

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761128Orig1s000

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: November 12, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761128
Product Name and Strength: Adakveo (crizanlizumab-tmca) Injection
10 mg/mL
Applicant/Sponsor Name: Novartis Pharmaceuticals (Novartis)
FDA Received Date: November 1, 2019
OSE RCM #: 2019-1074-2
DMEPA Safety Evaluator: Stephanie DeGraw, PharmD
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Novartis submitted revised carton and container labels for Adakveo (crizanlizumab-tmca) on November 1, 2019 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review^a and label and labeling review memo.^b

2 CONCLUSION

We note that all previous recommendations were accepted and implemented. DMEPA concludes the revised container label is acceptable from a medication error perspective. We have no additional recommendations at this time.

^a DeGraw, S. Label and Labeling Review for Adakveo (crizanlizumab-xxxx) BLA 761128. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 13. RCM No.: 2019-1074.

^b DeGraw, S. Label and Labeling Review for Adakveo (crizanlizumab-tmca) BLA 761128. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 25. RCM No.: 2019-1074-1.

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/s/

STEPHANIE L DEGRAW
11/12/2019 11:34:12 AM

HINA S MEHTA
11/18/2019 09:46:23 AM

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: October 25, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761128
Product Name and Strength: Adakveo (crizanlizumab-tmca) (b) (4) solution
10 mg/mL
Applicant/Sponsor Name: Novartis Pharmaceuticals (Novartis)
FDA Received Date: October 16, 2019
OSE RCM #: 2019-1074-1
DMEPA Safety Evaluator: Stephanie DeGraw, PharmD
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Novartis submitted revised carton and container labels for Adakveo (crizanlizumab-tmca) on October 16, 2019 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the revised labels to determine if they are acceptable from a medication error perspective. We note with regard to our recommendation to only include one barcode on the container label, Novartis stated in their response document that the horizontal component number barcode cannot be removed from the vial as it is an additional verification for version control that ensures the correct label for this MARS code during the production process per GMP requirements. The vertical barcode encodes the NDC number. As such, we have no further comments regarding the barcode on the container label.

^a DeGraw, S. Label and Labeling Review for Adakveo (crizanlizumab-xxxx) BLA 761128. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 13. RCM No.: 2019-1074.

Novartis also proposes [REDACTED] (b) (4) from the proposed US PI and carton labeling. However, based on discussion with the review team, the warning statement “Do not shake” should be retained.

We also note that Novartis revised the strength statement to include the total quantity per total volume and the concentration per mL as recommended; however, we identified spacing issues within the strength statement.

3 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. We provide recommendations below for the Sponsor.

3.1 RECOMMENDATIONS FOR NOVARTIS

We recommend the following be implemented prior to approval of this BLA:

A. Container Label

1. As currently presented, the “Rx Only” statement is of equal prominence to critical information on the label; therefore, we recommend de-bolding the “Rx Only” statement.
2. Revise your storage and handling statement to read: “Refrigerate at 2°C to 8°C (36°F to 46°F). Protect from light. Do not shake or freeze.” Ensure inclusion of the “Do not shake” handling condition to be consistent with the Prescribing Information.

B. Carton Labeling [REDACTED] (b) (4)

1. Revise the strength statement to remove extra spaces between the numbers, units, and slash mark. Additionally, we recommend centering the concentration per mL underneath the total quantity per total volume, like it appears on the container label. For example:

100 mg/10 mL
(10 mg/mL)

2. Revise your storage and handling statement to read: “Store and transport vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake. Do not freeze.” Ensure inclusion of the “Do not shake” handling condition to be consistent with the Prescribing Information.

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/s/

STEPHANIE L DEGRAW
10/25/2019 03:09:01 PM

HINA S MEHTA
10/28/2019 09:58:07 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 18, 2019

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Robert Nguyen, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ADAKVEO (crizanlizumab-tmca)

Dosage Form and Route: injection, for intravenous infusion

Application Type/Number: BLA 761128

Applicant: Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On May 16, 2019, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original Biologics License Application (BLA) 761128 for ADAKVEO (crizanlizumab-tmca) injection, for the proposed indication: for the prevention of vaso-occlusive crises in sickle cell disease patient aged 16 and over.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on June 27, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ADAKVEO (crizanlizumab-tmca) injection.

2 MATERIAL REVIEWED

- Draft ADAKVEO (crizanlizumab-tmca) injection PPI received on May 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 7, 2019.
- Draft ADAKVEO (crizanlizumab-tmca) injection Prescribing Information (PI) received on May 16, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on October 7, 2019 and October 18, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
10/18/2019 10:33:30 AM

ROBERT L NGUYEN
10/18/2019 10:47:07 AM

LASHAWN M GRIFFITHS
10/18/2019 11:17:54 AM

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

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

Memorandum

Date: October 17, 2019

To: Michael Gwathmey, Regulatory Project Manager, Division of Hematology Products (DHP)
Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ADAKVEO (crizanlizumab-tmca) injection, for intravenous use

BLA: 761128

In response to DHP's consult request dated June 27, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original BLA submission for Adakveo.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Michael Gwathmey) on October 7, 2019, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 15, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
10/17/2019 10:08:50 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 11, 2019

TO: Ann Farrell, M.D.
Director
Division of Hematology Products (DHP)
Office of New Drugs

FROM: Amanda Lewin, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Stanley Au, Pharm.D.
Deputy Director (Acting)
(DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: [REDACTED] inspection of [REDACTED] (b) (4)
[REDACTED]

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of St [REDACTED] 28, [REDACTED] (b) (4)) conducted at [REDACTED] [REDACTED].

I did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the inspectional findings, I conclude the PK and immunogenicity data from the audited study is reliable.

2. Inspected Study

Study CSEG101A2102 (BLA 761128)

"A Phase I single dose, randomized, open-label, parallel group, single-center trial to assess the comparability of crizanlizumab pharmacokinetics and pharmacodynamics administered as SEG101 in comparison to SelG1 in healthy subjects"

3. Scope of Inspection

OSIS scientist Amanda Lewin, audited the analytical portion of the above studies at (b) (4) from (b) (4). I audited both the PK and immunogenicity analysis that were conducted using ELISA method.

The inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff.

During the inspection, I also reviewed data for the parallelism assessment and the ISR results conducted in support of the PK analysis and not yet submitted to the Agency. The firm was in the process of preparing the report for Addendum II of Method Validation 1600631 (PK) and will submit it to the sponsor after it is finalized. **Attachment 1** includes the draft report of Addendum II collected during the inspection.

The previous inspection was conducted in (b) (4). At the conclusion of the inspection a Form FDA 483 was issued for the following reasons: 1) not using fresh controls for stability assessments, 2) not documenting sample movement during freeze thaw stability assessments, 3) not assessing sensitivity, and 4) using 3 low positive controls and 1 high positive control during one run in sample analysis. There was one discussion item pertaining to a mixing period during sample analysis that was longer than the validated process. I verified corrective actions were made where necessary.

4. Inspectional Findings

At the conclusion of the inspection, I did not observe objectionable conditions. I did not issue Form FDA 483 to (b) (4) and I did not present any discussion items at close out.

5. Conclusion

After review of the inspectional findings, I conclude that the PK and immunogenicity data from the audited studies are reliable.

Studies using similar (b) (4) SA) conducted between the previous inspection ((b) (4)) and the end of the current

surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI- [REDACTED] (b) (4)

cc: OTS/OSIS/Kassim/Dasgupta/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Au/Ayala/Biswas/Lewin
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly
ORA/OMPTO/OBIMO/[FDAInternational BIMO@fda.hhs.gov](mailto:FDAInternational_BIMO@fda.hhs.gov)

Draft: AL 10/09/2019; 10/11/19
Edit: GB 10/10/2019; SA 10/10/2019, 10/11/2019

ECMS:
<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881a1bf0b>

OSIS File #: BE 8615

FACTS: [REDACTED] (b) (4)

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/s/

AMANDA E LEWIN
10/11/2019 03:23:52 PM

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STANLEY AU
10/11/2019 03:40:00 PM



Date: 12 September 2019

From: James L. Weaver Ph.D., Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

Through: David Strauss M.D., Ph.D., Director; DARS/OCP

To: Ramadevi Gudi and Christopher M Sheth, DHP/OHOP/CDER/FDA

Subject: Vascular Injury and SelG1, BLA 761128

Executive Summary

DARS was asked to evaluate the sponsors claim that vascular injury observed in a nonclinical study was due to immune complex deposition. Evaluation of assays performed provides strong evidence of neutralizing anti-drug antibodies in one of two animals with vascular injury. No evidence was provided showing that immune complexes were associated with the vascular lesions. We suggest that immunohistochemical staining be performed on selected tissues with vascular lesions to determine if deposition of immune complexes can be detected in any of the high dose group animals.

Background

The monoclonal antibody crizanlizumab (SELG1) is proposed for the treatment of pain crisis in sickle cell disease (SCD). The fully humanized IgG2a antibody binds to the endothelial cell surface protein P-selectin and prevents its association with its ligand P-selectin glycoprotein ligand-1 (PSGL-1). In healthy individuals P-selectin is stored in the Weibel-Palade bodies of endothelial cells and in the secretory granules of platelets and megakaryocytes. During inflammation or clotting respectively, this protein appears on the cell surface where it acts to bind PSGL-1 on most leukocytes. There is evidence that the vasculature in SCD patients is in a chronically inflamed state and in an animal model of SCD that P-selectin is directly involved in the adhesion between blood elements and the endothelium in SCD (Wood et al, 2004).

In the 26-week repeat-dose toxicity study, crizanlizumab was administered by intravenous bolus administration once every 4-weeks at dose levels up to 50 mg/kg/dose to cynomolgus monkeys. At 50 mg/kg/dose, a minimal-to-moderate inflammation of the vessels in multiple tissues was observed in 2 (females) out of 10 animals (5 males and 5 females). The Applicant suggests that this finding is related to off-target immune-complex mediated reaction to primate antihuman antibody.

Evaluation

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov



The primary question is whether the vascular injury is due to anti-drug antibody (ADA) immune complexes or to drug-induced vascular injury caused by some other mechanism.

The presence of ADAs may or may not have effects on PK and/or PD. In this case, we have useful data from multiple assays. The assays include standard histopathology, where vascular injury in multiple tissues was observed in two of 10 animals. The PD assay measures the ability of serum to inhibit the binding of PSGL-1 to P-selectin using Surface Plasmon Resonance detection. A conventional assay for ADA was performed periodically. Drug levels were also measured. The summary of the findings for these assays is shown in Table 1. One animal (#10486) died early with the death attributed to technical issues. The pattern of results provides an interesting perspective. Animals 104856 and 104875 both show the constellation of (1) no detectable PD, (2) clearly positive ADA signals and (3) reduced PK values. This trifecta is highly consistent with the presence of neutralizing ADAs. Vascular injury was seen in #104875, which was a recovery animal but not in the other animal that died early. Confounding the picture is animal #104872 which had clear and convincing findings of vascular injury. However, there was minimal effect on PD, the complete absence of ADA and a normal PK value. Here there is no supporting evidence suggesting that the pathology was caused by ADA.

Table 1. Cross comparison in the high dose group



Source:	Report No. R8259995					
Cross Comparison of Group 4, 50 mg/kg/dose						
		PD	ADA	ADA	ADA	PK
		Inhibition of	days pos	max	max	d169
Group 4		P-Sel at		signal	day	+1 hr
Animal #	Histopath VI	d183 (%)				ng/ml
104856		0.0	29, 85	8758	29	1,078,000
104857		99.7		292		3,272,500
104858		58.4		213		2,492,500
104859		99.9		221		2,606,000
104860		87.4		225		2,173,000
104872	YES	65.3		211		2,198,000
104873		86.6		210		1,728,500
104874		100.0	169	909	169	1,530,500
104875	YES	0.0	29, 85,169, R	16010	85	830,500
104876		71.8		234		1,699,000
Animal died, d141	#104856 at			Pos cutoff		#104856 at
	day 85			344		day 113
				Avg:		1,960,850

While the evidence is strong for a finding of nADA in animal 104875, there is no direct evidence to link the ADA findings with the vascular injury. It is well recognized that the vascular injury seen in primate studies with biotherapeutics can sometimes be attributed to immune complex (IC) deposition in various vascular beds, most commonly the kidney (Frazier et al, 2014). These IC deposits consist of antibody and antigen and often contain detectable amounts of complement. In this case, the antibody would be the monkey anti-crizanlizumab antibodies and the antigen would be the crizanlizumab itself. Proof of the presence of IC is provided by routine immunohistochemistry. In this case staining for the presence of monkey and human IgG antibody as well as monkey complement in the vascular lesions would need to be done. Based on reported pathology findings (Appendix) we suggest that the following tissues should be evaluated: colon, heart, kidney, liver and stomach. We suggest that this evaluation be done for all



10 Group 4 animals. A more technical study of detection of IC in nonclinical studies published by Rojko et al (2014) serves as an excellent reference for this area. Findings from this study would provide direct evidence of whether or not the vascular injury was associated with IC deposition.

Summary and Conclusions

DARS was asked to evaluate the sponsors claim that vascular injury observed in a nonclinical study was due to immune complex deposition. Evaluation of assays performed provides strong evidence of neutralizing anti-drug antibodies in one of two animals with vascular injury. No evidence was provided showing that immune complexes were associated with the vascular lesions. We suggest that immunohistochemical staining be performed on selected tissues with vascular lesions to determine if deposition of immune complexes can be detected in any of the high dose group animals.

References and Supporting Documents

Scientific and Regulatory Policy Committee Points-to-consider Paper*: Drug-induced Vascular Injury Associated with Non-small Molecule Therapeutics in Preclinical Development: Part I. Biotherapeutics. Kendall S. Frazier, Jeffrey A. Engelhardt, Pierluigi Fant, Silvia Guionaud, Scott P. Henry, Michael Leach, Calvert Loudon, Marshall S. Scicchitano, James L. Weaver, and Tanja S. Zabka for the Society of Toxicologic Pathology Vascular Injury Working Group. *Toxicol. Pathol.* **43** 915-934 (2015). DOI: 10.1177/0192623315570340

Rojko JL, Evans MG, Price SA, Han B, Waine G, DeWitte M, Haynes J, Freimark B, Martin P, Raymond JT, Evering W, Rebelatto MC, Schenck E, Horvath C. Formation, Clearance, Deposition, Pathogenicity, and Identification of Biopharmaceutical-related Immune Complexes: Review and Case Studies. *Toxicol. Pathol.* **42** 725-764 (2014). DOI: 10.1177/0192623314526475

Wood KC, Hebbel RP, Granger DN. Endothelial cell P-selectin mediates a proinflammatory and prothrombotic phenotype in cerebral venules of sickle cell transgenic mice. *Am J Physiol Heart Circ Physiol* **286**: H1608–H1614, (2004). DOI: 10.1152/ajpheart.01056.2003.



Appendix

Summary of microscopic pathology findings for animals 104872 and 104875						
Animal #	tissue	findings ->				
104872	cecum	inflammation	vessel	slight	multifocal	submucosa
104875	cervix	inflammation	vessel	minimal	multifocal	
104872	colon	inflammation	vessel	slight	multifocal	submucosa
104875	colon	inflammation	vessel	slight	multifocal	submucosa
104872	gall bladder	infiltrate	mononuclear cell	minimal	multifocal	
104875	gall bladder	inflammation	vessel	minimal	multifocal	
104875	heart	infiltrate	mononuclear cell	minimal	multifocal	myocardium
104872	heart	inflammation	vessel	slight	multifocal	coronary artery
104875	heart	inflammation	vessel	moderate	multifocal	coronary artery
104875	ilium	inflammation	vessel	minimal	focal	mesentery
104875	jejunum	inflammation	vessel	minimal	focal	mesentery
104872	kidney	inflammation	vessel	slight	multifocal	bilateral
104875	kidney	inflammation	vessel	moderate	multifocal	bilateral
104872	liver	infiltrate	mononuclear cell	minimal	diffuse	periportal
104872	liver	inflammation	vessel	slight	multifocal	arteries and portal veins
104875	liver	inflammation	vessel	minimal	multifocal	arteries
104875	liver	mineralization		slight	multifocal	
104872	mandibular salivary gland	infiltrate	mononuclear cell	slight	multifocal	
104875	mandibular salivary gland	infiltrate	mononuclear cell	minimal	multifocal	
104872	ovary	inflammation	vessel	slight	multifocal	
104875	ovary	inflammation	vessel	minimal	multifocal	
104875	ovary	mineralization		minimal	multifocal	
104872	pancreas	inflammation	vessel	slight	multifocal	
104875	spleen	inflammation	vessel	slight	multifocal	arteries
104872	stomach	inflammation	vessel	moderate	multifocal	submucosa
104875	stomach	inflammation	vessel	minimal	multifocal	submucosa
104872	uterus	inflammation	vessel	slight	multifocal	myometrium
104872	vagina	inflammation	vessel	slight	multifocal	
104875	vagina	inflammation	vessel	minimal	focal	

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/s/

TRACEY B LEE
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JAMES L WEAVER
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DAVID G STRAUSS
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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:	September 13, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761128
Product Name and Strength:	Adakveo (crizanlizumab-xxxx)* (b) (4) solution 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals (Novartis)
FDA Received Date:	March 15, 2019, April 30, 2019, and July 9, 2019
OSE RCM #:	2019-1074
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

*The proper name for this BLA has not yet been determined; therefore, the placeholder "crizanlizumab-xxxx" is used throughout this review to refer to the proper name for this product. The proprietary name Adakveo has been found conditionally acceptable.

1. REASON FOR REVIEW

Novartis Pharmaceuticals submitted BLA 761128 Adakveo (crizanlizumab-xxxx) injection on March 15, 2019 as part of a rolling submission. Adakveo is a monoclonal antibody blocking P-selectin mediated multi-cellular adhesion indicated for the prevention of vaso-occlusive crises (VOCs) in sickle cell disease in patients aged 16 years and over. We evaluated the proposed container labels, carton labeling, and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

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

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 post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI for Adakveo (crizanlizumab-xxxx) to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the proposed PI identified the use of the abbreviation "IV" that may lead to misinterpretation of the route of administration (i.e. intravenous). Our review of the carton and container labels identified the use of a placeholder for the NDC. In addition, we identified areas in the PI, carton labeling and container labels that can be modified to improve the clarity of the information presented.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Novartis in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. General Comments

1. Replace "PROPRIETARY NAME" with the conditionally acceptable name "Adakveo" wherever it appears.
2. We note the use of the abbreviation "IV" throughout the PI. We recommend spelling out "intravenous" wherever "IV" appears to avoid misinterpretation of the route of administration.

B. Highlights of Prescribing Information

1. Dosage Forms and Strengths

- a. We recommend revising this statement to add the finished dosage form and total concentration of the vial. For example, "Injection: 100 mg/10 mL (10 mg/mL) in a single-dose vial".

C. Dosage and Administration [2]

1. Preparation and Administration [2.2]

a. Preparation

- i. Revise the second bullet to read "Calculate the dose (mg), the total volume (mL) of ADAKVEO solution required, and the number of ADAKVEO vials needed based on the patient's [actual or ideal] body weight.

b. Dilution

- i. We recommend (b) (4)

- ii. We recommend revising step 3 and separating it into 3 separate steps (now steps 3-5) to improve clarity. For example:

3. Obtain 100 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection infusion bag.

- Infusion bags/containers must be made of either polyvinyl chloride (PVC), polyethylene (PE), or polypropylene (PP).

4. Remove a volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection from the infusion bag/container that is equal to the required volume of ADVAKEO solution.

5. Withdraw the necessary amount of ADVAKEO solution and dilute by adding to the infusion bag/container containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection.

- iii. We recommend deleting the statement (b) (4) as it is incorporated in statement above.
 - iv. We recommend revising the bullet (b) (4) to only state the max volume of Adakveo to be added to the bag for clarity. Revise to "The volume of ADAKVEO added to the infusion bag should not exceed 96 mL."
 - v. We recommend revising the statement (b) (4) to accurately reflect the packaging type.^a Revise to "Single dose vials. Discard unused portion."
- c. Storage Conditions of the Diluted Solution
- i. We recommend confirming if the diluted product should have the same "protect from light" warning as the product in the vial. If so, we recommend including this information in this section.

D. Dosage Forms and Strengths [3]

- 1. We recommend revising this statement read "Injection: 100 mg/10 mL (10 mg/mL) as a clear to opalescent, colorless to slightly brownish-yellow solution in a single-dose vial."

E. How Supplied / Storage and Handling [16]

- 1. How Supplied (b) (4)
 - a. We recommend revising this section to improve clarity and to include the total concentration of the product. For example:

ADAKVEO (crizanlizumab-xxxx) injection is a sterile, clear to opalescent, colorless to slightly brownish-yellow solution supplied as:

Carton containing one 100 mg/10 mL (10mg/mL) single-dose vial
NDC XXXX-xxx-xx

The single-dose vial has a rubber stopper and an aluminum cap with a plastic flip-off disk. Each 10 mL vial is made of Type 1 glass.
 - b. The NDC is denoted by a placeholder. We recommend requesting the proposed NDC for review.

^a Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

4.2 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS

A. General Comments for the Container Label and Carton Labeling

1. Replace "TRADENAME" with the conditionally acceptable proprietary name "Adakveo" wherever it appears.
2. We note the use of a placeholder for the NDC (i.e., 0078-XXXX-XX). We request you submit the full proposed NDC for review.

B. Container Label

1. Consider including the finished dosage formulation, "Injection", directly beneath the proper name on the principal display panel.
2. Delete the phrase [REDACTED] (b) (4) from the side panel.
3. We recommend combining the administration statement "for intravenous infusion" with the dilution statement "dilute before use". Revise the statements to read "For intravenous infusion after dilution" to improve clarity and highlight the importance of this information.
4. Consider adding an "Rx Only" statement to the principal display panel.
5. As currently presented, there are two barcodes on the vial label. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers.^b Therefore, we recommend you remove the barcode that does not contain the NDC number.
6. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.^c
7. We recommend revising [REDACTED] (b) (4) to read "Single-Dose Vial. Discard Unused Portion." to minimize risk of the entire contents of the vial being given as a single dose when only a partial vial is required.
8. Consider adding storage information to the container label to ensure this important information is accessible to the end user. We recommend stating,

^b Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014;19(2):1-3.

^c Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

“Refrigerate at 2°C to 8°C (36°F to 46°F). Protect from light. Do not shake or freeze.”

C. Carton Labeling [REDACTED] (b) (4)

1. The placement of the graphic at the beginning of the proprietary name competes with the readability of the proprietary name, which may lead to misinterpretation of the proprietary name as “Oadakveo”. Therefore, we recommend moving or decreasing the prominence of the graphic at the beginning of the proprietary name.
2. Consider including the finished dosage formulation, “Injection”, directly beneath the proper name on the principal display panel.
3. Delete the phrase [REDACTED] (b) (4) from the side panel.
4. Revise the strength statement to include the total quantity per total volume and the concentration per mL to prevent confusion per USP General Chapters: <7> Labeling. For example:
100 mg/10 mL
(10 mg/mL)
5. We recommend revising the administration statement to read “For intravenous infusion after dilution” to ensure this important information is not overlooked. The [REDACTED] (b) (4) statement on the bottom right corner of the principal display panel may be deleted.
6. We recommend de-bolding the “Rx only” statement as it competes in prominence with critical information on the principal display panel.
7. We recommend removing the statement [REDACTED] (b) (4) as this information will be redundant once the concentration per mL is included as part of the strength statement.
8. We recommend revising the statements [REDACTED] (b) (4) to read “1 Single-Dose Vial. Discard Unused Portion.” to minimize risk of the entire contents of the vial being given as a single dose when only a partial vial is required.
9. The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (i.e., the carton) for tracking and tracing purposes. The product identifier data is specifically required under section 582(a)(9) of the FD&C Act to be in a “2D data matrix barcode” for

packages. As such, we recommend you add a product identifier in a 2D data matrix barcode format adjacent to the human-readable information per the FDA draft guidance on product identifiers.^d

10. To minimize the risk of storage information being overlooked, we recommend revising the storage information to read, “Store and transport vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake. Do not freeze.”
11. We recommend removing the trailing zeros that appear on the back panel (i.e., 2.000 mg) to avoid misinterpretation of the number (i.e., 2 *versus* 2000).

^d Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Adakveo received on April 30, 2019 from Novartis Pharmaceuticals.

Table 2. Relevant Product Information for Adakveo	
Initial Approval Date	N/A
Active Ingredient	crizanlizumab-xxxx
Indication	monoclonal antibody blocking P-selectin mediated multi-cellular adhesion indicated for the prevention of vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and over
Route of Administration	intravenous infusion
Dosage Form	(b) (4) solution
Strength	10 mg/mL
Dose and Frequency	5 mg/kg by intravenous infusion over a period of 30 minutes at Week 0, Week 2, and every 4 weeks thereafter.
How Supplied	Sterile, clear to opalescent, colorless to slightly brownish-yellow (b) (4) solution for intravenous infusion Supplied as a single-dose vial: Pack of 1 vial: 10mg/mL vial The single-dose vial has a rubber stopper and an aluminum cap with a plastic flip-off disk. Each 10 mL vial is made of Type 1 glass.
Storage	Store and transport refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Keep the vial in the outer carton, in order to protect from light. (b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,^e along with post-market medication error data, we reviewed the following Adakveo labels and labeling submitted by Novartis Pharmaceuticals:

- Container Label on March 15, 2019
- Carton Labeling on March 15, 2019
- [REDACTED] (b) (4)
- Prescribing Information (no image shown) on April 30, 2019
<\\cdsesub1\evsprod\bla761128\0003\m1\us\proposed-clean.doc>

G.2 Labels and Labeling

Container Label

(b) (4)



^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DIVISION OF HEMATOLOGY PRODUCTS
Associate Director for Labeling Review of the Prescribing Information

Product Title	TRADENAME (crizanlizumab-xxxx)
Applicant	Novartis
Application/Supplement Number	BLA 761128
Type of Application/Submission ¹	NME
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	For the prevention of vaso-occlusive crises in sickle cell disease in patients 16 and over
Approved Indication(s) (if applicable)	tba
Date FDA Received Application	05/16/19
Review Classification (Priority/Standard)	Priority
Action Goal Date	01/16/2020
Review Date	09/09/2019
Reviewer	Virginia E. Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements²
- Is consistent with labeling guidance recommendations³ and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

The applicant is seeking approval for crizanlizumab for the prevention of vaso-occlusive crises in sickle cell disease in patients 16 and over. This review is being completed between the first and second labeling meetings. Not all disciplines have reviewed the USPI at this time. ADL recommendations provided in this review (e.g., recommended edits and comments regarding parts of PI) are preliminary and pending discussion with other review team members for this product.

In the attached PI, ADL comments (in balloons) are labeled with my name. This review includes a high-level summary of the rationale for major changes to the PI as compared with the applicant's draft PI and currently approved PI.

¹ Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

² See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR [201.56\(e\)](#) and [201.80](#).

³ See [PLR Requirements for PI](#) website for PLR labeling guidances.

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CLINICAL INSPECTION SUMMARY

Date	September 5, 2019
From	Anthony Orenca M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Susan D. Thompson, M.D., Team Leader, <i>for</i> Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Patricia O’Neal, M.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Ann Farrell, M.D., Director Michael Gwathmey, Regulatory Project Manager Division of Hematology Products
BLA	761128
Applicant	Novartis Pharmaceuticals Corporation
Drug	Crizanlizumab
NME	Yes
Division Classification	IgG2 kappa humanized monoclonal antibody
Proposed Indication	Prevention of vaso-occlusive crisis in sickle cell patients age 16 years and older
Consultation Request Date	June 5, 2019
Summary Goal Date	September 15, 2019 (CDER Priority BLA)
Action Goal Date	November 16, 2019
PDUFA Date	January 16, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites were selected for inspection in support of BLA 761128.

Data as reported by the sponsor to the BLA from Dr. Abdullah Kutlar’s site in Georgia (Site 102) and Dr. Darla Liles’s site in North Carolina (Site 122) enrolling in Study CSEG101A2201, based on the clinical inspections, are considered to be reliable in support of the requested indication.

II. BACKGROUND

Crizanlizumab is a selective IgG2 kappa humanized monoclonal antibody that binds to P-selectin with high affinity and blocks interactions with its ligands including P-selectin glycoprotein ligand 1.

P-selectin is an adhesion molecule expressed on activated endothelial cells and platelets. P-selectin is an overexpressed protein in proinflammatory states. Such P-selectin protein abundance could play a role in vaso-occlusive conditions, such as sickle cell disease.

In this submitted application, the sponsor proposes crizanlizumab for the following drug label indication: prevention of vaso-occlusive crises in sickle cell disease patients.

A Phase 2 study, CSEG101A2201, is part of the basis for the regulatory decision-making process for this proposed application indication.

Study CSEG101A2201

This study was conducted as a multi-center, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of crizanlizumab (SelG1) in patients with sickle cell disease (SCD). A total of 198 patients with the diagnosis of SCD were to be randomized into 1 of three arms with a 1:1:1 ratio [high dose group (67 subjects), low dose group (66 subjects), and placebo (65 subjects)].

The primary objectives of this Phase 2 study were to investigate the annual rate of sickle cell-related pain crises (SCPC) per year in each active dosage arm as compared to placebo, and to assess the frequency and severity of adverse events and other safety data.

The primary efficacy endpoint was the adjudicated rate of sickle cell-related pain crises per year. Sickle cell-related pain was defined as an acute episode of pain with no medically determined cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility), were also considered sickle cell-related pain for analysis purposes. To ensure consistency across all sites, all crisis events identified by study Investigators were adjudicated by an independent, blinded Crisis Review Committee comprised of three independent hematologists who specialize in the treatment of sickle cell disease. Safety was assessed by reported adverse events, changes from baseline during treatment.

A total of 198 patients were randomized and included in the ITT population. There were 192 patients who received study treatment. The calendar date of the first subject visit was July 24, 2013. The calendar date that the last patient completed the study was March 23, 2016. This study randomized patients at 51 centers in the U.S., 8 centers in Brazil, and 1 center in Jamaica.

Sites 102 (Dr. Abdullah Kutlar) and 122 (Dr. Darla Liles) were selected for clinical inspections; inspection of these high enrollment clinical sites could have an impact in DHP's clinical decision-making process.

III. RESULTS (by site):

1. Abdullah Kutlar, M.D., Site 102
Sickle Cell Center, Augusta University
989 St. Sebastian Way (EF Bldg.)
Augusta, GA 30912
Inspection dates: August 19 to 21, 2019

A total of 14 subjects were screened and 10 patients were enrolled. Three enrolled study subjects who received treatment discontinued: two subjects moved out of the area and one subject withdrew consent due to an adverse event. Seven subjects who received treatment completed the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, medical progress notes, intravenous/infusion administration form notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also reviewed.

Source documents for the 14 screened subjects' informed consent form documentation were assessed. Source documents for 10 enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings for study eligibility, primary study endpoint assessment, adverse events, and serious adverse event reporting. Records review of these subjects indicated that the eligibility criteria for enrollment were met.

Source documents for the raw data used to assess the primary efficacy endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Darla Liles M.D., Site 122
East Carolina University Brody School of Medicine
Leo W. Jenkins Cancer Center
600 Moye Blvd.
Greenville, NC 27834
Inspection dates: August 12 to 15, 2019

A total of 11 subjects were screened and enrolled. Three subjects discontinued from the study due to non-compliance with the study medications (two subjects) or loss to follow-up (one subject). Eight subjects who received treatment completed the study.

For this inspection, a complete review of all regulatory documentation at the study site was performed. Source records for all the subjects enrolled at the site were reviewed. The records

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

Source documents for all enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings for eligibility, adverse events, and serious adverse event reporting. Source documents for the primary efficacy raw data endpoint were verifiable at the study site. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

{See appended electronic signature page}

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