

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761099Orig1s000

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: April 25, 2019
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: BLA 761099
Product Name and Strength: Zirabev (bevacizumab-bvzr) Injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Applicant/Sponsor Name: Pfizer, Inc.
FDA Received Date: April 18, 2019
OSE RCM #: 2018-258-2
DMEPA Safety Evaluator: Colleen Little, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Zirabev (Appendix A) to determine if they are acceptable from a medication error perspective. On March 27, 2018, we found the nonproprietary name suffix, -bvzr, conditionally acceptable.^a Thus, the proposed Zirabev container labels and carton labeling were revised to include the nonproprietary name suffix, -bvzr.

2 CONCLUSION

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

^a Mena-Grillasca, C. Nonproprietary Name Suffix Memo for Zirabev (BLA 761099). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 27. RCM No.: 2018-1732.

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/s/

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CHI-MING TU
04/25/2019 11:55:30 AM

Clinical Inspection Summary

Date	February 19, 2019
From	Navid Homayouni, M.D., Medical Officer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Shubhangi Mehta, Pharm.D., Regulatory Project Manager Sandra Casak, M.D., Clinical Reviewer Martha Donoghue, M.D., Cross Discipline Team Leader Division of Oncology Products 2
BLA #	761099
Applicant	Pfizer, Inc.
Drug	PF-06439535
NME	Yes
Therapeutic Classification	Standard
Proposed Indication	Treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer.
Consultation Request Date	September 14, 2018
Summary Goal Date	February 21, 2019
Action Goal Date	June 29, 2019
PDUFA Date	June 29, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Clinical Study, Protocol B7391003 was submitted to the FDA in support of a proposed indication for BLA 761099. This was a multinational, double-blind, randomized, parallel-group Phase 3 clinical trial comparing the efficacy and safety of PF-06439535 plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin in first-line treatment for patients with advanced (unresectable, locally advanced, recurrent, or metastatic) non-squamous NSCLC. The data for Study B7391003 submitted by the Sponsor to the Agency in support of BLA 761099 appear reliable based on available information from the inspections of four foreign clinical sites.

Four clinical sites, Igor M. Bondarenko, M.D. (Site 1325), Hryhoriy Adamchuk, M.D. (Site 1428), Ihor O. Vynnychenko, M.D. (Site 1327), and Michael Schenker, M.D. (Site 1045) were selected for audit.

There were no significant inspectional observations for the clinical investigators, Igor M. Bondarenko, M.D., Hryhoriy Adamchuk, M.D., Ihor O. Vynnychenko, M.D., and Michael Schenker, M.D., and the final compliance classification for these inspections is No Action

Indicated (NAI).

II. BACKGROUND

Pfizer, Inc., as sponsor of BLA 761099, seeks marketing approval for the use of PF-06439535, a proposed biosimilar to Avastin (bevacizumab) for the same indications as the reference product. Similar to Avastin, PF-06439535 is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to and inhibits the biological activity of vascular endothelial growth factor (VEGF). In the U.S., Avastin is indicated for the treatment of metastatic colorectal cancer (mCRC), advanced non-squamous non-small cell lung cancer (NSCLC), recurrent glioblastoma, metastatic renal cell carcinoma (mRCC), cervical cancer, and recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The key clinical study supporting this application is Study B7391003 in patients with non-squamous NSCLC of PF-06439535 and bevacizumab-EU in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced recurrent or metastatic disease to compare the safety and efficacy profile of PF-06439535 to bevacizumab-EU.

The trial initiation date was April 20, 2015 (First Subject First Visit). The primary completion date was May 8, 2017 (25 weeks after the last subject randomized). The trial completion date was December 22, 2017 (Last Subject Last Visit). Study B7391003 was conducted at 216 centers in 28 countries. A total of 714 patients (356 patients in the PF-06439535 group and 358 patients in the bevacizumab-EU group, respectively) completed or discontinued from the study. Patients were randomized (1:1) to receive at least 4 cycles and no more than 6 cycles of either PF-06439535 plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin, followed by the previously assigned blinded bevacizumab monotherapy. Randomization was stratified by region (according to the location of the drug depot supplying the site), sex (male/female), and smoking history (never/ever).

On treatment days when both bevacizumab and paclitaxel-carboplatin were administered, the order of administration was: 1) paclitaxel, 2) carboplatin, and 3) bevacizumab. Bevacizumab monotherapy was administered following completion of at least 4 cycles (21-day cycle) and no more than 6 cycles of chemotherapy. Assigned blinded bevacizumab monotherapy could be administered after chemotherapy had been discontinued until RECIST v1.1 defined disease progression, unacceptable toxicity occurred, discretion of the investigator, regulatory request, death, withdrawal of consent occurred, or End of Treatment, whichever came first.

The primary efficacy endpoint was Objective Response Rate (ORR). ORR was defined as the percent of patients within each treatment group who achieved a Best Overall Response (BOR; including Complete Response [CR] or Partial Response [PR]) by Week 19, in accordance with RECIST v1.1, and subsequently confirmed on a follow-up tumor assessment by Week 25, based on the Sponsor's derived BOR using tumor measurements reported by the investigator in the case report form (CRF).

GCP inspection was conducted at four foreign Clinical Investigator (CI) sites. Although 9 U.S. centers were opened for enrollment, only 11 patients enrolled across these centers. The CI sites were chosen primarily based on high enrollment and significant primary efficacy results.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # # of Subjects	Inspection Dates	Classification
Igor M. Bondarenko, M.D. Site Number: 1325 MI 'City Dnipropetrovsk Multi-field Clin. Hospital #4 of DRC Department of Chemotherapy 31, Blizhniaya Str., Dnipropetrovsk 49102 Ukraine	Study: B7391003 Enrolled: 39	November 26- 29, 2018	NAI
Hryhoriy Adamchuk, M.D. Site Number: 1428 MI 'Kryvyi Rih Oncology Dispensary of Dnipropetrovsk Regional Council Chemotherapy Department 41, Dniprovske shoes Kryvyi Rih 50048 Ukraine	Study: B7391003 Enrolled: 29	December 3-6, 2018	NAI
Ihor O. Vynnychenko, M.D. Site Number: 1327 "RMI " "Sumy Reg. Clin. Oncology Dispensary" Oncothoracic Department Surny State University 31 Pryvokzalna Str, Sumy 40022 Ukraine	Study: B7391003 Enrolled: 25	November 26- 30, 2018	NAI
Michael Schenker, M.D. Site Number: 1045 Centrul de Oncologie Sf. Nectarie Oncologie Str. Caracal nr 23A, parter si demisol, Bloc 17A, Oncologie Craiova 200347 Romania	Study: B7391003 Enrolled: 28	December 10-14, 2018	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Igor M. Bondarenko, M.D. (Site 1325)

The site screened 47 subjects and 39 were randomized. Thirty-one subjects completed the trial and 8 discontinued treatment. There were 2 Serious Adverse Events (SAEs) and one death during the treatment period of the study (Subject (b) (6)). Ten subjects died due to disease progression during long-term follow-up monitoring. An audit of all enrolled subject's records was conducted.

The inspection evaluated all subject's informed consent forms. The inspection reviewed FDA Form 1572's, financial disclosures, protocols, and amendments, Ethics Committee membership, communications, and approval process for protocols, amendments, and reporting requirements. The clinical facilities, and local laboratory facilities as well as the on-site study pharmacy were inspected. Additionally, the inspection included a review of subject records including primary and secondary end points, eligibility criteria, study monitoring, Case Report Forms (CRFs), correspondence, test article accountability, and Adverse Event (AE) reporting to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of SAEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1325 appear reliable based on available information.

2. Hryhoriy Adamchuk, M.D. (Site 1428)

The site screened 38 subjects and 29 were randomized. One Subject withdrew consent after randomization. Three Subjects were lost to follow-up. There were 2 Subjects with SAEs and one Subject death (Subject (b) (6)). Eighteen Subjects had a progression of disease during the study and long-term follow up. An audit of all enrolled subject's records was conducted.

The inspection evaluated all Subject's informed consent forms. The inspection reviewed FDA Form 1572's, financial disclosures, protocols and amendments, Ethics Committee membership, communications, and approval process for protocols, amendments and reporting requirements. The clinical facilities, local laboratory facilities as well as the on-site study pharmacy were inspected. Additionally, the inspection included a review of subject records including primary and secondary end points, eligibility criteria, study monitoring, CRFs, correspondences, test article accountability, and AE reporting to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were two discussion items during the close-out meeting with the Primary Investigator regarding the following inspectional observations:

- a) On May 30, 2017, a query was opened and the initial Overall Response assessment of 'Stable Disease' was changed to 'Partial Response' after re-evaluation of fluid on a CT-

scan dated January 17, 2017 for Subject (b) (6). The eCRF audit trail showed that the final entry was not in agreement with the initial 'Stable Disease' in source notes.

- b) A Note to File showed a telephone conversation on (b) (6) with the radiologist confirming the 'same' presence of the target and non-target lesions as the previous CT scan. This 'same' designation was interpreted as 12-mm similar to the previous value although the specific value was not recorded in the source document. However, the 12-mm value was entered as the target lesion in the pericardium for Subject (b) (6) for the CT scan dated (b) (6). However, there was a lack of source data verification reflecting this specific value. The Sub-Investigator expressed his understanding of this issue, and Dr. Adamchuk promised to conduct re-training for this topic. Subject (b) (6) only completed 2 cycles out of the required minimum 4 cycles due to disease progression. Dr. Adamchuk promised to conduct re-training for this topic.

Although discrepancies were noted as detailed, they were unlikely to have an impact on the efficacy data or patient safety. There were no other objectionable conditions noted, and no Form FDA-483, Inspectional Observations, was issued. The investigator determined that primary efficacy endpoint data were verifiable. There was no evidence of under reporting of SAEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1428 appear reliable based on available information.

3. Ihor O. Vynnychenko. (Site 1327)

The site screened 30 subjects and 25 were enrolled. Twenty-two subjects discontinued due to disease progression, one subject discontinued due to an SAE, one due to an AE, and one withdrew consent. An audit of all enrolled subject's records was conducted.

During the inspection, ethic committee approvals, monitoring reports, correspondence, drug accountability, informed consents, AE reporting, and all subject source documents and data were reviewed. Study source documents and records of the audited subjects were compared to the Sponsor provided data listings and were mostly found to be the same except for several discrepancies.

All source records including medical records were paper based. The data was entered into the Electronic Data Capture system (EDC) by one of the Sub-Investigators. There were several instances where the source data did not match the EDC after changes were either made to the source document and not the eCRF, or the eCRF and not the source document. For example:

- a) **Subject (b) (6) (PF-064395535):** An AE of pleural effusion was deleted from the EDC but was not deleted from the source note. Dr. Vynnychenko stated cytology confirmation would be needed to determine if the pleural effusion was malignant or not. Per the Protocol, for patients having effusions or ascites, cases having cytological proof of malignancy should be considered non-target lesions. Effusions that have not been evaluated using cytology or were found to be non-malignant, should not be considered to be lung cancer lesions.
- b) **Subject (b) (6) (Bevacizumab-EU):** The source documents from the screening

- visit/CT scan on [REDACTED] (b) (6) list five non-target lesions which were assessed, but the line listings and EDC only capture four. One non-target lesion was not entered. Due to deterioration in health, the patient discontinued treatment on [REDACTED] (b) (6) after the first cycle.
- c) **Subject** [REDACTED] (b) (6) **(PF064395535 arm)**: An AE for edema of the legs had an end date of [REDACTED] (b) (6) in the source note, but there was no end date in the EDC. An AE for anemia had an end date of [REDACTED] (b) (6) in the source note, but there was no end date in the EDC. Lastly, a tumor measurement on [REDACTED] (b) (6) was changed in the source from “13” to “15”, but the EDC was not changed to reflect this.
- d) **Subject** [REDACTED] (b) (6) **(Bevacizumab-EU)**: For assessment 1 conducted on [REDACTED] (b) (6) the source document for the LN2 measurement was recorded as “13”, but the EDC showed “15”.
- e) **Subject** [REDACTED] (b) (6) **(PF064395535 arm)**: There were two non-target lesions deleted from the EDC, but not from the source. Dr. Vynnychenko stated the first target lesion (a pleural effusion) was not present during screening and a pulmonary infiltrate (second target lesion) was deleted after an audit by the Sponsor because it was not measurable.

At the conclusion of the inspection, the above discrepancies were discussed with the Primary Investigator who acknowledged the findings and committed to verifying changes moving forward.

Although discrepancies were noted as detailed, they were unlikely to have an impact on the efficacy data or patient safety. During the inspection, the above findings were not considered objectionable conditions, as most appear to be transcription errors and should not materially impact subject outcome; no Form FDA-483, Inspectional Observations was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of SAEs. Other than the inspectional findings described above, the study conduct appears to be in compliance with good clinical practice and the data from Site 1325 appear reliable.

4. Michael Schenker, M.D. (Site 1045)

The site screened 29 subjects and 19 were enrolled. One subject withdrew before start of treatment. Three subjects discontinued treatment due to progressive disease. Fifteen subjects expired due to disease progression. An audit of all enrolled subject's records was conducted.

Documents reviewed during the inspection included ethics committee approvals, FDA 1572s, financial disclosures, training records, monitoring letters, informed consent forms, CRFs, and test article accountability records. All randomized subject records were reviewed in full. Source records, including the primary efficacy endpoint, concomitant medications, adverse events (AEs), serious adverse events (SAEs), randomization, and eligibility criteria were compared against the provided data line listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1045 appear reliable based on available information.

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OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Navid Homayouni
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MEMORANDUM

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

DATE: February 15, 2019

TO: Dale Conner, Pharm.D.
Director
Office of Bioequivalence
Office of Generic Drugs

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

Patricia Keegan, M.D.
Director
Division of Oncology Products 2 (DOP 2)
Office of New Drugs

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

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

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

1. Inspection Summary

OSIS and the Office of Regulatory Affairs inspected the analytical portion of B7391001 and B7391003 (BLA 761099, Bevacizumab), B3281001 (BLA 761103, rituximab), and [REDACTED] (b) (4) [REDACTED] (b) (4) conducted at [REDACTED] (b) (4)

We 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 data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

B7391001 (BLA 761099)

"Phase 1, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06439535 and Bevacizumab Sourced from US and EU Administered to Healthy Male Volunteers

Sample Analysis Period:

PK: (b) (4)
ADA: (b) (4)
NAB: (b) (4)

B7391003 (BLA 761099)

"A Phase 3, Randomized, Double-Blind Study of PF-06439535 Plus Paclitaxel-Carboplatin and Bevacizumab Plus Paclitaxel Carboplatin for the First-Line Treatment of Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer"

Sample Analysis Period:

PK: 05/05/2015 - 06/14/2017
ADA: 02/12/2016 - 06/14/2017
NAB: 06/20/2017 - 06/22/2017

Non-Responsive

3. Scope of Inspection

ORA investigator Joseph Despins, Ph.D. and OSIS scientist Amanda Lewin, Ph.D. audited the analytical portion of the above studies at [REDACTED] (b) (4) from [REDACTED] (b) (4).

The Previous FDA inspection of [REDACTED] (b) (4) was conducted from [REDACTED] (b) (4). The inspection of [REDACTED] (b) (4) was classified NAI and corrective actions from the previous FDA inspection were not necessary.

The current inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff and follow up on specific concerns from OND and OGD.

4. Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue Form FDA 483 to [REDACTED] (b) (4).

4.1 Specific concerns from OND/OGD

BLA 761099 (Bevacizumab)

Pharmacokinetic Assay:

[REDACTED] (b) (4)

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(b) (4)

Non-Responsive

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Non-Responsive

5. Conclusion

After review of the inspectional findings, I conclude that data from the audited studies are reliable. Studies using similar methods conducted between the previous inspection ([REDACTED] (b) (4) [REDACTED] (b) (4)) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI-

[REDACTED] (b) (4)

FEI#: [REDACTED] (b) (4)

cc: OTS/OSIS/Kassim/Choe/Kadavil/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
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Draft: AL 02/07/2019

Edit: GB 2/8/2019, 2/14/2019, 2/15/2018; AD 2/14/2019, 2/15/2019

ECMS:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

FACTS:

[REDACTED] (b) (4)

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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: December 31, 2018
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: BLA 761099
Product Name and Strength: Zirabev (bevacizumab-xxxx^a) Injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Applicant/Sponsor Name: Pfizer, Inc.
FDA Received Date: December 14, 2018
OSE RCM #: 2018-258-1
DMEPA Safety Evaluator: Colleen Little, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Zirabev (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

We note the container labels and carton labeling were revised to replace the placeholder "Tradename" with the conditionally acceptable proprietary name, Zirabev.^c

2 CONCLUSION

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

^a FDA has not yet designated a nonproprietary name for Pfizer's proposed biologic product that includes a distinguishing suffix (see Guidance on Nonproprietary Naming of Biological Products). Pfizer is using "-xxxx" as a placeholder and is not intended to be included in the final labels and labeling.

^b Little C. Label and Labeling Review for Bevacizumab-xxxx (BLA 761099). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 04. RCM No.: 2018-258.

^c Little, C. Proprietary Name Review for Zirabev (BLA 761099). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 10. Panorama No.: 2018-26371062.

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/s/

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LABEL AND LABELING REVIEW

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

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

Date of This Review:	December 4, 2018
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	BLA 761099
Product Name and Strength:	Bevacizumab-xxxx ^a Injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer, Inc.
FDA Received Date:	June 29, 2018 and October 2, 2018
OSE RCM #:	2018-258
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

^a FDA has not yet designated a nonproprietary name for Pfizer's proposed biologic product that includes a distinguishing suffix (see Guidance on Nonproprietary Naming of Biological Products). Pfizer is using "-xxxx" as a placeholder and is not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

As part of the 351(k) resubmission for BLA 761099, this review evaluates the proposed Bevacizumab-xxxx prescribing information (PI), container labels, and carton labeling to identify 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
Human Factors Study	C-N/A
ISMP Newsletters	D
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 postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of materials found that the proposed Bevacizumab-xxxx container labels, carton labeling and PI may be improved to promote safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

We conclude the container labels, carton labeling, and PI for Bevacizumab-xxxx may be improved to promote safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section

- a. Please see Appendix H for our PI recommendations in track changes.

4.2 RECOMMENDATIONS FOR PFIZER, INC.

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

A. General Comments (Container Labels & Carton Labeling)

1. Consider removing the following statements: [REDACTED] (b) (4)
[REDACTED] See the recommendation below to revise the route of administration statement to “For intravenous infusion after dilution.” We recommend this revision due to post-marketing reports that negative statements (e.g. do not) may have the opposite of the intended meaning because the word “not” can be overlooked and the warning may be misinterpreted as an affirmative action.^b Also, we recommend this to minimize the use of error prone abbreviations.
2. Revise the route of administration statement from “[REDACTED] (b) (4)” to read as follows: “For Intravenous Infusion After Dilution”.
3. Relocate the “Discard Unused Portion” statement to appear underneath the package type term statement “One Single-Dose Vial”.
4. Revise the storage statement to read as follows for clarity and consistency: **“Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.”** Ensure the storage statements on container labels, carton labeling, and in PI are consistent.
 - a. Revise the storage information to ensure the all storage information is presented in the same manner (e.g., bold and same font style and color). We recommend this to increase the prominence of this important information and to minimize the risk of a portion of the storage information being overlooked.
5. To improve readability of more important information, consider relocating the statement “No Preservative.” to the side panel of the labeling and revise to appear in mixed case letters as follows: “No Preservative.”
6. Consider revising the product code in the NDC number to ensure that the middle 3 or 4 digits are non-sequential [REDACTED] (b) (4). The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the product code is not a differentiating feature. If for some reason, the middle digits cannot be revised, consider increasing the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example, XXXX-**XXXX**-XX.^c
7. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable

^b Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

8. Ensure the lot number and expiration date are clearly differentiated from one another and are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.^{d,e}

B. Container Labels

1. For the 400 mg/16 mL vial and if space permits for the 100 mg/4 mL vial, consider adding the dosage form “Injection” to appear below the proper name as follows:

Tradename
(bevacizumab-xxxx)
Injection
400 mg/16 mL
25 mg/mL

Please note the example above demonstrates our recommendations only (not to size, spacing, color, etc.)

C. Carton Labeling

1. Consider adding the dosage form “Injection” to appear below the proper name as follows:

Tradename
(bevacizumab-xxxx)
Injection
400 mg/16 mL
25 mg/mL

Please note the example above demonstrates our recommendations only (not to size, spacing, color, etc.)

5 APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

^d Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

^e Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

Table 2 presents relevant product information for Bevacizumab-xxxx received on October 2, 2018 from Pfizer, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Bevacizumab-xxxx and the Listed Drug		
Product Name	Bevacizumab-xxxx	Avastin^f
Initial Approval Date	N/A	February 26, 2014
Active Ingredient	bevacizumab-xxxx	bevacizumab
Indication	Metastatic Colorectal Cancer (mCRC) First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC) Recurrent Glioblastoma (GBM) Metastatic Renal Cell Carcinoma (mRCC) Persistent, Recurrent, or Metastatic Cervical Cancer	Metastatic Colorectal Cancer (mCRC) First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC) Recurrent Glioblastoma (GBM) Metastatic Renal Cell Carcinoma (mRCC) Persistent, Recurrent, or Metastatic Cervical Cancer Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)	100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL)
Dose and Frequency	<u>Metastatic Colorectal Cancer (mCRC)</u> 5mg/kg every 2 weeks intravenously in combination with bolus-IFL 10 mg/kg every 2 weeks intravenously in combination with FOLFOX4 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line bevacizumab product-containing regimen	<u>Metastatic Colorectal Cancer (mCRC)</u> 5mg/kg every 2 weeks intravenously in combination with bolus-IFL 10 mg/kg every 2 weeks intravenously in combination with FOLFOX4 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line Avastin-containing regimen

^f Avastin [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 JUN 13. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf.

	<p><u>First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC)</u></p> <p>15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel</p> <p><u>Recurrent Glioblastoma (GBM)</u></p> <p>10 mg/kg intravenously every 2 weeks</p> <p><u>Metastatic Renal Cell Carcinoma (mRCC)</u></p> <p>10 mg/kg intravenously every 2 weeks in combination with interferon alfa</p> <p><u>Persistent, Recurrent, or Metastatic Cervical Cancer</u></p> <p>15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan</p>	<p><u>First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC)</u></p> <p>15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel</p> <p><u>Recurrent Glioblastoma (GBM)</u></p> <p>10 mg/kg intravenously every 2 weeks</p> <p><u>Metastatic Renal Cell Carcinoma (mRCC)</u></p> <p>10 mg/kg intravenously every 2 weeks in combination with interferon alfa</p> <p><u>Persistent, Recurrent, or Metastatic Cervical Cancer</u></p> <p>15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan</p> <p><u>Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer</u></p> <p>15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles or until disease progression, whichever occurs earlier</p> <p>10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week)</p> <p>15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks)</p>
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		<p>15 mg/kg intravenously every 3 weeks, in combination with carboplatin and paclitaxel for 6 to 8 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression</p> <p>15 mg/kg intravenously every 3 weeks, in combination with carboplatin and gemcitabine for 6 to 10 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression</p>
How Supplied	<p>Supplied in a carton containing 1 single-dose vial in the following strengths:</p> <p>100 mg/4 mL and 400 mg/16 mL</p>	<p>100 mg/4 mL and 400 mg/16 mL</p> <p>Each carton contains one vial.</p>
Storage	<p>Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light.</p>	<p>Store refrigerated at 2–8°C (36–46°F) in the original carton until time of use to protect from light.</p>
Container Closure	<p>Single-dose vial</p>	<p>Single-dose vial</p>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 8, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, bevacizumab, Avastin, Mvasi. Our search identified 3 previous reviews^{g,h,i}, and we confirmed that our previous recommendations were implemented.

^g Gao, T. Label and Labeling Review for Avastin (BLA 125085). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 08. RCM No.: 2017-2107.

^h Stewart, J. Label and Labeling Review for Mvasi (BLA 761028). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 22. RCM No.: 2016-2212.

ⁱ Mathew, D. Label and Labeling Review for Avastin (BLA 125085). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 2. RCM No.: 2014-1800.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On November 8, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Any of the Words: Avastin bevacizumab

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Bevacizumab-xxxx.

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,^j along with postmarket medication error data, we reviewed the following Bevacizumab-xxxx labels and labeling submitted by Pfizer, Inc..

- Container label received on June 29, 2018
- Carton labeling received on June 29, 2018
- Prescribing Information (Image not shown) received on October 2, 2018

G.2 Label and Labeling Images

Container Labels



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

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/

COLLEEN L LITTLE
12/04/2018

SEVAN H KOLEJIAN
12/04/2018