CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761128Orig1s000

PROPRIETARY NAME REVIEW(S)

MEMORANDUM

SUFFIX REVIEW FOR NONPROPRIETARY NAME

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:	August 30, 2019
Responsible OND Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761128
Product Name and Strength:	Adakveo (crizanlizumab-tmca) injection 100 mg/10 mL (10 mg/mL)
Product Type:	Single Ingredient Product
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
FDA Received Date:	March 29, 2019
OSE RCM #:	2019-1342
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, BS Pharm
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffixes proposed by Novartis for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761128.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

On March 29, 2019, Novartis submitted a list of ten suffixes, in their order of preference, to be used in the nonproprietary name of their product[a]. Novartis also provided findings from an external study conducted by the (b) (4), evaluating the proposed four-letter suffixes in conjunction with the nonproprietary name, for our consideration. Table 1 presents a list of suffixes submitted by Novartis:

Table 1. Suffixes submitted by Novartis***	
1.	tmca
2.	(b) (4)
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	

We reviewed Novartis's proposed suffixes in order of preference listed by Novartis, along with the supporting data they submitted, using the principles described in the applicable guidance.[c]

2.1 crizanlizumab-tmca

Novartis's first proposed suffix, -tmca, is composed of 4 distinct letters.

We determined that the proposed suffix -tmca, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

[a] Request for Non-Proprietary Name BLA 761128. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2019 Mar 29. Available from: \\cdsesub1\evsprod\bla761128\0002\m1\us\req-comm-nonproprietary-wave3-20190329.pdf

(b) (4)

[c] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. Per an email correspondence dated August 30, 2019, OPDP did not identify any concerns that would render this proposed suffix unacceptable. DMEPA also communicated our findings to the Division of Hematology Products (DHP) via e-mail on August 30, 2019.

4 CONCLUSION

We find Novartis's proposed suffix -tmca acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to crizanlizumab-tmca. DMEPA will communicate our findings to the Applicant via letter.

4.1 Recommendations for Novartis Pharmaceuticals Corporation

We find the nonproprietary name, crizanlizumab-tmca, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, crizanlizumab-tmca will be the proper name designated in the license. You should revise your proposed labels and labeling accordingly and submit the revised labels and labeling to your BLA for our review. However, please be advised that if your application receives a complete response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your suffix unacceptable upon our re-evaluation, we would inform you of our finding.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARLOS M MENA-GRILLASCA
08/30/2019 11:56:57 AM

DANIELLE M HARRIS
08/30/2019 02:03:51 PM

PROPRIETARY NAME 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)

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Date of This Review:	July 26, 2019
Application Type and Number:	BLA 761128
Product Name and Strength:	Adakveo (crizanlizumab-xxxx[*)] injection 100 mg/10 mL (10 mg/mL)
Total Product Strength:	100 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
Panorama #:	2019-31263789
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

[*] The proper name for Adakveo has not yet been determined; therefore, "crizanlizumab-xxxx" is used throughout this review as the proper name for this product.

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1 INTRODUCTION

This review responds to a April 30, 2019 request from Novartis to reconsider the proposed proprietary name, Adakveo, from a safety and misbranding perspective. Novartis submitted an external name study, conducted by (b) (4), for this proposed proprietary name.

1.1 REGULATORY HISTORY

Novartis Pharmaceuticals Corporation (Novartis) previously submitted the proposed proprietary name, Adakveo*** on December 3, 2018 under IND 110752. However, we found the name, Adakveo*** unacceptable due to orthographic similarities and shared product characteristics with the proprietary name, Adasuve on February 7, 2019.[a] Thus, Novartis submitted the name, Adakveo, for reconsideration on April 30, 2019 under BLA 761128.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on April 30, 2019.

- Intended Pronunciation: ah dak' vee oh
- Active Ingredient: crizanlizumab-xxxx*
- Indication of Use: Prevention of vaso-occlusive crises in patients with sickle cell aged 16 years and over.
- Route of Administration: Intravenous infusion
- Dosage Form: injection
- Strength: 100 mg/10 mL (10 mg/mL)
- Dose and Frequency: The recommended dose of crizanlizumab is 5 mg/kg administered over a period of 30 minutes by intravenous infusion on Week 0, Week 2, and every 4 weeks thereafter.
- How Supplied: 100 mg/10 mL single dose vial
- Storage: Vials are stored under refrigeration at 2-8°C and kept in the outer carton in order to protect from light. Do not freeze.

2 MATERIALS REVIEWED AND METHODS

We used Failure Mode and Effects Analysis (FMEA) in our review of Novartis Pharmaceuticals Corporation's request for reconsideration. We also considered the safety concerns described in our previous review of the proposed proprietary name, Adakveo, as well as information provided by Novartis, in the request for reconsideration.

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[a] Straka M. Proprietary Name Review for Adakveo (IND 110752). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 07. Panorama No. 2018-25790946.

* The proper name for Adakveo has not yet been determined; therefore, "crizanlizumab-xxxx" is used throughout this review as the proper name for this product.

In the April 30, 2019 request for reconsideration, Novartis stated:

1. The potential for numerically similar doses is highly unlikely.
2. There is minimal look-alike similarity beyond the first three letters of each name and no sound alike similarity between the name pair, Adakveo and Adasuve.
3. Adakveo and Adasuve have clinical attributes which can impact the risk of confusion between the two products.
4. The context of use mitigates risk of confusion.
5. Adasuve Risk Evaluation and Mitigation (REMS) program mitigates risk of confusion.
6. Storage conditions/packaging mitigate risk of confusion.
7. Low utilization of Adasuve mitigates risk of confusion.

The following sections provide information obtained and considered in the overall reconsideration of the proposed proprietary name.

3 DISCUSSION

This section summarizes our evaluation of the information provided by Novartis in support of a reconsideration of the proposed proprietary name, Adakveo.

Potential for Numerically Similar Doses

In our previous evaluation of the name, we note that the proposed indication for Adakveo was noted as prevention of vaso-occlusive crises in sickle cell patients aged (b) (4) .[b] Thus, our calculation of a dose range for this product was based on this indication. Since then Novartis has revised the indication to prevention of vaso-occlusive crises in sickle cell disease patients aged 16 years and over. The proposed dose of Adakveo is 5 mg/kg and in clinical studies, crizanlizumab was evaluated in sickle cell disease patients aged 16 years of age to 65 years of age with body weights ranging from 39.4 kg to 134 kg. Therefore, per Novartis, the theoretical total dose per infusion would range from approximately from 197 mg to 670 mg. The recommended dose of Adasuve (indicated only in adults), is 10 mg. (b) (4)

Given the revised indication, we acknowledge that there is no longer a potential for dose overlap or similarity between these products and the doses are sufficiently different to reduce the risk of confusion.

Differences in Orthographic and Phonetic Similarity

Novartis states that there is minimal look-alike similarity beyond the first three letters of the name ('Ada-') and no sound-alike similarity between the name pair. Orthographically, Novartis acknowledges that the names are identical in length (7 letters), contain identical prefixes and have upstroke letters in similar locations ('d' in the 2nd position). However, Novartis states that Adakveo contains an additional upstroke letter 'k' in the 4th position, which is absent from Adasuve and the last letters are different (o *versus* e). The Applicant also asserts that there are no

[b] Straka M. Proprietary Name Review for Adakveo (IND 110752). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 07. Panorama No. 2018-25790946.

downstroke, cross-stroke, or dotted letters in similar positions between the name pair. Although, we agree that there may be some orthographic differences in the suffixes of the name, we have seen name confusion errors with other products that begin with identical letters and have differences in the shape of the names (e.g., number of downstroke letters) and in the last letters.[c] Furthermore, the orthographic similarity of the name pair, Adakveo and Adasuve, is further supported by FDA's Phonetic and Orthographic Computer Analysis (POCA) which calculates a 71% orthographic score, indicating high orthographic similarity.[d]

Therefore, we continue to find that the names are orthographically similar.[e]

Differences in Product Characteristics

Novartis states that there are important differences in product characteristics that mitigate the risk of confusion and medication error between Adakveo and Adasuve (see Appendix A). The Applicant states that Adakveo and Adasuve have differences in therapeutic categories (monoclonal antibody blocking P selectin mediated multicellular adhesion *versus* antipsychotic) and proposed indications (prevention of vaso-occlusive crises in sickle cell disease patients aged 16 years and over *versus* acute treatment of agitation associated with schizophrenia or bipolar 1 disorder), which result in the products being prescribed by different types of healthcare providers (psychiatrists with in-patient hospital privileges *versus* hematologists in the outpatient setting). This difference in indication may not prevent confusion between this name pair, as despite widespread recommendations only a small percentage of medications ordered include the indication.[f] Additionally, differences in the prescribers are unlikely to impact the likelihood of misinterpretation that may occur during other phases of the medication use system (e.g., transcription, selection).

Furthermore, Novartis outlines differences in the medicinal ingredient, strength, dosage form, route of administration, proposed dose, dosing interval/frequency, and storage. As stated in our previous evaluation of the name, the strength, dosage form, and route of administration may be omitted from a prescription. However, we acknowledge that these elements, if included on a prescription, would help to differentiate the products. Additionally, Novartis states that Adakveo is intended for preventative/chronic use and is not designed to be used in the acute/emergency room setting, whereas Adasuve is intended for the acute management of agitation, and not as a chronic/preventative therapy. However, as stated in our previous evaluation of the name, as the frequency of administration of Adakveo is once every four weeks, both products may be written on a prescription with a frequency of 'once'.

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[c] Institute for Safe Medication Practices. Another case of name confusion (what else is Neu?). ISMP Med Saf Alert. 1998;3(15):1. This article describes confusion between Neupogen and Neumega where an order for Neumega 3,500 mcg was misread, and the patient received Neupogen 350 mcg.

[d] POCA search conducted on December 28, 2018 in version 4.3.

[e] Straka M. Proprietary Name Review for Adakveo (IND 110752). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 07. Panorama No. 2018-25790946.

[f] Schiff GD Mirica MM, Dhavle AA, Galanter WL, Lambert B, Wright A. A Prescription for Enhancing Electronic Prescribing Safety. Health Affairs 2018; 37(11): 1877-1883.

Please see the other sections of this review regarding our evaluation of the proposed doses, clinical setting of dispensing, and packaging/storage.

REMS Program

Novartis states that Adasuve is subject to a REMS program, which would also contribute to the prevention of Adasuve being dispensed in place of Adakveo or Adakveo being dispensed or administered in place of Adasuve. Healthcare settings must be certified in order to dispense and administer Adasuve only for inpatient facilities. Wholesalers must be certified, keep records of distribution/sales and cannot provide Adasuve to a non-certified healthcare facility. Healthcare facilities must document and maintain records of training of all relevant staff, establish procedures, protocols, and/or order sets to help ensure compliance with safe use conditions. Facilities must also designate an authorized representative at healthcare facility who will complete certification process to enroll facility, ensure relevant staff are trained, maintain facility is compliant to REMS. Facilities cannot sell, transfer, or loan Adasuve between facilities. Facilities must recertify in REMS program within three years from date of initial certification, every three years thereafter, or if a new representative is in place. Furthermore, patients must also be prescreened for pulmonary conditions (e.g., asthma, Chronic Obstructive Pulmonary Disease (COPD), etc.), counseled, and monitored for breathing/any side effects (every 15 minutes for at least one hour after administration). Novartis states that Adasuve is unlikely to be stocked or administered in an infusion center or clinic where Adakveo would be administered and considers inpatient administration of Adakveo unlikely and not a primary environment of use.

However, as stated in our previous evaluation of the name pair, the REMS may not reduce risk associated with confusion of similar names as we have reports of name confusion with other products marketed under restricted distribution systems.[g,h] Additionally, although unlikely, there is the potential for both products to be prescribed and dispensed in the same medication use system (i.e., a certified inpatient healthcare facility) as both products are administered by a healthcare professional.

Storage Conditions/Packaging

Novartis proposes that the storage conditions and packaging of Adakveo will differ significantly from Adasuve, thus, minimizing the potential for medication errors. Adakveo will be supplied in a single-dose 10 mL vial which are refrigerated whereas Adasuve is an oral inhaler which will be stored at room temperature. Furthermore, Novartis states that there are strong visual differences in the packaging and actual product presentation. The difference in storage, packaging, and product appearance may mitigate potential product selection errors; however,

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[g] Straka M. Proprietary Name Review for Adakveo (IND 110752). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 07. Panorama No. 2018-25790946.

[h] Institute for Safe Medication Practices. Safety briefs: Don't Confuse TRACLEER (bosentan) with TRICOR (fenofibrate). ISMP Med Saf Alert Acute Care. 2003;8(13):2.

Institute for Safe Medication Practices. Safety briefs: Mifepristone (MIFEPREX) and Misoprostol (CYTOTEC) mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2003;2(1):1.

these differences are unlikely to impact the likelihood of misinterpretation that may occur during the prescribing or transcription phases of the medication use system.

Low Utilization of Adasuve

Novartis supplied data demonstrating that there is low utilization of Adasuve, with less than or equal to (b) (4)% of loxapine units sold per year (see Appendix B). Per Novartis, only (b) (4) units of Adasuve were sold in 2018 versus (b) (4) units of loxapine (capsule or tablet). We note the low utilization of Adasuve and the lower frequency of use may reduce some of the risk for name confusion errors; however, wrong drug errors may still occur.

Summary of our evaluation

We carefully considered the rationale raised by Novartis in the supporting documentation on each of the points above, and when considered independently, we find that with the exception of nonoverlapping doses, none of the mitigations presented by Novartis are sufficient to prevent name confusion between Adakveo and Adasuve when considered independently. However, given the revised indication and no overlapping doses between the two products, we note that when all of the mitigations described above are considered in totality, we find that the proposed mitigations minimize the risk of name confusion between Adakveo and Adasuve to an acceptable level.

4 CONCLUSION

We conclude that the proposed proprietary name, Adakveo, for crinzanlizumab injection (BLA 761128) is conditionally acceptable and recommend that this be conveyed to the applicant.

If you have any questions or need clarifications, please contact Deveonne Hamilton-Stokes, OSE project manager, at 301-796-2253.

4.1 COMMENTS TO NOVARTIS PHARMACEUTICALS CORPORATION

We have completed our review of the information submitted in support of your Request for Reconsideration of the proposed proprietary name, Adakveo. We conclude that your proposed name, Adakveo, is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 30, 2019, submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

APPENDICES

Appendix A: Comparative information: Non-name attributes as provided in the Applicant's Request for Reconsideration

Product profile criteria (Non-name attributes)			Same	Different
	ADAKVEO®	**adasuve®**		
1. Marketing status (RX/OTC)	RX	RX	X	
2. Therapeutic category	Monoclonal antibody blocking P-selectin mediated multicellular adhesion	First-generation (i.e., typical) antipsychotic		X
3. Medicinal ingredient(s)	Crizanlizumab	Loxapine		X
4. Indication	(*Proposed*) prevention of vaso-occlusive crises in sickle cell disease patients aged 16 years and over.	acute treatment of agitation associated with schizophrenia or bipolar I disorder		X
5. Clinical setting for dispensing	Out-patient, clinic or infusion center, home infusion	Enrolled healthcare facility	X	
6. Strengths	10 mg/mL (total strength 100 mg/10 mL)	10 mg/inhaler		X
7. Dosage form(s)	Concentrate for solution for infusion	Inhalation powder		X
8. Route(s) of administration	Intravenous infusion over 30 minutes	Oral inhalation		X
9. Proposed dose	5 mg/kg (average dose 300-400 mg)	10 mg		X
10. Dosing interval/frequency	Chronic Week 0, Week 2, and every 4 weeks thereafter	Acute One-time dose		X
11. Storage	Vials: refrigerated	Inhaler: room temperature		X

Appendix B: Adasuve, Loxapine and Conventional Antipsychotics sales (2016-2018, units sold) as provided in the Applicant's Request for Reconsideration

	Units (number of Packs sold)			
Product	**2016**	**2017**	**2018**	**2019 (Jan & Feb)**
adasuve® (inhalation)				(b) (4)
Loxapine +Loxitane (capsule/Tablets				
Conventional Antipsycotics (minus all Loxapine)				
% adasuve® of all Loxapine				

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NICOLE B GARRISON
07/26/2019 10:56:54 AM

HINA S MEHTA
07/26/2019 11:16:25 AM

MISHALE P MISTRY
07/26/2019 11:43:22 AM