy's Law (i.e., aminotransferases >3x ULN with total bilirubin >2x ULN). The Division of Hematological Malignancies 2 (DHM2) asked the DILI Team to "evaluate whether these cases were Hy's Law cases and comment on labeling." DHM2 did not request study level analyses or opinion on approvability based on DILI risk.

Executive Summary: None of the ten subjects of concern met Hy's Law. While the subjects exhibited jaundice with significant transaminase elevations, all had alternate explanations for the liver injury making DILI unlikely. The label may reflect this lack of association with any Hy's Law cases. We provide more detailed comments for labeling in Sections 4.3 and 5.2 below.

Consultation Sections:

Section 1.0 – Target Disease and Rationale
Section 2.0 - ADME pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.

Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations.
Appendix: Study schematics

Abbreviations:
ADC: antibody-drug conjugate
ALP or AP: alkaline phosphatase
ALT: alanine aminotransferase
AP: alkaline phosphatase
AST: aspartate aminotransferase
AT: aminotransferase (ALT and/or AST)
BMI: body mass index
CPK: creatinine phosphokinase
CT: computerized tomography
CYP: cytochrome P450
DB: direct bilirubin
DILI: drug-induced liver injury
DLBCL: diffuse large B-cell lymphoma
FL: follicular lymphoma
GGT: gamma-glutamyl transferase
HBV: hepatitis B virus
HCV: hepatitis C virus
HDS: herbal and dietary supplements
IP: investigational product
MMAE: monomethyl auristatin E
MRI: magnetic resonance imaging
Pola-v: polatuzumab vedotin
R-value: ALT/ULN ÷ ALP/ULN
TB: total bilirubin
US: ultrasound
ULN: upper limit of normal

1.0 Target Disease and Rationale

1.1. Disease: Diffuse Large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) accounting for 30% of all lymphomas. It occurs most commonly in middle-aged or older adults. The average age at the time of diagnosis is 64 years. Men are slightly more at risk than women.[1]

In the United States, DLBCL affects seven in 100,000 people annually with Caucasians more likely to develop DLBCL than Asians or Blacks. It is a fast-growing, aggressive form of NHL, and fatal if untreated.[1] However, with timely and appropriate treatment, two-thirds of patients can be cured. DLBCL is not an inherited disease, but approximately nine percent of patients who have DLBCL also have a first degree relative with lymphoma or chronic lymphocytic leukemia.[1]

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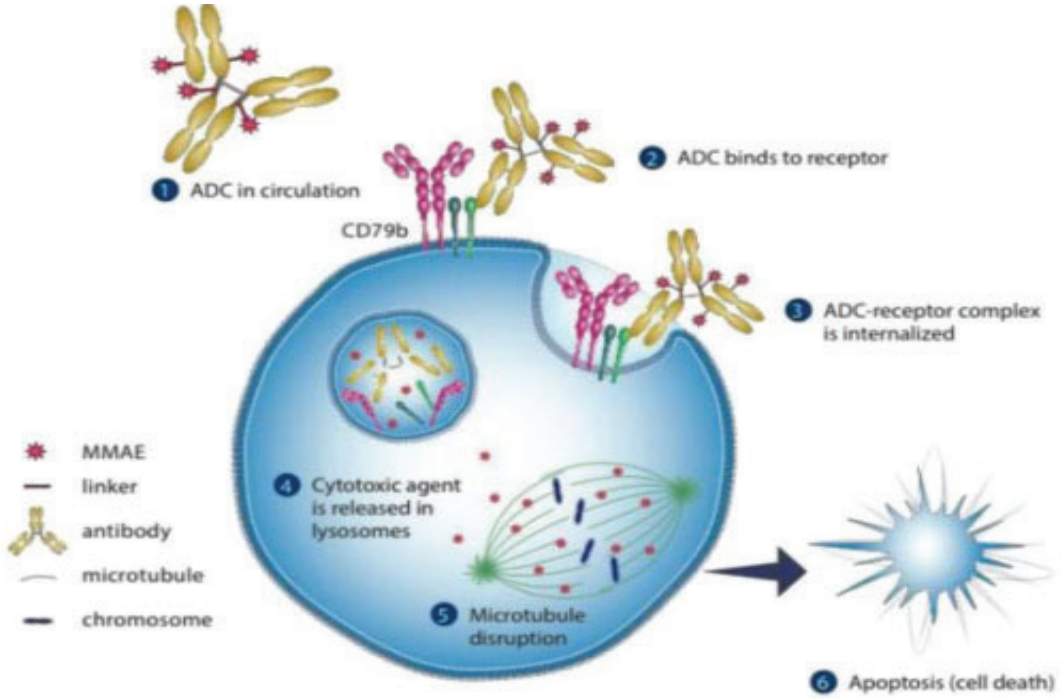
[1] https://www.uptodate.com/contents/diffuse-large-b-cell-lymphoma-in-adults-beyond-the-basics#:~:text=DLBCL%20is%20a%20fast%2Dgrowing,all%20people%20can%20be%20cured.

Treatment for DLBCL depends on whether the disease is advanced or localized. In advanced disease, a combination of chemotherapy and immunotherapy is standard of care. For localized disease, patients may be treated with several cycles of chemotherapy and radiation therapy.[1]

1.2. Rationale: Polatuzumab vedotin (Pola-v) is an antibody drug conjugate (ADC) that binds the B cell surface protein, CD79b, thereby preferentially delivering a potent anti-mitotic agent (monomethyl auristatin or MMAE) to B-cells. The anti-mitotic activity hinders malignant B cell proliferation. Pola-v has potent, selective inhibition of CD79b-positive Ramos B cells, a B lymphocyte cell line from a Burkitt's Lymphoma patient. After binding, Pola-v is internalized by endocytosis. Once inside the cell, proteolytic cleavage releases the MMAE which then binds to microtubules leading to a G2/M phase arrest and tumor cell apoptosis.[2] (**Figure 1**) The sponsor suggests Pola-v is broadly active and highly potent in DLBCL.[3]

Figure 1: Polatuzumab vedotin mechanism of action.[4]



ADC = antibody–drug conjugate; MMAE = monomethyl auristatin E.

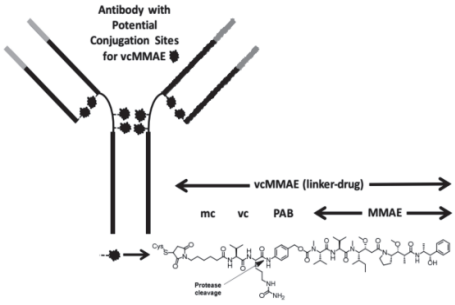
[2] BLA761121 (761121 - 0359 - (361) - 2022-12-16 - MARKETING-227 /Marketing/2253 Professional) - Nonclinical Overview (#6)
[3] BLA761121 (761121 - 0359 - (361) - 2022-12-16 - MARKETING-227 /Marketing/2253 Professional) - Nonclinical Overview (#18)
[4] BLA761121 (761121 - 0359 - (361) - 2022-12-16 - MARKETING-227 /Marketing/2253 Professional) - Nonclinical Overview (#7)

2.0 ADME data pertinent to DILI

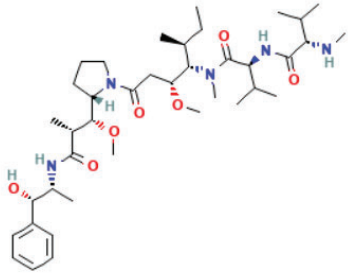
2.1. Structure: **(Figure 2)**

Figure 2: (a) Structure of polatuzumab vedotin and (b) structural formula for monomethyl auristatin E. [5],[6]

(a)



(b)



2.2. Absorption: Plasma exposure of Pola-v was dose proportional with moderate (1.1 to 1.7-fold) plasma accumulation in rats following four weekly doses. Pola-v showed no plasma accumulation in monkeys. Hence, exposure of total antibody and MMAE increased dose-dependently in rats but not monkeys.

2.3. Distribution: Extensive tissue distribution was reported in monkeys receiving intravenous (IV) MMAE. MMAE is moderately bound (71-77%) to human plasma proteins and is unlikely to displace or to be displaced by other highly protein-bound drugs. MMAE showed nonspecific distribution and was rapidly distributed into multiple highly perfused tissues (including liver, lungs, heart, kidneys) following a single dose radiolabeled (0.2 mg/kg IV) in rats. This dose of MMAE is equivalent to the approximate amount of MMAE delivered in a Pola-v dose of 10 mg/kg. Thus, unconjugated MMAE is well and rapidly distributed into highly perfused tissues.

2.4. Metabolism: MMAE is not extensively metabolized in vitro, but metabolites are detectable at very low levels. In rat, >99% of radioactivity in plasma remained as MMAE. Parent compound was the only component identified in rat plasma and urine following 0.2 mg/kg IV dose of radiolabeled MMAE. (MMAE dose equivalent to the amount delivered in a Pola-v dose of 10 mg/kg). Unchanged MMAE was the main component in rat bile and represented 46% of the injected radioactivity dose and 63% of the radioactivity recovered in bile collected over 6 hours. No unique human metabolites were identified among the 15 MMAE metabolites detected in liver microsomes. Hence, MMAE was not extensively metabolized. Unchanged MMAE was the main component in bile.

2.5. Excretion: Over 95% of injected Pola-v radioactivity was excreted via feces and five percent in urine within 14 days following a single IV administration of 10 mg/kg Pola-v in mice. Pola-v had slow clearance leading to a long elimination half-life of ten to twelve days following a single IV dose of 5 mg/kg in mice. On the other hand, MMAE alone was rapidly cleared from the blood following a single dose (0.2 mg/kg IV) in rats. Thus,

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[5] BLA761121 (761121 - 0359 - (361) - 2022-12-16 - MARKETING-227 /Marketing/2253 Professional) - Nonclinical Overview (#15)

[6] PubChem https://pubchem.ncbi.nlm.nih.gov/compound/Monomethyl-auristatin-E (accessed Jan 10, 2023)

slow clearance was reported with Pola-v. Slow clearance may lead to accumulation. Radiolabeled Pola-v was mainly excreted via feces and minimally in urine.

3.0 **Non-clinical data:**

3.1. In vitro data: MMAE is a substrate for CYP3A4/5 and does not competitively inhibit these CYPs in vitro. MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. It does not inhibit P-gp, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, BSEP, MRP2 or BCRP in vitro at clinically relevant concentrations. Hence, substantial drug-drug interactions would not be expected with Pola-v as it does not inhibit or induce the main CYPs or drug transporters.

3.2. Animal data:

3.2.1. *Liver injury marker data:* MMAE in rats resulted in a dose-dependent increase in aminotransaminases and bilirubin following four weekly doses of Pola-v in rats.

3.2.2. *Liver histopathology:* In rats, MMAE (single and repeat doses) and Pola-v (repeat doses) resuted in elevated transaminases and hepatocellular apoptosis, necrosis, and increased mitosis. Hepatic centrilobular degeneration, sinusoidal cell (endothelial and Kupffer cells), bile duct epithelium and focal necrosis with inflammatory cells and hemorrhage occured after four weekly doses of Pola-v in rats. Thus, Pola-v caused significant liver histopathology in rodents.

Table 1: ADMET summary table[7]

Item	Finding
Absorption	Rapid
Distribution	Extensive tissue distribution
Metabolism	Not extensive for MMAE
Elimination	Pola-v (MMAE) à mainly via feces

Table 2: Toxicology summary table[8]

Item	Finding
In Vitro Studies	
Major CYPs	MMAEà CYP3A4/5
Reaction metabolites (i.e., glutathione trapping)	No data found
Mitochondria studies/inhibition	No data found
Transporter (BSEP or MRP2 inhibition)	No inhibition observed
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	Increase in liver parameters reported with MMAE
Liver histopathology findings (animal species)	Inflammation, necrosis, hepatic centrilobular degeneration, hepatocellular apoptosis seen with MMAE

The antibody portion of the Pola-v is not expected to cause liver injury because such immunoglobulins are typically metabolized in the peripheral vasculature. However monoclonal antibodies may result in liver injury as a consequence of perturbations in the immune system in the liver or neoantigen formation.

[7] Table made by DILI Team
[8] Table made by DILI Team

The small molecule MMAE portion of Pola-v did not have in vitro data suggesting liver injury risk. Metabolite formation was minimal and there was no time-dependent inhibition of its major CYP nor binding of BSEP or MRP2. Nevertheless, Pola-v resulted in significant liver histopathology in rodents. The contrast in data between the in vitro and in vivo studies could indicate non-specific delivery of MMAE to hepatocytes leading to cell cycle arrest in the liver. However, as a potential liver-related injury mechanism, this is speculative.

4.0 Clinical data.

4.3 Study level data: The subjects with liver injury on Pola-v were identified by DHM2 for our review. These subjects arose from two studies: (1) Study GO29365 (*Phase Ib/II study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab or obinutuzumab plus bendamustine in relapsed or refractory follicular or diffuse large B-cell lymphoma*) and (2) Study GO39942 (*A phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with rituximab and CHP (R-CHP) versus rituximab and CHOP (R-CHOP) in previously untreated patients with diffuse large B-cell lymphoma*). Schematics with dosing for these studies are in the **Appendix**. For study GO29365, 24 subjects entered phase 1b and received Pola-v, but only 13 completed all treatment cycles. For phase II, 120 randomized to a Pola-v arm with 69 completing planned therapy.[9] For study GO39942, 407 subjects received at least six cycles of Pola-v.[10] Further study level analyses (e.g., eDISH, shift plots, shift tables) were not requested for this consult.

4.2 Case level assessments: We assessed ten subjects who met liver biochemistry criteria for Hy's Law. Six were exposed to Pola-V while the other four were in the comparator arm. We deemed all ten cases as unlikely DILI due to Pola-V. For one subject (ID (b) (6)), the latency was long at 406 days making DILI unlikely. Also, all ten had alternative explanations as causal for liver injury. (**Table 3**)

[9] BLA761121 (761121 - 0364 - (366) - 2023-01-18 - MARKETING-230 /Marketing/2253 Professional) - CSR GO29365 Interim: Phase IB/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 B-cell lymphoma. (#108)

[10] BLA761121 (761121 - 0364 - (366) - 2023-01-18 - MARKETING-230 /Marketing/2253 Professional) - Supplemental Safety Update Report for POLIVY (#7)

Table 3: Ten subjects meeting liver biochemistry criteria for Hy's Law (ALT or AST >3x ULN and TB >2x ULN)[11]

ID	+/- Pola-V	Causality Score*	Alternate diagnosis	Study	Age (yr)	Sex	Race	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)~	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak**
(b) (6)	(+)	5	Unknown + Gilbert's	GO29365 Phase II	54	M	White	No	14	[155]	236	124	115	3.57	6.28
	(+)	5	Disease progression	GO29365 Phase II	64	M	White	No	155	49	239	141	1030	9.24	0.71
	(+)	5	Sepsis	GO29365 Phase II	80	F	Asian	No	181	117	70	124	104	2.22	2.06
	(+)	5	Disease progression	GO29365 Phase II	71	M	White	No	27	27	116	127	760	10.5	0.47
	(+)	5	DLBCL	Polarix GO39942	55	F	White	No	21	0	189	92	948	2.57	0.61
	(+)	5	Biliary obstruction	Polarix GO39942	60	M	White	No	406	289	281	190	303	3.92	2.84
	(-)	5	Bactrim injury	Polarix GO39942	64	M	Unknown	No	99	72	159	150	1765	5.61	0.28
	(-)	5	Biliary obstruction	Polarix GO39942	49	M	Asian	No	11	[99]	507	374	389	3.39	3.99
	(-)	5	Shock liver	Polarix GO39942	69	M	White	No	89	7	661	1584	104	3.39	19.44
	(-)	5	Disease progression	GO29365 Phase II	61	F	White	No	42	20	176	210	1075	2.4	0.50
				Mean	***63***				***104.5***	***32.7***	***263***	***312***	***659.3***	***4.7***	***3.7***
				Std dev	*8.6*				*115.5*	*113.6*	*174*	*431*	*523.4*	*2.8*	*5.6*
				Median	***63***				***65.5***	***23.5***	***213***	***146***	***574.5***	***3.5***	***1.4***
				Min	*49*				*11*	*[155]*	*70*	*92*	*104*	*2.2*	*0.3*
				Max	*80*				*406*	*289*	*661*	*1584*	*1765*	*10.5*	*19.4*

+/- Pola-V = exposed (+) or not exposed (-) to polatuzumab verdotin

DLBCL = diffuse large B-cell lymphoma

R-value = (ALT/ULN) ÷ (AP/ULN); R > 5: hepatocellular; R between 2 & 5 mixed; R < 2 cholestatic

*1=definite, 2=highly likely, 3=probable, 4=possible, **5=unlikely**, 6=indeterminate

^For purposes of R-value calculations, the ULN (104) was imputed if AP never rose to > ULN

** ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

~[ ] day values means the drug continued for that many days *after* injury onset.

4.3 Labeling input: As of Jan 31, 2022, the sponsor's proposed labeling lists hepatotoxicity under Warnings and Precautions. Section 5.7 describes liver enzyme elevations consistent with possible hepatotoxicity. All current labeling language is in blue italics.

Proposed label, Section 5.7 Hepatotoxicity (as of Jan 31, 2022).[12]

(b) (4)

[redacted]

[11] Table made by DILI Team

[12] Provided to DILI Team by direct correspondence from Maryam SarrafYazdy, MD, Jan 31, 2022

(b) (4)

Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk of hepatotoxicity. Monitor liver enzymes and bilirubin level.

We have the following comments for proposed label Section 5.7:

1. Our case level analysis did not attribute any of the severe liver injuries to Pola-V (brand name POLIVY). (b) (4) wording could be "*Polivy is associated with acute hepatocellular liver injury*" if a causal relationship was unclear.
2. We confirm that several subjects had resolution of the severe liver injury, but DILI was unlikely.
3. (b) (4) Liver biochemistry elevations are suggestive of non-specific liver injury and not necessarily DILI. There are no laboratory markers or enzyme patterns specific to DILI.
4. We suggest the second sentence, third paragraph, be edited to (b) (4)
5. We suggest the following sentence be added to the third paragraph: (b) (4)
6. We suggest the fourth paragraph of section 5.7 be changed from

   "Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk of hepatotoxicity. Monitor liver enzymes and bilirubin level. "

   to

   "Preexisting liver disease or impairment may increase the risk of severe hepatotoxicity. Elevated baseline liver enzymes and bilirubin make detecting liver injury more difficult. Monitor liver enzymes and bilirubin level."

   a. In this target population, some patients may not have an identified "*liver disease*" causing the elevation in liver analytes, but they can have hepatic impairment (e.g., cholestasis of sepsis, jaundice of unknown cause) that may make patients less tolerant of a DILI.
   b. Abnormal baseline enzymes obscure DILI early in its onset. In other words, clinicians tend to dismiss or ignore elevations as normal fluctuations for that patient leading to a delay in DILI recognition and withdrawing the drug.

c. We suggest removing "*concomitant medications*" unless there are specific DDIs in mind. Polypharmacy increases adverse events like DILI overall, but this seems self-evident unless there are specific DDIs to highlight. Our assessment of the ADME and non-clinical studies (i.e., transporter inhibition and CYP studies) suggest a low risk for DDI, overall.

5.0 Assessment & Recommendations

5.1 Assessment: Polatuzumab vedotin (Pola-v) is an antibody-drug conjugate (ADC) that delivers monomethyl auristatin E (MMAE), a small molecule, which binds microtubules thereby inhibiting mitosis. The monoclonal antibody portion of the drug targets CD79b, a signal receptor on B-cells, and the target disease for this NDA is diffuse large B cell lymphoma (DLBCL). DHM2 requested a focused consultation on ten subjects with liver injury and jaundice, as well comments on labeling. Study level analyses and opinion on approvability were not requested.

Non-clinical data for DILI risk with Pola-v are mixed. We do not expect the antibody portion of the ADC to cause liver injury via reactive metabolites. Immunoglobulins are typically metabolized to smaller peptides in the peripheral vasculature and not preferentially in the liver. Nevertheless, liver injury from neoantigen formation or downstream perturbations in the immune response to other antigens are theoretical concerns with all monoclonals. In vitro studies for MMAE did not suggest liver injury risk either. However, there was significant liver histopathology associated with MMAE in rodents. The difference in DILI risk data between in vitro and animal studies could indicate non-specific delivery of MMAE to hepatocytes leading to cell cycle arrest in the liver. However, as a liver-related injury mechanism this explanation is speculative.

For our clinical analysis, we focused on the ten subjects with liver injury and jaundice, and assessed all ten as unlikely DILI due to Pola-v. Alternative causes and/or timing inconsistent with DILI were present in all ten subjects. (**Table 3**). Only two of the ten had hepatocellular injury by R-value.[13],[14] The other eight subjects had liver injury that were mixed or cholestatic reflecting biliary obstruction, sepsis and lymphoma involvement of the liver that often occurs in this target population.

Therefore, the label should reflect that jaundice-associated liver injury is not clearly attributable to Pola-v. We provided labeling input and edits through DHM2's shared label document but summarize our recommendations below. We did not assess study level data nor non-jaundiced liver injury cases; hence we cannot comment on such data for the label. For more detailed description of our labeling suggestions, please Section 4.3 above.

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[13] R-value = ALT/ULN ÷ ALP/ULN; R-value >5 suggests hepatocellular liver injury, R < 2 suggests cholestatic, and 2 < R < 5, mixed.

[14] Danan G, et al., Causality Assessment of Adverse Reactions to Drugs I-A Novel Method Based the Conclusions of International Consensus Meetings: Application to Drug-Induced Liver Injuries. *J Clin Epidemiol*, 1993; 46:1323-1330.

5.1 Recommendations for labeling

1. If a causal relationship between elevation in liver enzymes and Pola-v is unclear then [redacted] (b) (4) *"Polivy is associated with acute hepatocellular liver injury…"*
2. Based on our review of cases, the label should reflect the lack of an established causal link between Pola-v and jaundiced liver injury cases. [redacted] (b) (4)
3. We agree with the label stating [redacted] (b) (4)
4. We suggest [redacted] (b) (4)
5. We suggest the following wording for paragraph 4, Section 5.7: "*Preexisting liver disease or impairment may increase the risk of severe hepatotoxicity. Elevated baseline liver enzymes and bilirubin make detecting liver injury more difficult. Monitor liver enzymes and bilirubin level."*

Ling Lan -S
Digitally signed by Ling Lan -S
Date: 2023.02.23 10:23:10 -05'00'

Ling Lan, MD, PhD
Clinical Analyst, DILI Team, DHN
CDER/OND

Paul H. Hayashi -S
Digitally signed by Paul H. Hayashi -S
Date: 2023.02.23 12:08:08 -05'00'

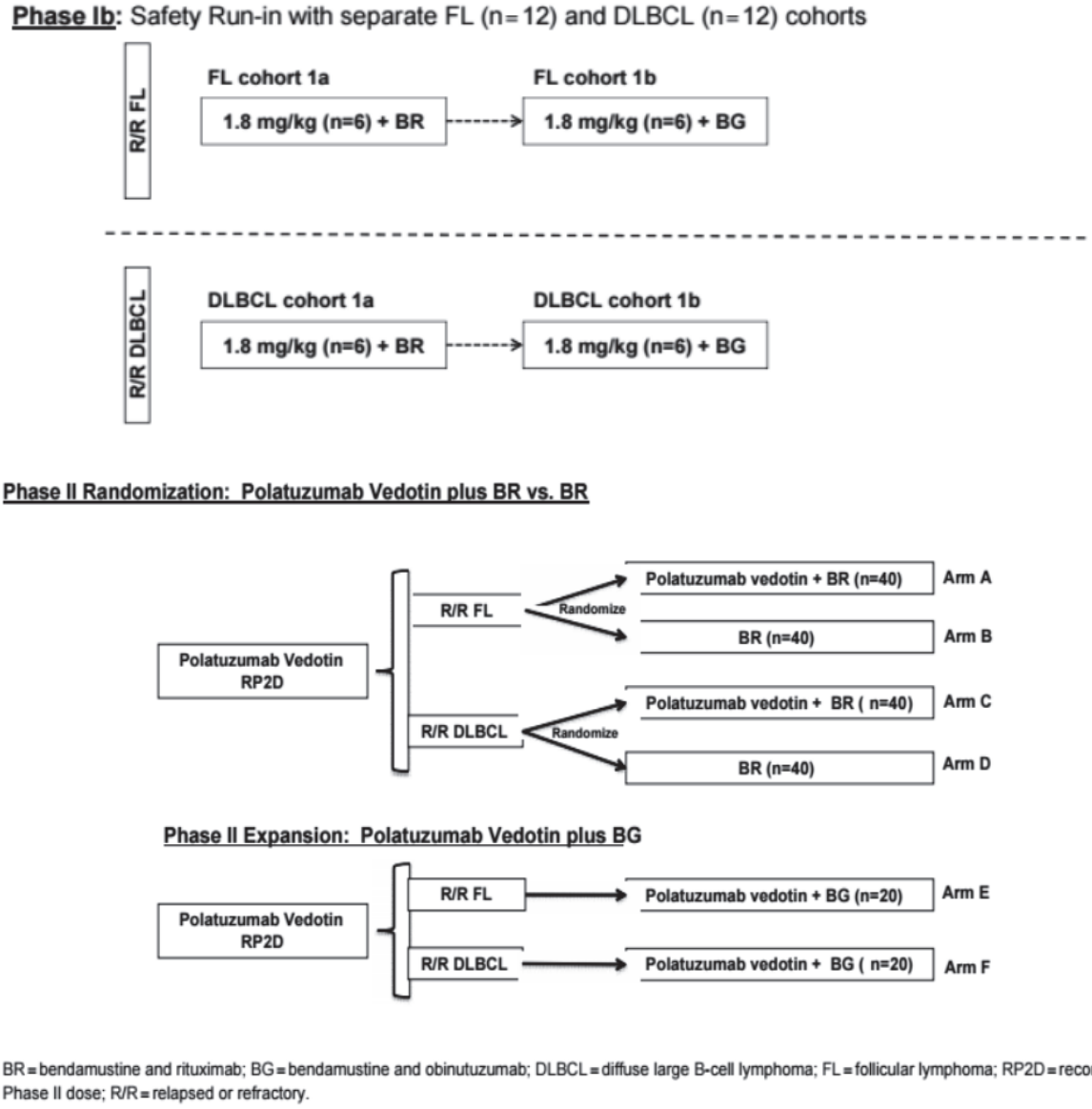
Paul H. Hayashi, MD, MPH
DILI Team Lead, DHN
CDER/OND

Frank A. Anania -S
Digitally signed by Frank A. Anania -S
Date: 2023.02.23 21:00:53 -05'00'

Frank A. Anania, MD
Acting Director, DHN
CDER/OND

Appendix: Study schematics

Figure A: Study GO29365 schematic[15]



BR = bendamustine and rituximab; BG = bendamustine and obinutuzumab; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; RP2D = recommended Phase II dose; R/R = relapsed or refractory.

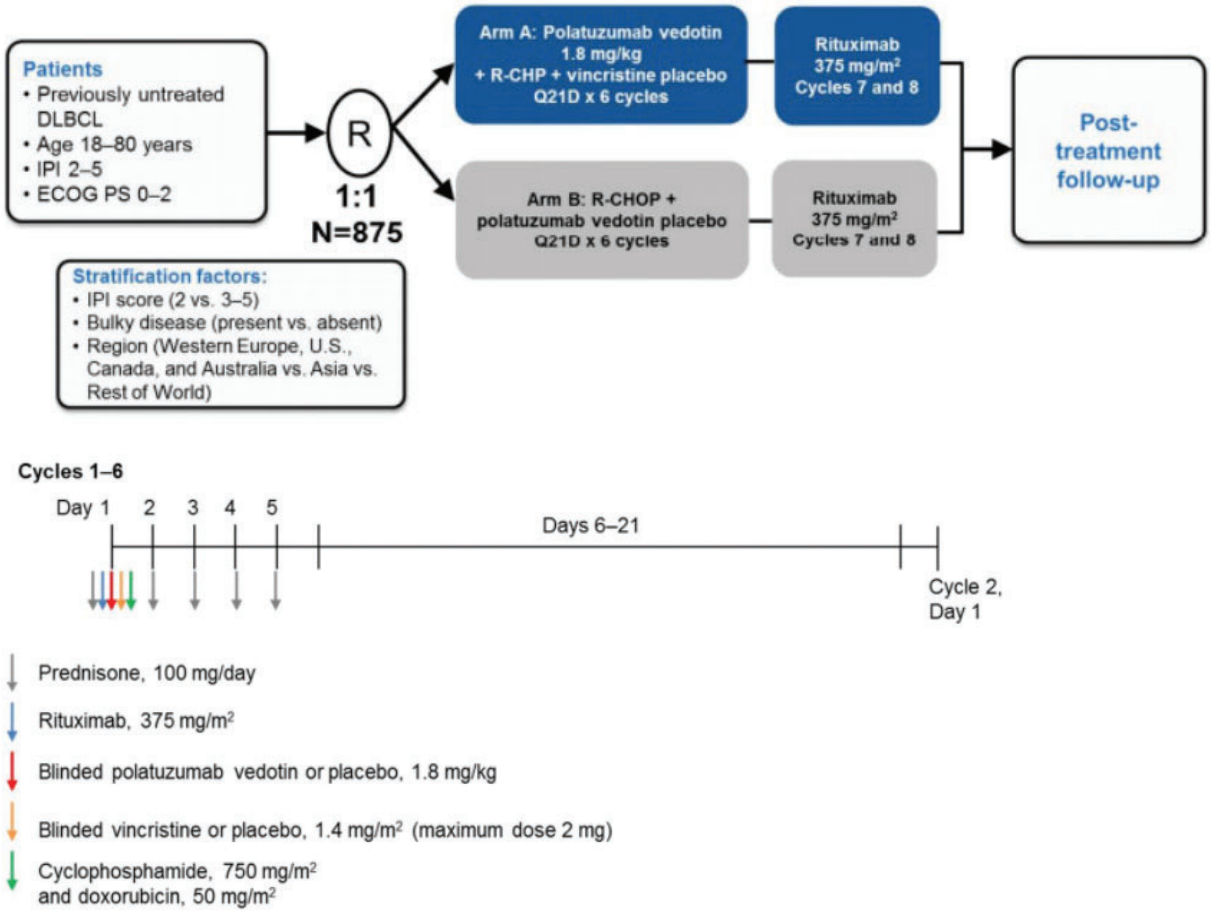
Rituximab (375 mg/m^2) D1 of each cycle, or obinutuzumab (1000 mg) D1, D8, D15 in Cycle 1, then D1 of each subsequent cycle plus bendamustine (90 mg/m^2) D2 and D3 in Cycle 1, then D1 and D2 in each subsequent cycle. Polatuzumab vedotin (1.8 mg/kg) D2 in C1 then D1 of each subsequent cycle.

FL: Treatment administered every 28 days × 6 cycles.

DLBCL: Treatment administered every 21 days × 6 cycles.

[15] BLA761121 (761121 - 0364 - (366) - 2023-01-18 - MARKETING-230 /Marketing/2253 Professional) - CSR GO29365 Interim: Phase IB/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 B-cell lymphoma. (#70)

Figure B: Study GO39942 schematic[16],[17]



R-CHP (or R-CHOP): rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone. POLV (polatuzumab vedotin) is taken in place of vincristine in the active arm. Comparator arm receives standard R-CHOP with vincristine. R-CHOP cycle is 3 weeks.

[16] BLA761121 (761121 - 0364 - (366) - 2023-01-18 - MARKETING-230 /Marketing/2253 Professional) - 16.1.1 Protocol and Amendments (#40)
[17] BLA761121 (761121 - 0364 - (366) - 2023-01-18 - MARKETING-230 /Marketing/2253 Professional) - 16.1.1 Protocol and Amendments (#55)

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CLINICAL INSPECTION SUMMARY

Date	November 9, 2022
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Acting Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Maryam Sarraf-Yazdy, M.D., Medical Officer Yvette Kasamon, M.D., Ph.D., Medical Team Leader Nicole Gormley, M.D., Division Director Wanda Nguyen, Pharm.D., Senior Health Project Manager Division of Hematology Malignancies 2 (DHM2) Office of Oncology Drugs
BLA	BLA 761121 S-008
Applicant	Genentech, Inc.
Drug	Polivy® (polatuzumab vedotin)
NME	No
Division Classification	CD79b-directed antibody-drug conjugate
Proposed Indication	Treatment of with previously untreated diffuse large B-cell lymphoma
Review Type	Standard
Consultation Request Date	June 15, 2022
Summary Goal Date	December 1, 2022
Action Goal Date	March 15, 2023
PDUFA Date	April 2, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study GO39942 (POLARIX) were submitted to the Agency in support of a Biologics License Application (BLA) supplement for polatuzumab vedotin for the proposed new indication for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma. The sponsor also intended this study to support conversion of polatuzumab vedotin from an accelerated approval to a regular approval. The sponsor, Genentech, Inc., and a clinical investigator (John Burke, M.D.) were inspected for Study GO39942.

Based on the above inspections, the study data derived from Dr. Burke's clinical study site are considered reliable. The sponsor's oversight of Study GO39942 appears adequate.

The study data submitted to the Agency for assessment appear acceptable in support of the proposed indication.

II. BACKGROUND

Polatuzumab (Polivy) is an antibody-drug conjugate (ADC), a CD79b-directed antibody-drug conjugate, indicated in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies. The drug received accelerated approval in 2019. The current submission is intended to fulfill the accelerated approval requirement for a confirmatory trial to support the benefit and conversion of polatuzumab vedotin's accelerated approval to a regular approval for the treatment of diffuse large B-cell lymphoma.

Study GO39942, a single Phase 3 clinical trial was submitted in support of the current applicant's BLA supplement, proposed for the treatment of adult patients with previously untreated diffuse large B cell lymphoma (DLBCL).

Study GO39942 (POLARIX)

Study GO39942 (POLARIX) was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, two-arm study to compare the efficacy, safety, pharmacokinetics, and patient-reported outcomes of rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) in combination with polatuzumab vedotin 1.8 mg/kg (polatuzumab+R-CHP) with those of rituximab plus cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone (R-CHOP) in patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

Patients, age 18 to 80 years, received six cycles of polatuzumab+R-CHP or standard R-CHOP chemotherapy at 21-day intervals. Both arms then received two additional cycles of single agent rituximab.

Patients were randomized in a 1:1 ratio to either the Arm A, polatuzumab+R-CHP or Arm B, R-CHOP. Both study patients and the investigator were blinded to the assigned active microtubule inhibitor (i.e., polatuzumab or vincristine) and placebo control.

The primary efficacy endpoint was progression-free survival (PFS) based on independent central review.

There were 879 patients who were enrolled across 211 sites in 22 countries. The study randomized 440 subjects in the polatuzumab+R-CHP arm and 439 subjects in the in the R-CHOP arm.

The date of the first patient randomization was November 15, 2017. The data cutoff date for the submission was June 28, 2021. The study is ongoing.

III. RESULTS

1. John Burke, M.D. / Site 307348
Rocky Mountain Cancer Centers, LLP
1700 S. Potomac St.
Aurora, CO 80012

Inspection dates: July 26 to 29, 2022

A total of 35 subjects were screened, and 31 subjects were enrolled to participate in the study. The study is closed to enrollment, but ongoing.

The FDA inspection covered the authority and administration of the clinical trial, the study protocol and amendments, study selection criteria, informed consents, investigational product controls, source data evaluation, adverse event reporting, and concomitant medication. Further, the audit comprised also a review of study subject evaluation forms, investigational drug accountability records, and sponsor monitoring activities.

A total of 20 study subjects' records were reviewed during the inspection for the 31 enrolled subjects. Study subject data line listings were compared to source documents. No discrepancies were reported.

The primary efficacy endpoint (progression-free survival) was verifiable during the study site inspections. Records were also assessed for adverse events. No underreporting for adverse events were found at this study site.

At the FDA close-out meeting with the study site, a single late reporting of one serious adverse event occurred for Subject (b) (6) hospitalized for scrotal abscess on (b) (6) with a notification of study site research coordinators on (b) (6), and a subsequent notification of sponsor on (b) (6). Dr. Burke mentioned that the study staff were retrained on reporting of serious adverse events during the clinical study site monthly meetings to emphasize the importance of reporting serious adverse events in a timely manner for this isolated late reporting occurrence.

The inspection was unremarkable in general. No FDA Form 483 (Inspectional Observations) was issued at the end of the inspection.

2. Genentech, Inc./Sponsor
1 DNA Way
South San Francisco, CA 94080-4990

Inspection dates: September 29 to October 7, 2022

During the FDA inspection of the sponsor, an evaluation of the clinical trial overview was performed and comprised the following activities: sponsor oversight, clinical investigator site and monitor selection, record collection (e.g., financial disclosures, Form FDA 1572), electronic records and electronic signatures, monitoring activities by the sponsor and site monitors quality assurance, safety assessments, adverse event reporting, blinding (e.g., blinding of clinical trial staff, site monitors, biostatisticians, investigational product), investigational product (i.e., distribution and blinding), transfer of regulatory obligations, contractual agreements site monitoring (i.e., procedure, monitoring reports, frequency or qualification of monitors), and electronic data capture (i.e., validation, user acceptance testing, audit trail).

FDA evaluated the meeting minutes from the Independent Data Monitoring Committee for the study. This committee was tasked with risk identification/mitigation. The committees reviewed all aspects of the study from a clinical trial Good Clinical Practice standard perspective, such as adverse events (e.g., possible toxicity consideration for study changes), major and minor protocol deviations, or drug accountability issues. No discrepancies were found in FDA's audit.

There were five clinical sites whose clinical trial monitoring activities were assessed. For example, clinical site monitoring for a large patient accrual site in Rouen, France (Site 314403) was audited. Appropriate corrective actions were completed for the investigator sites. Monitoring actions taken for those clinical investigators who did not comply with the investigational plan appeared to be adequate. Adverse events were comprehensively reported to the Agency.

At the end of the sponsor inspection, no FDA Form 483 was issued.

In general, the sponsor oversight of this clinical investigative study was acceptable.

{See appended electronic signature page}
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	September 13, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761121/S-008
Product Name, Dosage Form, and Strength:	Polivy (polatuzumab vedotin-piiq) for Injection, 30 mg/vial, 140 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	June 2, 2022, July 20, 2022, and July 22, 2022
OSE RCM #:	2022-1098
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Genentech, Inc. submitted supplemental BLA 761121/S-008 for Polivy (polatuzumab vedotin-piiq) for Injection to propose addition of a new indication for the treatment of adult patients with previously untreated diffuse large B cell lymphoma (DLBCL). This submission also fulfills Postmarketing Requirement (PMR) 3630-1.

PMR 3630-1: Complete Study GO39942, a randomized, double-blind, placebo-controlled trial that evaluates polatuzumab vedotin-piiq in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma. The primary endpoint would be progression-free survival. Key secondary endpoints would include complete remission rate per independent review committee and overall survival.

We reviewed the proposed Polivy Prescribing Information (PI) for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Polivy (polatuzumab vedotin-piiq) is a CD79b-directed anti-body drug conjugate that was approved on June 10, 2019. Polivy (polatuzumab vedotin-piiq) for Injection is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies. It is currently available in a 30 mg/vial and 140 mg/vial lyophilized powder single-dose vials. Dosing is based on mg/kg basis.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

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

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Labels and Labeling	G

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Genentech, Inc. is proposing the addition of a new indication for Polivy for the treatment of adult patients with previously untreated DLBCL. We performed a risk assessment of the proposed PI to determine if it is acceptable from a medication error perspective. We have identified areas of concern in the PI that should be revised to improve clarity and readability of the information presented. Specifically, we note the PI lacks clarity in the administration instructions, which may confuse the user and inadvertently lead to medication errors. Additionally, the PI contains trailing zeros and large numbers appearing without commas. We provide recommendations for the Applicant in Section 4.1 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We have identified areas in the proposed PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Applicant.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Prescribing Information

1. Dosage and Administration Section

a. Section 2.1 Recommended Dosage

i. We recommend relocating administration information, "Administer the initial dose of POLIVY over 90 minutes. Monitor patients for infusion-related reactions during the infusion and for a minimum of 90 minutes following completion of the initial dose. If the previous infusion was well tolerated, the subsequent dose of POLIVY may be administered as a 30-minute infusion and

patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion." to Section 2.4 Administration as Instructions for Preparation and Administration.

b. Section 2.2 Management of Adverse Reactions

    i. The dose of Polivy is presented with a trailing zero (e.g., 1.0 mg). Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 1.0 mg is seen as 10 mg). We recommend revising the dose statement to remove the trailing zero.

    ii. Laboratory values are presented as a large number and appears without comma(s) to improve readability. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000". We recommend revising laboratory values to include a comma, for example, to read as 1,000/microliter instead of 1000/microliter.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Polivy received on July 22, 2022 from Genentech, Inc..

Table 2. Relevant Product Information for Polivy	
Initial Approval Date	June 10, 2019
Proper Name	polatuzumab vedotin-piiq
Indication	*in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL)* in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies
Route of Administration	Intravenous infusion
Dosage Form	for Injection
Strength	30 mg/vial, 140 mg/vial
Dose and Frequency	The recommended dose of Polivy is 1.8 mg/kg as an intravenous infusion every 21 days for 6 cycles.
How Supplied	Polivy (polatuzumab vedotin-piiq) for injection is a preservative-free, white to grayish-white lyophilized powder, which has a cake-like appearance. • One 30 mg single-dose vial • One 140 mg 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 shown on the carton. Do not freeze. Do not shake.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 6, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Polivy. Our search identified 3 previous reviews[a,b,c], and we considered our previous recommendations to see if they are applicable for this current review.

[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.

[b] Garrison, N. Label and Labeling Review for Polivy (BLA 761121/S-003). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 31. RCM No.: 2018-2556-1.

[c] Iverson, N. Label and Labeling Review for Polivy (BLA 761121/S-003). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 10. RCM No.: 2020-1542.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Prescribing Information (Image not shown) received on July 22, 2022, available from \\CDSESUB1\EVSPROD\bla761121\0309\m1\us\draft-labeling-text-redline.docx

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

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