CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761381Orig1s000
761429Orig1s000

OTHER REVIEW(S)

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:	December 19, 2024
To:	Gina Davis, MT Senior Regulatory Health Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Andrew Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Numbers:	BLA 761381 and BLA 761429
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On February 29, 2024, and March 29, 2024, Bristol-Myers Squibb Company submitted for the Agency's review original Biologics License Application (BLA) 761381 and BLA 761429, respectively, for OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) injection. With these submissions, the Applicant is proposing the following indications:

Under BLA 761381:

Advanced Renal Cell Carcinoma

- (b) (4) for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC) following treatment with (b) (4) and ipilimumab combination therapy.
- in combination with cabozantinib, for the first-line treatment of adult patients with advanced RCC.
- (b) (4) for the treatment of adult patients with advanced RCC who have received prior anti-angiogenic therapy.

Adjuvant Treatment of Melanoma

- for the adjuvant treatment of adult patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

Unresectable or Metastatic Melanoma

- (b) (4) for the treatment of adult patients with unresectable or metastatic melanoma.
- (b) (4) for the treatment of adult patients with unresectable or metastatic melanoma following treatment with (b) (4) and ipilimumab combination therapy.

Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

- in combination with platinum-doublet chemotherapy, for neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

Metastatic Non-Small Cell Lung Cancer

- for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

Squamous Cell Carcinoma of the Head and Neck

- for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

Urothelial Carcinoma

- for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
- for the treatment of adult patients with locally advanced or metastatic UC who:
  - have disease progression during or following platinum-containing chemotherapy.
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

- (b) (4), for the treatment of adult patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) following combination treatment with (b) (4) and ipilimumab.
- (b) (4) for the treatment of adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Hepatocellular Carcinoma

- (b) (4) is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib and following treatment with (b) (4) and ipilimumab combination therapy.

Esophageal Cancer

- for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).
- in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- for the treatment of adult patients with unresectable advanced, recurrent, or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Under BLA 761429:

Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

- in combination with platinum-doublet chemotherapy, for the neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) NSCLC, followed by OPDIVO QVANTIG as (b) (4) in the adjuvant setting after surgical resection.

Urothelial Carcinoma

- in combination with cisplatin and gemcitabine, for the first-line treatment of adult patients with unresectable or metastatic UC.

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 Oncology III (DO3) on April 12, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) injection.

2 MATERIAL REVIEWED

- Draft OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) injection MG received on February 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on December 10, 2024, and OPDP on December 2, 2024.
- Draft for OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) injection Prescribing Information (PI) received on February 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on December 10, 2024, and OPDP on December 2, 2024.
- Approved OPDIVO (nivolumab) injection comparator labeling dated October 3, 2024.

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 APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

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ANDREW D NGUYEN
12/19/2024 12:41:28 PM

RUTH I MAYROSH
12/19/2024 02:10:56 PM

LASHAWN M GRIFFITHS
12/19/2024 02:48:01 PM

M E M O R A N D U M

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

DATE: December 19, 2024

TO: Steven Lemery, M.D.
Director
Division of Oncology III (DOIII)
Office of Oncologic Diseases (OOD)
Office of New Drug (OND)

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspection of Centro Privado de RMI Rio Cuarto SA, Cordoba, Argentina.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of the PK assessment of study CA20967T (BLA 761381) conducted at Centro Privado de RMI Rio Cuarto SA, Cordoba, Argentina.

Form FDA 483 was not issued at the inspection close-out. However, there were two items discussed with the site management regarding discrepancy between source and submitted study records for 8 subjects, and poor record keeping practices. Based on the inspection findings, there are identified concerns for Centro Privado de RMI Rio Cuarto SA, Cordoba, Argentina regarding the reliability of data from subject (b) (6) and adverse event reporting for subject (b) (6) participated in the study CA20967T for the review division consideration.

Please note the OSIS review of clinical inspection of study CA20967T (BLA 761381) conducted at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zunbirán, Mexico City, Mexico was finalized on 10/28/2024.

2. Inspected Study:

BLA 761381

Study Number: CA20967T
Study Title: "A Phase 3, Open label, Randomized, Noninferiority Trial of Subcutaneous Formulation of Nivolumab Versus Intravenous Nivolumab in Participants with Advanced or Metastatic Clear Cell Renal Cell Carcinoma Who Have Received Prior Systemic Therapy"
Dates of study conduct: 05/24/2021 – 07/24/2023

Clinical site: Centro Privado de RMI Rio Cuarto SA, Sarmiento 1200, Rio Cuarto, Cordoba, Argentina

3. Inspectional Findings

Centro Privado de RMI Rio Cuarto SA, Sarmiento 1200, Rio Cuarto, Cordoba, Argentina

OII investigator Dina A Tallman inspected Centro Privado de RMI Rio Cuarto SA, Sarmiento 1200, Rio Cuarto, Cordoba, Argentina from October 28-November 1, 2024.

3.1 Previous Inspection(s)

This was the first OSIS inspection of Centro Privado de RMI Rio Cuarto SA (hereafter CPR), and the first inspection of the clinical investigator Dr. Ignacio Magri under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs)
-Informed consent process
-Protocol deviations
-Institutional review board approvals
-Test article accountability and storage
-Randomization
-Adverse events

3.3 Inspection finding(s)

At the conclusion of the inspection, investigator Dina A Tallman did not issue Form FDA 483 to the CPR. However, there were three

Reference ID: 5499314

items discussed verbally during inspection closing. The discussion item (DI) and my evaluation of the DI were provided below:

3.3.1. Discussion Item

Discussion item 1: Discrepancies found between the source and eCRF for 8 subjects

OSIS Evaluation:
Subject (b) (6): The source records (from ARM B, Cycle 15 Day 1 Visit) of the subject (b) (6) indicates that on (b) (6), the subject had a headache, an adverse event Grade 1, reportedly unrelated to the drug (page 26 of **Attachment 01**). This AE was not recorded in eCRF for the same visit day (see page 264 of 2567 in Subject (b) (6) eCRF). Per study protocol BMS 986298 (version 02, page 87) "*All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study*". Thus, this discussion item points to a protocol deviation.

Additionally, this subject's International Metastatic RCC Database Consortium (IMDC) score was listed as "2 Intermediate" in the source document (page 25 of **Attachment 01**), thus placing the subject in the IMDC risk group of "intermediate" in the IRT (Interactive Response Technology) program, yprime (page 27 of **Attachment 01**). This IMDC score was reported as "3 Poor" in eCRF (see page 30 of 2567 in Subject (b) (6) eCRF).

Furthermore, please also note that, based on the source records, this subject underwent humeral replacement surgery on (b) (6) (b) (6) (see page 32 of **Attachment 01**), and received the first investigational drug treatment on (b) (6), thus meeting exclusion criteria 2 Prior/Concomitant Therapy section "g" "*Major surgery (e.g., nephrectomy, hip, or spine surgery) less than 28 days prior to the first dose of study drug. Minor surgery (e.g., biopsy or chest tube placement) less than 14 days prior to the first dose of study drug.* This was reported as protocol deviation under "Inclusion/Exclusion" category.

Because the subject met exclusion criteria 2, I recommend review division to exclude the subject (b) (6) from the review of the study data.

Subject (b) (6)*:* Blood samples from this subject were collected for clinical diagnostics test during an unscheduled visit on (b) (6) (see page 1 of **Attachment 02**). Bases on the

Reference ID: 5499314

clinical diagnostic lab results, the subject had elevated transaminases, and this was recorded as AE, NCI CTC AE (National Cancer Institute Common Terminology Criteria for Adverse Events) grade "2" (see page 3 and 6 of **Attachment 02**). However, the same AE was reported as grade 1 in eCRF for the same subject. I recommend review division to consider the CTC AE grade of "2" when reviewing the adverse event data from subject (b) (6) during an unscheduled visit on (b) (6).

Subjects (b) (6): per EIR, the IMDC score for these subjects differed between source documents and the reported eCRFs. Because OII investigator did not collect source documents as exhibits for these subjects, I am not able to make a determination for the reliability of reported IMDC scores for the (b) (6) (b) (6).

Discussion item 2: AEs/SAEs are not fully captured on the AE/SAE log, but instead documented in the progress notes that were taken during screening and site visits and handwritten in Spanish. The interpreter had difficulty reading the handwriting for translation during inspection.

OSIS Evaluation: Per study protocol, the required method for SAE data reporting is through the eCRF (see page 138, under Appendix 3, Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting). During the inspection, OII did not collect additional or specific source documents demonstrating AE/SAEs were not fully captured on the AE/SAE log when they were documented in the progress notes. In addition, there is no evidence to indicate that AE/SAEs are not reported in eCRF. Therefore, this discussion item has no impact on data or subject safety.

Attachments:

Attachment 01: Ex 9-Subject (b) (6) Screening notes
Attachment 02: Ex 10-Subject Source documents

Hasan A. Irier, Ph.D.
Pharmacologist

Reference ID: 5499314

Draft: HAI 12/6/2024, 12/18/2024
Edit: MO 12/17/2024; JC 12/17/2022, 12/18/2024

OSIS File #: BE 10229

eNSpect/AMS Assignment ID: 243787
eNSpect OpID: 286382

Reference ID: 5499314

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/s/

HASAN A IRIER
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12/19/2024 09:45:51 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	December 18, 2024
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761381 and BLA 761429
Product Name, Dosage Form, and Strength:	Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) Injection, 600 mg nivolumab and 10,000 units hyaluronidase/5 mL (120 mg nivolumab and 2,000 units hyaluronidase/mL)
Applicant Name:	Bristol-Myers Squibb Company
FDA Received Date:	December 17, 2024
TTT ID #:	2024-8596-2; 2024-8941-2
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Tingting Gao, PharmD

Reference ID: 5499071

1 PURPOSE OF MEMORANDUM

Bristol-Myers Squibb Company submitted revised container labels and carton labeling received on December 17, 2024 for Opdivo Qvantig. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Opdivo Qvantig (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Bristol-Myers Squibb Company implemented all of our recommendations[b] and we have no additional recommendations at this time.

[a] Mahmoud, S. Label and Labeling Review Memo for Opdivo Qvantig (BLA 761381 and BLA 761429). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 Dec 04. TTT ID: 2024-8596-1 and 2024-8941-1.

[b] Response to FDA Labeling Request Dated 11-Dec-2024. Princeton (NJ): Bristol Myers Squibb. 2024 DEC 17. Available from: \\CDSESUB1\EVSPROD\bla761381\0029\m1\us\2024-12-11-bms986298-response-us-nivolumab-labeling-q1-q5.pdf.

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/s/

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12/18/2024 04:28:41 PM

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12/18/2024 04:30:01 PM

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

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

Memorandum

Date: December 16, 2024

To: Gina Davis, MT, Regulatory Project Manager
Division of Oncology 3 (DO3)

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

CC: Emily Dvorsky, PharmD, Team Leader, OPDP

Doris Auth, PharmD, Associate Director for Labeling, DO3

Subject: OPDP Labeling Comments for OPDIVO QVANTIG™ (nivolumab and hyaluronidase-nvhy) injection, for subcutaneous use

BLA: 761381 and 761429

Background:
In response to DO3's consult requests dated April 12, 2024 (BLA 761381) and May 30, 2024 (BLA 761429), OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), and carton and container labeling for the original applications for OPDIVO QVANTIG™ (nivolumab and hyaluronidase-nvhy) injection, for subcutaneous use.

PI/MG:
OPDP's review of the proposed PI is based on the draft labeling sent by electronic mail to OPDP on December 2, 2024 (accessed via SharePoint on December 3, 2024), and our comments are provided below.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room via BLA 761381 on February 29, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Andrew Nguyen at 240-402-0512 or andrew.nguyen@fda.hhs.gov.

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/s/

ANDREW D NGUYEN
12/16/2024 11:13:57 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	December 4, 2024
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761381 and BLA 761429
Product Name, Dosage Form, and Strength:	Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) injection, 600 mg nivolumab and 10,000 units hyaluronidase/5 mL (120 mg nivolumab and 2,000 units hyaluronidase/mL)
Applicant Name:	Bristol-Myers Squibb Company
FDA Received Date:	November 27, 2024
TTT ID #:	2024-8596-1; 2024-8941-1
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Tingting Gao, PharmD

Reference ID: 5490062

1 PURPOSE OF MEMORANDUM

Bristol-Myers Squibb Company submitted revised container labels and carton labeling received on November 27, 2024 for Opdivo Qvantig. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Opdivo Qvantig (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The container labels and carton labeling are unacceptable from a medication error perspective. Critical information on the principal display panel is not displayed clearly.

3 RECOMMENDATIONS FOR BRISTOL-MYERS SQUIBB COMPANY

A. General Comments (Container Label(s), Carton Labeling, and Syringe Labels)

1. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
2. As currently presented, there is insufficient contrast between the (b) (4) font color and the orange background used to highlight the strength statement, which may make the text difficult to read. We recommend you revise the colors to improve the contrast between the font and the background colors to improve readability and legibility of the strength statement.
3. We recommend increasing the font size of the total quantity per total volume (e.g., "600 mg and 10,000 units/5 mL") to ensure this important information is prominently displayed, and unbolding the concentration per mL "e.g., (120 mg and 2,000 units/mL)" to bring prominence to the total quantity per total volume in accordance with USP General Chapter <7>.

B. Carton labeling

1. We recommend adding sufficient space between the "Discard unused portion." statement and the (b) (4) to improve readability.

[a] Mahmoud, S. Label and Labeling Review for Opdivo Qvantig (BLA 761381 and BLA 761429). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 AUG 07. TTT ID: 2024-8596 and 2024-8941.

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M E M O R A N D U M

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

DATE: October 25, 2024

TO: Steven Lemery, M.D.
Director
Division of Oncology III (DOIII)
Office of Oncologic Diseases (OOD)
Office of New Drug (OND)

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspection of Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zunbirán, Mexico City, Mexico

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of the PK assessment of study CA20967T (BLA 761381) conducted at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zunbirán, Mexico City, Mexico.

Form FDA 483 was not issued at the inspection close-out. One discussion item regarding a protocol deviation was verbally provided to the site management. Based on the inspection findings, there are no identified concerns for Instituto Nacional de Ciencias Médicas y Nutrición regarding reliability of PK data for inspected study CA20967T for the review division consideration.

Please note that there is another pending inspection of a clinical site, Centro Privado de RMI Rio Cuarto SA, Cordoba, Argentina, that participated in the study CA20967T. OSIS will provide a review once the inspection of that site is completed and EIR is received.

2. Inspected Studies:

BLA 761381

Study Number: CA20967T
Study Title: "A Phase 3, Open label, Randomized, Noninferiority Trial of Subcutaneous Formulation of Nivolumab Versus Intravenous Nivolumab in Participants with Advanced or Metastatic Clear Cell Renal Cell Carcinoma Who Have Received Prior Systemic Therapy"
Dates of study conduct: 05/24/2021 – 07/24/2023

Clinical site:
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zunbirán, Avenida Vasco de Quiroga, No. 15 Col Belisario Dominguez, Section 16, Alcaldía Tlalpan, Mexico City, Mexico

3. Inspectional Findings

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zunbirán, Mexico City, Mexico

OII investigator Roberto A Dookhan inspected Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zunbirán, Avenida Vasco de Quiroga, No. 15 Col Belisario Dominguez, Section 16, Alcaldía Tlalpan, Mexico City, Mexico from September 02-10, 2024.

3.1 Previous Inspection(s)

This was the first OSIS inspection of Instituto Nacional de Ciencias Médicas y Nutrición under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs)
-Informed consent process
-Protocol deviations
-Institutional review board approvals
-Test article accountability and storage
-Randomization
-Adverse events

3.3 Inspection finding(s)

Reference ID: 5469136

At the conclusion of the inspection, investigator Roberto A Dookhan did not issue Form FDA 483 to the clinical site. However, there was one item discussed verbally during inspection closing. The discussion item (DI) and my evaluation of the DI were provided below:

3.3.1. Discussion Item

Discussion item 1: Subject (b) (6) had a protocol deviation listed where the subject was treated with IV nivolumab 24 hours after receiving radiation therapy rather than wait the one week as required by the protocol, section 7.7.3, "Treatment of Nivolumab-related Infusion/Injection Reactions (IV or SC Nivolumab).

OSIS Evaluation: Per study protocol CA20967T, section 7.7.1 Prohibited and/or Restricted Treatments states that "Any non-palliative radiation therapy: In participants undergoing palliative radiotherapy, nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation". The source documents for subject (b) (6) indicate that the subject received palliative radiotherapy on (b) (6) (**Attachment 01, page 1**), and received IV nivolumab on (b) (6) (**Attachment 01, page 9 and 11**), thus this discussion item indicates a protocol deviation.

However, please note that date of this protocol deviation does not coincide with any of the PK sample collection date/time for the subject (b) (6). Therefore, this discussion item is unlikely to have impacted the PK data for the subject (b) (6).

Attachment(s)
Attachment-01-Subject (b) (6) Deviation Visit-Source document

Hasan A. Irier, Ph.D.
Pharmacologist

Draft: HAI 10/21/2024, 10/24/2024
Edit: MO 10/22/2024; JC 10/22/2022, 10/23/2024, 10/25/2024

OSIS File #: BE 10229

eNSpect/AMS Assignment ID: 243787
eNSpect OpID: 285405

Reference ID: 5469136

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/s/

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10/28/2024 07:15:38 AM

Clinical Inspection Summary

Date	10/17/2024
From	Courtney McGuire, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Michael Fusco, Medical Officer Jamie Brewer, MD, Clinical Team Leader Gina Davis, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	BLAs 761381 and 761429
Applicant	Bristol-Myers Squibb Company
Drug	Nivolumab and hyaluronidase
NME (Yes/No)	Yes
Therapeutic Classification	PD-1 blocking antibody / endoglycosidase
Proposed Indication	Treatment of advanced renal cell carcinoma, adjuvant treatment of melanoma, unresectable or metastatic melanoma, neoadjuvant treatment of resectable non-small cell lung cancer, metastatic non-small cell lung cancer, squamous cell carcinoma of the head and neck urothelial carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, hepatocellular carcinoma, esophageal cancer, gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma
Consultation Request Date	5/10/2024
Summary Goal Date	11/14/2024
Action Goal Date	12/29/2024
PDUFA Date	2/29/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMEBLATIONS

The Applicant, Bristol Myers Squibb (BMS), submitted clinical data from Study CA20967T (NCT04810078) to the Agency in support of Biologics License Applications (BLAs) 761381 and 761429 for subcutaneous nivolumab and hyaluronidase (nivo SC). The proposed indications are for the treatment of adult patients with

- Advanced renal cell carcinoma
- Adjuvant treatment of melanoma

- Unresectable or metastatic melanoma
- Neoadjuvant treatment of resectable non-small cell lung cancer
- Metastatic non-small cell lung cancer
- Squamous cell carcinoma of the head and neck
- Urothelial carcinoma
- Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer
- Hepatocellular carcinoma
- Esophageal cancer
- Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma

One foreign clinical investigator (CI), Dr. Maria Teresa Bourlon de los Rios, and the imaging contract research organization (CRO), (b) (4) were inspected.

Inspection of the imaging CRO, (b) (4) revealed no significant discrepancies or regulatory violations or Good Clinical Practice (GCP) noncompliance. The inspection for Dr. Bourlon de Los Rios did not find significant concerns regarding the study conduct and management of the clinical trial, GCP, or regulatory compliance. Based on the results of these inspections, data generated by Dr. Bourlon and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indications.

II. BACKGROUND

On February 29, 2024, and March 29, 2024, BMS submitted BLAs 761381 and 761429, respectively, seeking approval of nivo SC for the following adult indications:

- Advanced renal cell carcinoma
- Adjuvant treatment of melanoma
- Unresectable or metastatic melanoma
- Metastatic non-small cell lung cancer
- Urothelial carcinoma
- Neoadjuvant treatment of resectable non-small cell lung cancer
- Squamous cell carcinoma of the head and neck
- Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer
- Hepatocellular carcinoma
- Esophageal cancer
- Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma

The primary evidence of safety and efficacy for nivo SC for the proposed indications under both BLAs 761381 and 761429 and the focus of the BIMO inspections was a single phase 3 trial, Study CA20967T.

Study Design

Study CA20967T was a phase 3, multicenter, global, open-label, randomized, noninferiority study of nivo SC vs nivolumab intravenous (nivo IV) in subjects with previously treated advanced or metastatic clear cell renal cell carcinoma (ccRCC) who had evidence of progression after having received no more than 2 prior systemic treatment regimens. Following a 28-day screening period, subjects were randomized 1:1 into the following two treatment arms:

- Arm A: nivo SC, 1200 mg coformulated with rHuPH20 20,000 units every 4 weeks ± 3 days.
- Arm B: nivo IV, 3 mg/kg every 2 weeks ± 3 days.

Randomization was stratified by weight (< 80 kg vs ≥ 80 kg) and International Metastatic Renal Cell Carcinoma Database Consortium risk classification (favorable vs intermediate vs poor risk). Study drug dosing continued until disease progression as assessed by investigator, unacceptable toxicity, withdrawal of consent, completion of 2 years (104 weeks) of treatment, death, study termination by the Sponsor, or the end of study, whichever occurred first.

Pharmacokinetic (PK) endpoints

- Co-primary endpoints:
  - Cavgd28, time-averaged serum nivo concentration over the first 28 days of treatment.
  - Cminss, trough serum nivo concentration at steady state.

Clinical Endpoints (<u>focus of OSI inspection</u>**)**

- Key secondary efficacy endpoints:
  - Objective response rate (ORR)
  - Best overall response (BOR)

- Other secondary endpoints:
  - Disease Control Rate (DCR)
  - Duration of response (DOR)
  - Time to response (TTR)
  - Progression free survival (PFS)
  - Overall survival (OS)

All imaging endpoints were assessed by blinded independent central review (BICR) per RECIST v1.1.

Study Status

The study enrolled the following subjects at 73 sites across 17 countries across Australia, Asia, Europe, South America, and North America, including 8 subjects enrolled at 1 site in US.

- Safety population: N= 492
- Efficacy population: N= 495

Dr. Bourlon (Site 89) and the imaging CRO ((b) (4) were inspected.

RESULTS

1. **Dr. Maria Teresa Bourlon de los Rios (Site 89 / CA20967T)**
   Avenida Vasco de Quiroga No 15
   Texcoco, Pueblo Nextlalpan, Mexico, 14080

Inspection Dates: September 2, 2024, to September 10, 2024

This investigator was inspected as a routine PDUFA inspection for Study CA20967T. This was the first FDA inspection for this investigator.

As of the data cutoff (July 24, 2023), the site screened 38 subjects, and 33 subjects were enrolled and received treatment. Twenty-four subjects discontinued treatment because of disease progression, and 2 subjects discontinued treatment due to an adverse event (AE).

The inspection reviewed informed consent forms (ICFs) for all 38 screened subjects and the following additional subject-related source documents for 15 enrolled subjects (7 Arm A, 8 Arm B): progress notes, visit day reports, demographics, lab reports, imaging reads, and medical history records. The inspection also reviewed these source documents, as applicable, to verify inclusion / exclusion criteria for all 33 randomized subjects.

The inspection reviewed the following study-related documents: protocol and amendments, ICFs, curriculum vitae, Investigator's GCP Agreement for Non-US Sites, financial disclosures, ethics committee and research committee approvals / acknowledgments, correspondence, investigational product accountability records, site training records, Delegation of Authority log, screening and enrollment log, Notes to Files, Pharmacy binders (including temperature logs), site initiation visit and visit log, AE reporting, and monitoring documents.

For the key secondary imaging endpoints, the inspection verified that radiographic scans and investigator's assessments were performed at specified time points and submitted to the central imaging CRO. The secondary endpoint, OS, was verified by comparison of the subject source data against the provided data line listings for subject survival status and cause of death.

There was no apparent evidence of underreporting of AEs and protocol deviations. There was no evidence of incomplete/and or inaccurate records or evidence of data fabrication.

Based on the results of the inspection, Study CA20967T data generated at Dr. Bourlon's site appear acceptable in support of the proposed indications in the BLAs.

2. (b) (4) **(Study CA20967T)**

(b) (4)

Inspection dates: (b) (4)

(b) (4) was inspected as a routine PDUFA inspection for Study CA20967T. The firm was previously inspected in April 2024, and there were no regulatory or GCP deviations observed.

This inspection reviewed (b) (4) responsibilities to perform a BICR for Study CA20967T, which included collection, medical assessment, and project management of imaging data. Records reviewed included written procedures, firm history, quality assurance activities, training, reader qualifications, financial conflicts of interest, outsourced services, contacts / agreements with sponsors/CROs, communication plans, record retention, electronic systems and validations, and blinding activities. (b) (4) data collection and handling procedures, data transfer, adherence to the protocol and Independent Review Charter, and adjudication procedures were also reviewed and found to be adequate.

The inspection verified the key secondary efficacy endpoint, ORR, for 132 efficacy responders by comparison of tumor dimensional measurements and tumor response / progression source records with data line listings at baseline and key secondary endpoint time points, inclusive of the 4-week objective response confirmation. There were no discrepancies identified. Table 1 lists the subjects whose tumor measurements were verified:

Table 1. Unique Subject IDs for Verified Measurements

(b) (6)

Based on the results of the inspection, the imaging review data generated by (b) (4) appear acceptable in support of the proposed indications in the BLAs.

{See appended electronic signature page}

Courtney McGuire, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
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CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
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cc:
Review Division/Division Director acting/ Steven Lemery

Review Division/Project Manager/ Gina Davis
Review Division/Clinical Team Lead/ Jamie Brewer
Review Division/Clinical Reviewer/ Michael Fusco
OSI/Office Director / David Burrow
OSI/GCP Program Analysts/ Yolanda Patague

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/

COURTNEY S MCGUIRE
10/17/2024 07:08:55 AM

MICHELE B FEDOWITZ
10/17/2024 08:37:23 AM

JENN W SELLERS
10/17/2024 09:46:23 AM

M E M O R A N D U M

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

DATE: 9/3/2024

TO: Division of Oncology III (DO III)
Office of Oncologic Diseases (OOD)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761381

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

(b) (4)**:** OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4). The RRA was conducted under the following submission: NDA NON-RESPONSIVE. OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/

FELECIA P HAGOOD
09/16/2024 02:30:16 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	August 7, 2024
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761381 and BLA 761429
Product Name, Dosage Form, and Strength:	Opdivo Qvantig (nivolumab and hyaluronidase-xxxx)[a] injection, 600 mg nivolumab and 10,000 units hyaluronidase/5 mL (120 mg nivolumab and 2,000 units hyaluronidase/mL)
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Bristol-Myers Squibb Company
FDA Received Date:	February 29, 2024 and March 29, 2024
TTT ID #:	2024-8596 and 2024-8941
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Acting Team Leader:	Tingting Gao, PharmD

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder nivolumab and hyaluronidase-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

Reference ID: 5426027

1 INTRODUCTION

As part of the approval process for Opdivo Qvantig (nivolumab and hyaluronidase-xxxx) injection, the Division of Oncology 3 (DO3) requested that we review the proposed Opdivo Qvantig Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761381 and BLA 761429.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

The proposed Opdivo Qvantig Medication Guide (MG) is acceptable from a medication error perspective.

The proposed Opdivo Qvantig Prescribing Information (PI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 3 (DO3) in Section 4 and for Bristol-Myers Squibb Company in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 3 (DO3)

Table 2. Identified Issues and Recommendations for the Division of Oncology 3 (DO3)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently presented, the proprietary name is denoted by the placeholder "TRADENAME".	The proposed proprietary name "Opdivo Qvantig" has been found conditionally acceptable and is not reflected in current prescribing information.	We reference our May 9, 2024 Proprietary Name Request Conditionally Acceptable[b] letter informing you that the proprietary name, Opdivo Qvantig, was found conditionally acceptable. Replace the placeholder

[b] Latonia, F. Proprietary Name Request Conditionally Acceptable for Opdivo Qvantig BLA 761381. Silver Spring (MD): FDA, CDER, OSE (US); 2024 MAY 09.

Table 2. Identified Issues and Recommendations for the Division of Oncology 3 (DO3)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			"TRADENAME" with the conditionally acceptable proprietary name, Opdivo Qvantig.
Highlights of Prescribing Information			
1.	Dosage and administration section does not indicate that Opdivo Qvantig dosage and administration is different than Opdivo.	Inadvertent substitution can lead to medication errors such as, but not limited to, wrong drug errors leading to no treatment effect, overdose or underdose leading to adverse events or lack of efficacy.	After "For subcutaneous use only", we recommend adding the statement "Opdivo Qvantig has different dosage and administration instructions than intravenous nivolumab products." in the Dosage and Administration section in the Highlights of PI.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The instruction "[TRADENAME] should be administered by a healthcare professional." is currently embedded in Section 2.4.	This information may be overlooked and may lead to wrong administration errors.	Add the statement "[TRADENAME] should be administered by a healthcare professional." to Section 2.1 in addition to Section 2.4.
2.	As currently presented in Section 2.4, the statement (b) (4)	The statement lacks clarity.	Revise the statement to "To avoid clogging of the hypodermic injection needle, attach a 23G-25G (3/8"-5/8") hypodermic injection needle to the syringe immediately prior to administration. If the dose is not to be used immediately, attach a tip cap to the syringe prior to storage."

Table 2. Identified Issues and Recommendations for the Division of Oncology 3 (DO3)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	[redacted] (b) (4) appears redundant.		
3.	As currently presented in Section 2.4, the instruction to apply syringe label appears AFTER the discard instruction.	The instruction to apply the syringe label should appear immediately after the instruction to withdraw Opdivo Qvantig solution from the vial to minimize confusion regarding the contents in the syringe.	Reorder the instructions so that the apply syringe label instruction is presented BEFORE the discard statement. For example: Select the appropriate syringe label provided in the carton that matches the prescribed dose and apply to the prepared syringe. Discard partially used or empty vials of [TRADENAME].
4.	As currently presented, the sentence "Once withdrawn into the syringe, [TRADENAME] should be used immediately. If not used immediately, the…" is unclear.	The statement lacks clarity.	We recommend revising to "If not administered immediately after it is drawn into the syringe, [TRADENAME] syringe can be stored in the refrigerator…"
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The unit of measure for hyaluronidase is in title case (e.g., Units).	This is inconsistent with how the hyaluronidase units is presented throughout labels and labeling.	We recommend presenting the "units" in lowercase. For example, "600 mg nivolumab and 10,000 units hyaluronidase/5 mL (120 mg and 2,000 units/mL)".

5 RECOMMENDATIONS FOR BRISTOL-MYERS SQUIBB COMPANY

Table 3. Identified Issues and Recommendations for Bristol-Myers Squibb Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s), Carton Labeling, and the Syringe Label			
1.	The proprietary name "Opdivo Qvantig" is presented in different colors, typography, and capitalization (dark blue for "Opdivo", and teal for "Qvantig"). OPDIVO Qvantig	The current presentation of the proprietary name, "Opdivo Qvantig" may be confused with the intravenous formation of Opdivo. *Proprietary Name presentation for intravenous formulation* Opdivo® *Proposed proprietary name presentation for subcutaneous formulation* OPDIVO Qvantig	Revise the "Opdivo Qvantig" proprietary name presentation such that both words comprising the proprietary name appear in the same font, same color, same title case and is adequately differentiated from the intravenous formulation of Opdivo.
2.	The suffix placeholder is presented in (b) (4).	Inconsistency in the presentation of the suffix may lead to confusion about the nonproprietary name for this product.	Ensure the suffix is presented in the same color as the nonproprietary name "nivolumab and hyaluronidase".
3.	The strength statement "600 mg and 10,000 units/5 mL" does not include the concentration per mL.	The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling.	Revise the strength statement to "600 mg and 10,000 units/5 mL (120 mg and 2,000 units/mL)".
4.	The dosage form statement is overcrowded with	Redundancy and clutter on the principal display panel reduces readability.	After the word "injection", delete (b) (4) .

Table 3. Identified Issues and Recommendations for Bristol-Myers Squibb Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	redundant information that is duplicated elsewhere on the principal display panel.		
5.	As currently presented, the storage information (b) (4) is inconsistent with the storage information in the Prescribing Information.	This inconsistency may lead to confusion and wrong storage errors.	Revise the storage information to "Store in the original carton to protect from light."
6.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA

Table 3. Identified Issues and Recommendations for Bristol-Myers Squibb Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*
Container Label(s)			
1.	The route of administration statement appears separated on two lines on the principal display panel. (b) (4)	Lack of clarity.	Display the route of administration statement "For Subcutaneous Use Only" to appear on one unbroken line.
2.	The terminology within the statement of dosage statement (i.e., (b) (4)) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information."
Carton Labeling			
1.	As currently presented, the product identifier is missing a placeholder for the machine-readable, 2D data matrix barcode format.	The Drug Supply Chain Security Act states that drug package label must include the product identifier information in both human-readable form and the machine-readable, 2D data matrix barcode format.	Ensure the 2D data matrix barcode is included as part of the product identifier. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

Table 3. Identified Issues and Recommendations for Bristol-Myers Squibb Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	As currently presented, the time interval for administration "3-5 minutes" contains a dash.	'-' Dash may lead to misinterpretation and medication error.	We recommend replacing the dash with the intended meaning, For example, "3 to 5 minutes".
3.	The statement (b) (4) is ambiguous.	Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.	We recommend changing to "Dispense the enclosed Medication Guide to each patient."
4.	The terminology within the statement of dosage statement (i.e., (b) (4)) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	Revise the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information."

Stickers for Syringe Label			
1.	As currently presented, the time interval for administration "3-5 minutes" contains a dash.	'-' Dash may lead to misinterpretation and medication error.	We recommend replacing the dash in "3-5 minutes" with the intended meaning. For example, "3 to 5 minutes".
2.	As currently depicted, it appears that (b) (4) are required for the Opdivo Qvantig 900 mg and 15,000 units dose. (b) (4)	Presenting a pictogram (b) (4) (b) (4) for the 900 mg and 15,000 units dose may lead to wrong dose errors (b) (4) (b) (4)	Revise the pictogram on the Opdivo Qvantig 900 mg and 15,000 units above the syringe label sticker to show that one and one-half vials are required, (b) (4)
3.	As currently presented, the statement (b) (4) is inconsistent with the discard statement on the container label and carton labeling.	Inconsistency may lead to confusion.	We recommend revising the discard statement to "Discard unused portion."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Opdivo Qvantig[c] received on February 29, 2024 from Bristol-Myers Squibb Company.

Table 4. Relevant Product Information for Opdivo Qvantig	
Initial Approval Date	NA
Nonproprietary Name	nivolumab and hyaluronidase-xxxx
Indication	Renal Cell Carcinoma (RCC) Melanoma Non-Small Cell Lung Cancer (NSCLC) Squamous Cell Carcinoma of the Head and Neck (SCCHN) Urothelial Carcinoma (UC) Colorectal Cancer Hepatocellular Carcinoma (HCC) Esophageal Cancer Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
Dosage Form	injection
Strength	600 mg nivolumab and 10,000 units hyaluronidase/5 mL (120 mg nivolumab and 2,000 units hyaluronidase/mL)
Route of Administration	Subcutaneous

[c] Proposed prescribing information for Opdivo Qvantig. Princeton (NJ): Bristol Myers Squibb Co.; 2024 FEB 29. Available from: \\CDSESUB1\EVSPROD\bla761381\0001\m1\us\initial-bla-nivo-hyal-markup.docx

Table 4. Relevant Product Information for Opdivo Qvantig

Dose and Frequency

The recommended dosages of [TRADENAME] as a single agent are presented in Table 1.

Table 1: Recommended Dosages for [TRADENAME] as (b) (4)

Indication	Recommended [TRADENAME] Dosage	Duration of Therapy
Advanced renal cell carcinoma	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	Until disease progression or unacceptable toxicity
Unresectable or metastatic melanoma		
Metastatic non-small cell lung cancer		
Squamous cell carcinoma of the head and neck		
Locally advanced or metastatic urothelial carcinoma		
Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer		
Esophageal squamous cell carcinoma		
Adjuvant treatment of melanoma	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	Until disease recurrence or unacceptable toxicity for up to 1 year
Adjuvant treatment of urothelial carcinoma		
Adjuvant treatment of resected esophageal or gastroesophageal junction cancer		

* Administer over approximately 3-5 minutes.

Table 4. Relevant Product Information for Opdivo Qvantig

Table 2: Recommended Dosages for [TRADENAME] in Combination with Other Therapeutic Agents

Indication	Recommended [TRADENAME] Dosage	Duration of Therapy
Advanced renal cell carcinoma	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks Administer [TRADENAME] in combination with cabozantinib 40 mg orally once daily without food	[TRADENAME]: Until disease progression, unacceptable toxicity, or up to 2 years Cabozantinib: Until disease progression or unacceptable toxicity
(b) (4)		
Neoadjuvant treatment of resectable non-small cell lung cancer	900 mg nivolumab and 15,000 units hyaluronidase* with platinum-doublet chemotherapy on the same day every 3 weeks	In combination with platinum-doublet chemotherapy for 3 cycles
(b) (4)		
Esophageal squamous cell carcinoma	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks Administer [TRADENAME] in combination with fluoropyrimidine- and platinum-containing chemotherapy	Until disease progression, unacceptable toxicity, or up to 2 years
Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma	600 mg nivolumab and 10,000 units hyaluronidase* with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks or 900 mg nivolumab and 15,000 units hyaluronidase* with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks	[TRADENAME]: Until disease progression, unacceptable toxicity, or up to 2 years Chemotherapy: Until disease progression or unacceptable toxicity

* Administer over approximately 3-5 minutes.

How Supplied	Individually packaged single-dose vials providing 600 mg of nivolumab and 10,000 units of hyaluronidase per 5 mL

Table 4. Relevant Product Information for Opdivo Qvantig	
Storage	Store in vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.
Container Closure	(b) (4) rubber (b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Opdivo Qvantig labels and labeling submitted by Bristol-Myers Squibb Company.

- Prescribing Information and Medication Guide received on February 29, 2024, available from \\CDSESUB1\EVSPROD\bla761381\0001\m1\us\initial-bla-nivo-hyal-markup.docx
- Container label(s) received on February 29, 2024
- Carton labeling received on February 29, 2024

B.2 Container Label(s) and Carton Labeling Images

Container label(s)

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

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/s/

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