CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761234Orig1s000

OTHER REVIEW(S)

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:	November 30, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761234
Product Name, Dosage Form, and Strength:	Opdualag (nivolumab and relatlimab-rmbw[a]) injection, 240 mg nivolumab and 80 mg relatlimab/20 mL (12 mg and 4 mg/mL)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bristol-Myers Squibb
FDA Received Date:	July 19, 2021 and October 5, 2021
OSE RCM #:	2021-1435
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

[a] The proposed nonproprietary name (nivolumab and relatlimab-rmbw) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Opdualag (IND 136382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Nov 10. OSE RCM No.: 2020-1018.

1 REASON FOR REVIEW

As part of the approval process for Opdualag (nivolumab and relatlimab-rmbw) injection, the Division of Oncology 3 (DO3) requested that we review the proposed Opdualag prescribing information (PI), medication guide (MG), container label, and carton labeling for areas of vulnerability that may 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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Upon review of the proposed container label, carton labeling, PI, and MG, we noted areas of the labels and labeling that could be improved to promote the safe use of this product. Specifically for the dilution and preparation instructions in the PI, we noted incongruency between the dose (80 mg relatlimab and 240 mg nivolumab up to 160 mg relatlimab and 480 mg nivolumab), concentration parameters (b) (4) [redacted] 4 mL/kg for adult patients weighing less than 40 kg). We noted some of the parameters are not achievable (b) (4) [redacted] Therefore, we

communicated an information request on September 17, 2021[b] to clarify the expected final targeted concentration and final volume of the infusion bag required for dilution and preparation of the intravenous infusion to ensure they are achievable with the entire proposed dosing range. We also inquired in the information request if it is safe and effective for the proposed product to be administered without dilution, as well as if there is a minimum amount of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP needed to dilute the proposed product prior to intravenous infusion.

Bristol-Myers Squibb responded on September 24, 2021[c] that the (b) (4) Bristol-Myers Squibb revised the minimum concentration value for the adult patient group to 1 mg/mL relatlimab and 3 mg/mL nivolumab, which we find acceptable and is congruent with the proposed final volume parameters and the proposed dose for adults (please see below Table 1 with revised concentration values). In addition, Bristol-Myers Squibb responded that there is no minimum amount of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP needed to dilute the proposed product prior to intravenous infusion, and that the product labeling supports infusion of Opdualag injection, undiluted, to provide sites the flexibility to administer in cases where infusion fluids may be in short supply or the patient health condition requires fluid restriction. Bristol-Myers Squibb's full response to the September 17, 2021 information request is provided in Appendix F.

Table 1: Maximum Infusion Volumes and (b) (4) Concentration Ranges by Patient Population

Patient Population	Dose (mg or mg/kg)	Maximum Infusion Volume (mL or mL/kg)	Concentration Range (mg/mL)*
Pediatric (≥12 years and ≥ 40 kg)	(b) (4)	160 mL	(b) (4)
Adult ≥ 40 kg	Relatlimab: 160 mg Nivolumab: 480 mg	160 mL	Relatlimab: 1 mg/mL to 4 mg/mL Nivolumab: 3 mg/mL to 12 mg/mL
Adult < 40 kg	Relatlimab: 160 mg Nivolumab: 480 mg	4 mL/kg	Relatlimab: 1 mg/mL to 4 mg/mL Nivolumab: 3 mg/mL to 12 mg/mL

*The concentration range in each group includes 4 mg/mL relatlimab and 12 mg/mL nivolumab as the upper limit, which represents a scenario in which the drug product is infused without dilution.

[b] Leach, C. FDA Communication: BLA 761234 Nivolumab and relatlimab-rmbw; Information Requests. Silver Spring (MD): FDA, CDER, DO3 (US); 2021 SEPT 17. BLA 761234.

[c] Response to FDA Request for Information dated 17-Sep-2021 for BLA 761234, nivolumab and relatlimab-rmbw. Princeton (NJ): Bristol-Myers Squibb; 2021 SEPT 24. Available from: \\CDSESUB1\evsprod\bla761234\0022\m1\us\2021-09-17-response-us-fda-clinical-q1-q3.pdf

We note [redacted] (b) (4) We again ask Bristol-Myers Squibb in Section 4 below to revise their proposed concentration range and/or maximum infusion bag volume parameters required for dilution and preparation of the intravenous infusion for the pediatric population to ensure they are achievable with the entire proposed dosing range (80 mg relatlimab and 240 mg nivolumab up to 160 mg relatlimab and 480 mg nivolumab).

We also acknowledge Bristol-Myers Squibb's comment that the proposed drug product does not require dilution prior to administration, but we note that the proposed PI labeling does not clearly specify this. Therefore, we provide a related recommendation for the PI labeling in section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling, PI, and MG may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Dosage and Administration Section, Highlights

a. We recommend adding the route of administration to the first and second bullets under the Dosage and Administration Section in the Highlights, as follows:

[redacted] (b) (4)

[redacted] (b) (4)

b. We recommend replacing the ">" symbol with words in the second bullet under the Highlights Dosage and Administration section as the

greater than and less than symbols can be mistaken as the opposite of their intended meaning[d], as follows:

- (b) (4) [redacted]

c. Consider adding the following statement at the end of the Highlights, Dosage and Administration section to alert the end-user that there is additional preparation and administration instructions and dosage modifications for adverse reactions provided in the Dosage and Administration section of the full PI: "See full Prescribing Information for dosage modifications for adverse reactions (2.2) and preparation and administration instructions for the injection (2.3)."

2. Dosage and Administration Section, full PI

a. We recommend adding the route of administration to the dosage regimens provided in Table 1, as follows:

(b) (4) [redacted]

b. We note in Bristol-Myers Squibb's September 24, 2021 response[e] to FDA's September 17, 2021 information request[f] that the proposed concentration range and maximum prepared volume of infusion parameters for pediatric patients still results in incongruency between the full dose range (b) (4) [redacted] We recommend revising your proposed

[d] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 JULY 8]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

[e] Response to FDA Request for Information date 17-Sep-2021 for BLA 761234, nivolumab and relatlimab-rmbw. Princeton (NJ): Bristol-Myers Squibb; 2021 SEPT 24. Available from: \\CDSESUB1\evsprod\bla761234\0022\m1\us\2021-09-17-response-us-fda-clinical-q1-q3.pdf

[f] Leach, C. FDA Communication: BLA 761234 Nivolumab and relatlimab-rmbw; Information Requests. Silver Spring (MD): FDA, CDER, DO3 (US); 2021 SEPT 17. BLA 761234.

concentration range and/or maximum infusion bag volume parameters required for dilution and preparation of the intravenous infusion for the pediatric population to ensure they are achievable with the entire proposed dosing range (80 mg relatlimab and 240 mg nivolumab up to 160 mg relatlimab and 480 mg nivolumab). Consider revising the minimum concentration value to 1 mg/mL relatlimab and 3 mg/mL nivolumab similar to how the concentration range was revised for the adult patient group.

c. We note in Bristol-Myers Squibb's September 24, 2021 response[g] to FDA's September 17, 2021 information request[h] that the proposed drug product does not require dilution prior to administration. The proposed PI labeling does not clearly specify this. Therefore, we recommend you edit your proposed preparation instructions in the proposed PI labeling to clearly specify that Opdualag can be administered undiluted or diluted (see suggested language to add in recommendation 2d below, and we recommend bolding as shown to increase the prominence of this important information).

d. Instead of providing three sets of similar preparation instructions with the differing maximum infusion volume and concentration range parameters specified for the three patient groups, we recommend providing one set of preparation instructions that references a table presenting the maximum infusion volume and concentration range parameters for the three patient groups as shown below. This will help to present the different parameters for the three patient groups in an organized manner and improve readability of the preparation instructions in the proposed PI labeling.

"Preparation

- During preparation of the infusion solution, (b) (4) to assure sterility, as the product does not contain a preservative.
- OPDUALAG can be administered diluted or undiluted and administered at a final concentration as specified in Table (#) below.

[g] Response to FDA Request for Information date 17-Sep-2021 for BLA 761234, nivolumab and relatlimab-rmbw. Princeton (NJ): Bristol-Myers Squibb; 2021 SEPT 24. Available from: \\CDSESUB1\evsprod\bla761234\0022\m1\us\2021-09-17-response-us-fda-clinical-q1-q3.pdf

[h] Leach, C. FDA Communication: BLA 761234 Nivolumab and relatlimab-rmbw; Information Requests. Silver Spring (MD): FDA, CDER, DO3 (US); 2021 SEPT 17. BLA 761234.

- Withdraw the required volume of OPDUALAG and transfer into an intravenous container.
- If diluting OPDUALAG prior to administration:
  - Dilute OPDUALAG solution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion meeting the final concentration and maximum infusion volume parameters as specified in Table (#) below.
  - Then mix the diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials following infusion preparation.

Table (#):	Maximum Infusion Volumes and Concentration Ranges by Patient Group	
Patient Group	Maximum Infusion Volume (mL or mL/kg)	Concentration Range (mg/mL)*
Pediatric (12 years of age and older and weighing at least 40 kg)	160 mL	Relatlimab: (b) (4) 1 mg/mL to 4 mg/mL Nivolumab: (b) (4) 3 mg/mL to 12 mg/mL
Adults weighing at least 40 kg	160 mL	Relatlimab: 1 mg/mL to 4 mg/mL Nivolumab: 3 mg/mL to 12 mg/mL
Adults weighing less than 40 kg	4 mL/kg	Relatlimab: 1 mg/mL to 4 mg/mL Nivolumab: 3 mg/mL to 12 mg/mL
*The concentration range in each group includes 4 mg/mL relatlimab and 12 mg/mL nivolumab as the upper limit, which represents a scenario in which the drug product is infused without dilution."		

e. We note the proposed storage instructions for the prepared infusion provided in the proposed PI references the (b) (4) However, Opdualag can be administered undiluted or diluted. Please clarify the proposed storage instructions for the prepared infusion when diluted versus when prepared undiluted. If the proposed storage instructions apply to both the diluted and undiluted infusion, we recommend revising the proposed instructions as follows:

"Storage of Prepared Infusion

Store the prepared (b) (4) solution either:

- At room temperature and room light for no more than 8 hours from the time of preparation to the end of the infusion. Discard the [redacted]–solution if not used within 8 hours from the time of preparation;

  or

- Under refrigeration at 2°C to 8°C (36°F to 46°F) with protection from light for no more than 24 hours from the time of preparation [redacted] Discard [redacted] solution if not used within 24 hours from the time of preparation.
- Do not freeze."

f. Clarify if the storage timeframe of 24 hours under refrigeration for the prepared intravenous infusion solution includes the time allowed for equilibration of the infusion bag to room temperature prior to infusion. If so, we recommend adding this to the proposed storage instructions as follows:

- "Under refrigeration at 2°C to 8°C (36°F to 46°F) with protection from light for no more than 24 hours from the time of preparation, which includes the time allowed for equilibration of the infusion bag to room temperature and the duration of the infusion. Discard [redacted] solution if not used within 24 hours from the time of preparation."

3. How Supplied/Storage and Handling Section

a. We recommend providing the mg/mL concentration[i] of relatlimab and nivolumab [e.g., (4 mg and 12 mg/mL)] after the following phrase in the table displaying carton contents: "80 mg relatlimab and 240 mg nivolumab/20 mL single-dose vial (4 mg and 12 mg/mL)".

b. We note the description for the injection provided in Section 16 does not match that provided in Section 3 (e.g., section 16 has the added description: [redacted] and "sterile, preservative-free, [redacted] We also note the instructions in section 2.3 to "discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white particles." We defer to the review team on determining the accuracy of the additional descriptor statements in sections 2 and 16 (e.g., section 16 has the added description: [redacted]

[i] 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

[redacted] and "sterile, preservative-free, [redacted]" and section 2 has the following description: "few transluscent-to-white particles"), and we recommend providing a consistent description of the injection across the labeling.

B. Medication Guide

1. We recommend revising the instructions regarding pregnancy and breastfeeding for clarity and to add that breastfeeding should not occur during treatment as well as for 5 months after the last dose of Opdualag (in order to match section 8.2 instructions and instructions provided in section 17, Patient Counseling Information), as follows:

"For ~~F~~females who are able to become pregnant:

- Your healthcare provider ~~should do~~ will administer a pregnancy test before you start receiving OPDUALAG.
- ~~You should~~ Use an effective method of birth control during and for at least 5 months after the last dose of OPDUALAG. Talk to your healthcare provider about birth control methods that you can use during this time.
- Tell you healthcare provider right away if you become pregnant during treatment with OPDUALAG.

For females who are breastfeeding or plan to breastfeed:

- ~~are breastfeeding or plan to breastfeed.~~ It is not known if OPDUALAG passes into your breast milk. Do not breastfeed during treatment with OPDUALAG and for 5 months after the last dose of OPDUALAG."

4.2 RECOMMENDATIONS FOR BRISTOL-MYERS SQUIBB

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

A. General Comments (Container label & Carton Labeling)

1. To ensure consistency with the Prescribing Information, we recommend revising the usual dose statements on the container label and carton labeling, respectively, from [redacted] to "Recommended Dosage: See Prescribing Information.".
2. We suggest removing the phrase [redacted] from the Principal Display Panel (PDP) of the container label and carton labeling. As presented, this statement distracts from the other required statements on the PDP.
3. 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. 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 recommends that a slash or a hyphen be used to separate the portions of the expiration date.[j]

4. Revise and bold the storage instructions provided for the vial on the side panels of the container label and carton labeling to state that "the vial" must be refrigerated, and replace the term [(b) (4)] with "carton" in order to more appropriately describe the outer packaging for the vial, as follows:
Container Label: The vial must be refrigerated at 2°C to 8°C (36°F to 46°F). Protect vial from light by storing in the original [(b) (4)] carton until time of use. Do not freeze or shake.

   Carton Labeling: "Storage: The vial must be refrigerated at 2°C to 8°C (36°F to 46°F). Protect vial from light by storing in the original [(b) (4)] carton until time of use. Do not freeze or shake."

   (Of note, underline intended to indicate the location of the proposed edit and not for implementation.)

   We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

A. Container Label
   1. Confirm there is enough white space around the linear barcode on the container label to allow the barcode to be read. The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

B. Carton Labeling
   1. We recommend deleting the phrase, [(b) (4)], under the "Administration:" heading on the side panel, [(b) (4)] In addition, the usual dose

[j] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

statement provided above the "Administration:" heading will point the end-user to the PI labeling to obtain the storage information for the prepared infusion.

2. In the contents description on the side panel, provide the mg/mL concentration[k] of relatlimab and nivolumab [e.g., (4 mg and 12 mg/mL)] after the following phrase: (b) (4) [redacted]
3. We note the absence of a lot number and expiration date on the proposed carton labeling. Provide the lot number in accordance with 21 CFR 201.10(i)(1), and the expiration date in accordance with 21 CFR 211.137.
    a. Ensure the lot number and expiration date are clearly differentiated from one another.[l]
    b. Also ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[m]
4. We note the lot number, expiration date, and serial number are missing from the carton labeling. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.
   The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier.
   The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following:

   NDC: [insert NDC]
   SERIAL: [insert serial number]
   LOT: [insert lot number]
   EXP: [insert expiration date]

   We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.[n]

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[k] 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

[l] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

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

[n] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Opdualag received on October 5, 2021 from Bristol-Myers Squibb.

Table 2. Relevant Product Information for Opdualag	
Initial Approval Date	N/A
Nonproprietary Name	nivolumab and relatlimab-rmbw
Indication	Treatment of adults and pediatric patients (12 years and older (b) (4) with unresectable or metastatic melanoma.
Route of Administration	intravenous
Dosage Form	injection
Strength	240 mg nivolumab and 80 mg relatlimab/20 mL (12 mg and 4 mg/mL)
Dose and Frequency	• Adult patients: 480 mg nivolumab and 160 mg relatlimab intravenously every 4 weeks. • Pediatric patients 12 years and older and weighing at least 40 kg: (b) (4) intravenously every 4 weeks. • No dose reduction for Opdualag is recommended. In general, withhold Opdualag for severe (Grade 3) immune-mediated adverse reactions (IMARs). Permanently discontinue Opdualag for life-threatening (Grade 4) IMARs, recurrent severe (Grade 3) IMARs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids. • Dose modifications for adverse reactions that require management different from these general guidelines are summarized in Table (b) (4) of the full PI.
How Supplied	Opdualag injection is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to slightly yellow solution (b) (4) (b) (4)

Storage	Store OPDUALAG [redacted] at 2°C to 8°C (36°F to 46°F). Protect from light [redacted] until time of use. Do not freeze or shake.
Container Closure	[redacted] Type [redacted] clear [redacted] glass vial, stoppered with a 20-mm [redacted] rubber stopper, and yellow Flip-Off seal. The presentation is packaged in a paperboard folding carton.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 29, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Opdualag, nivolumab and relatlimab, and BLA # 761234. Our search did not identify any previous reviews.

APPENDIX F. OTHER

Bristol-Myers Squibb September 24, 2021 Response to Our September 17, 2021 Information Request:

2021-09-17-bms9862
13-Response-FDA-FIN

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,[o] along with postmarket medication error data, we reviewed the following Opdualag labels and labeling submitted by Bristol-Myers Squibb.

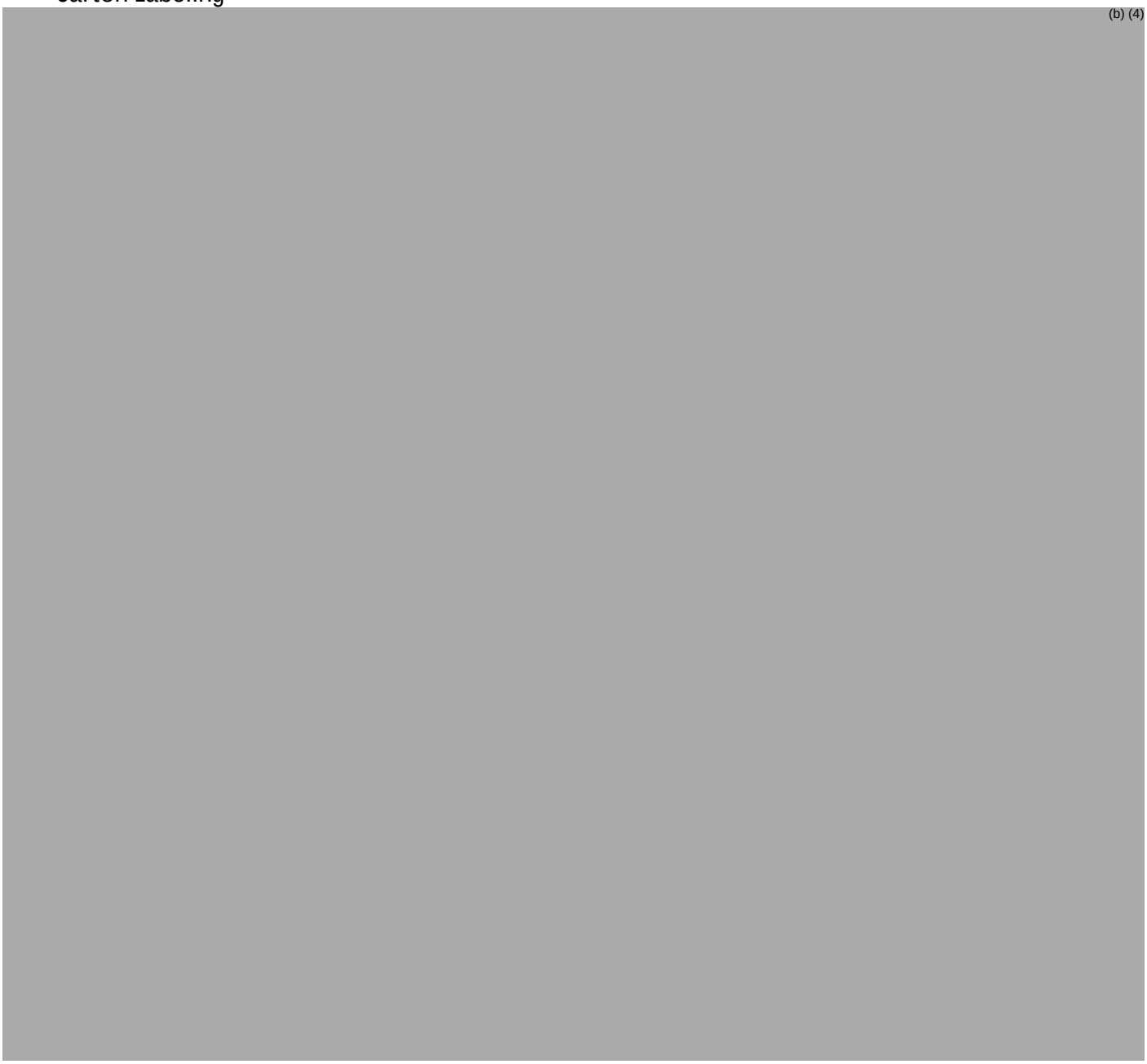
- Container label received on July 19, 2021
- Carton labeling received on July 19, 2021
- Prescribing Information and Medication Guide (Image not shown) received on October 5, 2021, available from \\CDSESUB1\evsprod\bla761234\0024\m1\us\04oct2021-advanced-melanoma-relat-nivol-rmbw-pro.docx

G.2 Label and Labeling Images

Container Label

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

Carton Labeling



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/

SARAH E THOMAS
11/30/2021 11:19:04 AM

ASHLEIGH V LOWERY
11/30/2021 06:40:33 PM

Clinical Inspection Summary

Date	2/10/2021
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Leslie Doros MD, Clinical Reviewer Jamie Brewer MD, Clinical Team Leader Christina Leach, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	761234
Applicant	Bristol-Myers Squibb Company
Drug	OPDUALAG (Relatlimab/Nivolumab fixed dose combination [FDC])
NME (Yes/No)	No
Therapeutic Classification	Relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody Nivolumab, a programmed death receptor-1 (PD-1) blocking antibody
Proposed Indication	Treatment of unresectable or metastatic uveal melanoma
Consultation Request Date	8/25/2021
Summary Goal Date	2/19/2022
Action Goal Date	3/19/2022
PDUFA Date	3/19/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study CA224047 (NCT 03470922) were submitted to the Agency in support of a New Biologics Application (BLA 761234) for Relatlimab/Nivolumab FDC (also known as BMS-986213) for the treatment of adults and children with unresectable or metastatic melanoma.

Three clinical investigators, Drs. Long (Site 0042), Alvarez (Site 0092), and Ramirez (Site 0094) were selected for clinical inspections. Drs. Alvarez and Ramirez's inspections were conducted onsite and Dr. Long's inspection was conducted as a remote regulatory assessment due to site and/or travel restrictions related to the Covid-19 pandemic.

Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of this BLA.

II. BACKGROUND

Bristol-Myers Squibb seeks approval of Relatlimab/Nivolumab FDC for the proposed indication. In support of the BLA, the Applicant submitted clinical data from Study CA224047, a phase 2/3, multi-center, randomized, double-blind, study comparing relatlimab combined with nivolumab versus nivolumab monotherapy in subjects with previously treated, unresectable melanoma.

The **primary objective of Study CA224047 is** to compare the efficacy of BMS-986213 with nivolumab monotherapy. The **primary endpoint** is progression free survival (PFS), determined by Blinded Independent Central Review (BICR) using the Response Evaluation Criteria in Solid Tumors v1.1 guidelines (RECIST 1.1). PFS is defined as the time between the date of randomization and the first date of documented progression, or death due to any cause.

The **key secondary endpoints** are overall survival (OS) and overall response rate (ORR).

Key inclusion criteria include adult subjects with:

- Diagnosis of histologically confirmed Stage III (unresectable) or Stage IV melanoma
- No prior systemic anticancer therapy for unresectable or metastatic melanoma.
  Note: Prior adjuvant or neoadjuvant melanoma therapy with a specified regimen was allowed:
  - Anti-PD-1, anti-CTLA-4 containing regimen if ≥ 6 months between last dose and date of recurrence,
  - Interferon with last dose ≥ 6 weeks before randomization
  - BRAF- or MEK- inhibitor containing regimens with at least 6 months between the last does and the date of recurrence
- Prior radiotherapy must have completed at least 2 weeks prior to study treatment administration
- Known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the screening period
- Provide tumor tissue from an unresectable or metastatic site of disease for biomarker analysis
- Measurable disease by CT or MRI according to RECIST v1.1
- Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤1
- Life expectance of > 3 months based on investigator's judgement
- Participants must be ≥ 12 years at the time of informed consent if local regulations and/or institutional policies allow for participants < 18 years of age (pediatric population). If pediatric population is not allowed to participate, then ≥ 18 years applies.

Key Exclusion criteria, subjects could not have:

- Active autoimmune disease,

- Medical conditions requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medications, and
- Active or untreated brain or leptomeningeal metastases - *Participants with brain metastases were eligible if these had been treated and there was no MRI evidence of progression for at least 8 weeks after treatment was complete and within 28 days prior to first dose of study treatment administration.*

Eligible subjects were to be stratified by PDL-1 status, LAG-3 status, BRAF status, and AJCC M stage. Subjects were to be randomized 1:1 to receive either Relatlimab 160 mg and Nivolumab 480 mg by intravenous infusion every 4 weeks (Arm 1), or Nivolumab 480 mg by intravenous infusion every 4 weeks (Arm 2).

Subjects were to be treated until disease progression, treatment discontinuation, unacceptable toxicity, withdrawal of consent, or the study ends.

Primary efficacy analysis was to be based on the tumor response by blinded independent central readers (BICR). Tumor imaging assessments for ongoing study treatment decisions were to be completed by the investigator using RECIST v1.1 criteria. Treatment beyond initial investigator-assessed RECIST v1.1-defined progression was to be permitted if the participant had investigator-assessed clinical benefit and was tolerating study treatment.

Study Assessments

Imaging during screening and treatment:

- Subjects were to sign informed consent before any screening procedures
- Screening CT of the chest, abdomen, and pelvis was to be completed 28 days prior to randomization and have target lesion confirmed by independent BICR
- MRI of the brain without and with contrast was required for *all* participants during screening to rule out brain metastases within 28 days prior to randomization. CT of the brain (without and with contrast) could be performed if MRI is contraindicated
- Tumor assessments were to be conducted 12 weeks after randomization and continued every 8 weeks up to week 52 and then every 12 weeks until disease progression by BICR or treatment discontinuation, whichever occurred later
- All SAEs and non-serious AEs were to be collected continuously during the treatment period

Follow-up:

- Follow-up for OS was to be conducted up to approximately 5 years after the randomization of the last participant
- All SAEs and non-serious AEs were to be collected continuously or a minimum of 100 days following discontinuation of study treatment

This study was conducted at 114 sites in 25 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, New Zealand, Norway, Poland, Romania, Russian Federation, Spain, Sweden, UK, and USA). The database lock for the current submission is March 9, 2021.

By the data cutoff, 714 subjects were randomized and treated in this study (355 in the BMS-986213 arm, and 359 in the nivolumab monotherapy arm). The study is ongoing to assess the key secondary endpoints of OS and ORR. Drs. Long (Site 0042), Alvarez (Site 0092), and Ramirez (Site 0094) were selected for clinical inspections, because they were high enrolling sites with high treatment efficacy in the treatment arm relative to the control arm (Sites 0092 and 0094) and relative to the overall study treatment efficacy rate (Site 0042).

III. RESULTS

1. **Dr. Georgina Long, (Site 0042)**
   40 Rocklands Road
   North Sydney, New South Wales 2060
   Australia

   Remote Regulatory Assessment Dates: January 19 – February 2, 2022.

   A remote regulatory assessment (RRA) was conducted because, due to the Covid-19 pandemic, travel to the site was not possible. This RRA summary was generated from a preliminary report from the inspector. A RRA summary addendum will be generated in the event there are any changes to the remote regulatory assessment results upon receipt and review of the RRA memo. Video conferencing via WebEx and document sharing via an online platform (b) (4) were utilized for the assessment of Study CA224047. A previous onsite inspection of this clinical investigator conducted (b) (4) was classified as no action indicated (NAI).

   At the time of the data cutoff, the investigator had screened 43 subjects and enrolled 32. There were no discrepancies between the source documents and the data line listings for subject enrollment.

   Selected redacted source records reviewed included those related to study eligibility, such as labs, biomarker testing, concomitant medications, medical history, pathology reports, and sponsor communication records. All subjects enrolled at the site were found to have met the eligibility criteria.

   For some subjects, records related to protocol deviations and SAEs reported in the data listings were reviewed. Complete subject study records were not reviewed for any of the subjects enrolled at the site, limiting the ability to identify unreported PDs or AEs.

   The primary endpoint was based on independent review of imaging. The local imaging studies were collected and transferred to the BICR for central review according to the protocol for all subjects. The imaging assessment dates at the site were compared to the dates of the imaging studies in the data listings, and there were no imaging studies that had not been sent to the central imaging facility.

2. Dr. Alejandro Molina Alavez-Merida (Site 0092)
Centro de Atencion e Investigacion Clinica en Oncologia
SCP (Office)
CALLE 7 #552 Interior 4 Plaza
Merida, Yucatan 97134, Mexico

Inspection Dates: November 8-12, 2021

This investigator was inspected as an onsite surveillance inspection for Study CA224047. This was the first FDA inspection for this investigator.

At the time of the data cutoff, the investigator had screened 21 subjects and enrolled 15. There were no discrepancies between the source documents and the data listings for subject enrollment and disposition. At the time of inspection, 4 subjects were still on treatment or in follow up and 11 subjects discontinued due to disease progression.

The source documents for the 15 enrolled subjects were reviewed and compared to the subject data listings. The reviewed subject records included medical records, including progress notes, imaging records, and laboratory evaluations, informed consent, eligibility criteria, concomitant medications, adverse events, SAEs, and protocol deviations. Study records were also reviewed including financial disclosure forms, delegation of authority log, screening and enrollment log, monitoring site visit logs, IEC approvals, and the site protocol with amendments.

The primary endpoint (PFS) and key secondary endpoint (ORR) were based on independent central review of imaging data. All local imaging was performed and sent to the central imaging facility as per the protocol. The date of tumor assessment by the BICR was compared to the source data and there were no discrepancies. The key secondary endpoint of OS was verified against the source data at the site.

There were 2 subjects who were enrolled who did not meet eligibility criteria. Subject (b) (6) finished radiotherapy for brain metastases two days before the first dose of study drug and no MRI was performed. Subject (b) (6) finished radiotherapy 1 month before their first dose of study drug, and no MRI was performed prior to treatment.

Table 1: Enrolled Subjects not meeting Eligibility Criteria

Subject	Arm	Date of IC	Date of CNS radiotherapy	C1D1	Reported as a PD
(b) (6)	BMS-986213	(b) (6)			Yes
	NIVOLUMAB				No

Inclusion criteria (2g) states subjects are to have stopped radiotherapy 2 weeks before treatment. Exclusion criteria (1a) states subjects who have had radiotherapy for brain mets are eligible if there is no evidence of progression via MRI for at least 8 weeks after treatment is complete and within 28 days of first dose of study treatment.

The deviations were detected by the August 2019 Sponsor site audit. The clinical investigator stated in his 483 response that he had contacted the study monitor, who agreed verbally to randomization and treatment of both subjects, however, there was no written documentation of this communication at the site. The site was closed to further enrollment by the Sponsor after the audit.

Reviewer's comments: The Clinical investigator stated in his response that the enrollment of ineligible subjects occurred due to confusion in inclusion/exclusion criteria (2 week vs. 8 week interval between radiotherapy and treatment) and he cleared the enrollment with the study monitor, although this is not documented. The investigator submitted a preventive action plan to prevent future enrollment of ineligible subjects into clinical trials; the plan is adequate. The deviation did not affect the data reliability in favor of efficacy as both subjects progressed rather quickly. Subject (b) (6) *discontinued after 3 cycles and Subject* (b) (6) *discontinued after one cycle, both due to disease progression. There was no evidence of compromise to subject safety. It does not appear that this was a study wide issue.*

Additional regulatory violations were identified and contributed to Dr. Molina's regulatory classification. These included the late reporting of SAEs, minor unreported AEs, and several additional protocol violations, specifically not documenting consent from the study monitor to treat subjects after progression or when they met exclusion criteria. In all instances, the inspection findings are adequately reported in the CSR and data listings. Because of these violations, the site was closed to further enrollment by the Sponsor after the site audit.

In conclusion, the site was properly audited by the Sponsor and appropriately closed to further enrollment after the site audit. The protocol deviations were largely reported and corrected, when able. There was no evidence of compromise to subject safety or data integrity. The SAEs and subject's dates of progression were accurately reported.

3. Dr. Emilio Murillo Ramirez (Site 0094)
Investigacion Biomedica Para el Desarrollo de Farmacos, S.A. de C.V.(Office)
Volcan Popocatepetl 3352, Colli Urbano
Zapopan, JALISCO 45070
Mexico

Inspection dates: November 11-17, 2021

This investigator was inspected as an onsite surveillance inspection for Study CA224047. This was the first FDA inspection for this investigator.

At the time of the data cutoff, 42 subjects were screened, 20 were enrolled and treated in the study. At the time of inspection, eight subjects were still receiving treatment, 2 were on follow up and 10 had discontinued due to disease progression. There were no discrepancies between

the source documents and the data line listings for subject enrollment and disposition.

The source documents for the 20 enrolled subjects were reviewed and compared to the subject data line listings. The reviewed subject records included informed consent forms, medical records, including imaging records and required labs and ECGs, inclusion/exclusion criteria, adverse events, protocol deviations. Study records were also reviewed including financial disclosure forms, delegation of authority log, screening and enrollment log, monitoring site visit logs, IEC approvals, and the site protocol with amendments.

The primary endpoint data (PFS) and key secondary endpoint (ORR) were based on independent central review of imaging data. All local imaging was performed and sent to the central imaging facility as per the protocol. The date of tumor assessment by the BICR was compared to the source data and there were no discrepancies. The key secondary endpoint of OS was verified against the source data at the site No unreported protocol deviations were identified.

The following adverse events were identified in the subject source records but not included in the data listings: Subject (b) (6) (neck pain and vitiligo), Subject (b) (6) (Palpitations, Muscle Weakness, Cellulitis, and Urinary Tract Infection), and Subjects (b) (6) (low grade laboratory abnormalities that were reported in the lab data listings). In all cases, the unreported AEs had not been entered into the electronic system used to convey study data to the sponsor.

Reviewer's Comments: The unreported adverse events were typically low-grade and the laboratory abnormalities were reported in the lab data to the BLA. There was no evidence of subject harm and the AEs do not impact the safety profile of the drug.

No significant regulatory violations or data integrity concerns were identified.

{See appended electronic signature page}

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
Branch Chief
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cc:

Review Division /Division Director/ 'Lola Fashoyin-Aje, MD
Review Division /Project Manager/ Christina Leach
Review Division/Cross Discipline Team Lead/Jamie Brewer, MD
Review Division/Clinical Reviewer/ Leslie Doros, MD
OSI/Office Director/Dave Burrow
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

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KAREN B BLEICH
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KASSA AYALEW
02/10/2022 11:35:23 AM

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

PATIENT LABELING REVIEW

Date:	February 1, 2022
To:	Christina Leach, PharmD Regulatory Project Manager **Division of Oncology 3 (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	OPDUALAG (nivolumab and relatimab-rmbw)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761234
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On July 19, 2021, Bristol-Myers Squibb Company submitted for the Agency's review an original Biologics License Application (BLA) 761234 for OPDUALAG (nivolumab and relatlimab-rmbw) injection, for the proposed indication for the treatment of adults and pediatric patients (12 years and older (b) (4) with unresectable or metastatic melanoma.

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 3 (DO3) on August 20, 2021 and August 6, 2021, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPDUALAG (nivolumab and relatlimab-rmbw) injection.

2 MATERIAL REVIEWED

- Draft OPDUALAG (nivolumab and relatlimab-rmbw) injection MG received on July 19, 2021 and revised on October 5, 2021, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on January 24, 2022.
- Draft OPDUALAG (nivolumab and relatlimab-rmbw) injection Prescribing Information (PI) received on July 19, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 24, 2022.
- Approved OPDIVO (nivolumab), [BLA 125554] labeling dated August 19, 2021.

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. In our review of the MG the target reading level is at or below an 8th grade 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. We reformatted the MG document using the Arial font, size 10.

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

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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SHARON R MILLS
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LYNN M PANHOLZER
02/01/2022 11:24:08 AM

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

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

Memorandum

Date: February 1, 2022

To: Christina Leach, Regulatory Project Manager
Division of Oncology 3 (DO3)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for OPDUALAG™ (nivolumab and relatlimab-rmbw) injection, for intravenous use (Opdualag)

BLA: 761234

In response to DO3's consult request dated August 6, 2021, OPDP has reviewed the proposed prescribing information (PI), Medication Guide, and carton and container labeling for the original BLA submission for Opdualag.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DO3 on January 24, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the proposed Medication Guide was completed, and comments on the proposed Medication Guide were sent under separate cover on February 1, 2022.

Carton and Container Labels: OPDP has reviewed the attached proposed carton and container labels submitted by the Applicant to the electronic document room on December 8, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
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MEMORANDUM

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

Date of This Memorandum:	January 5, 2022
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761234
Product Name and Strength:	Opdualag (nivolumab and relatlimab-rmbw[a]) injection, 240 mg nivolumab and 80 mg relatlimab/20 mL (12 mg and 4 mg/mL)
Applicant/Sponsor Name:	Bristol-Myers Squibb
OSE RCM #:	2021-1435-1
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Janine Stewart, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 8, 2021 for Opdualag. The Division of Oncology 3 (DO3) requested that we review the revised container label and carton labeling for Opdualag (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.[b]

2 CONCLUSION

Upon review of the container label and carton labeling and Bristol-Myers Squibb's response to our recommendations, we note that Bristol-Myers Squibb plans to use the expiration date format of "MMM YYYY". Bristol-Myers Squibb reports that this is the format used on multiple products since 2017 and ensures clarity of the expiration dating without the necessity of punctuation marks (such as a slash or a hyphen) (b) (4)

[a] The proposed nonproprietary name (nivolumab and relatlimab-rmbw) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Opdualag (IND 136382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Nov 10. OSE RCM No.: 2020-1018.
[b] Thomas, S. Label and Labeling Review for Opdualag (BLA 761234). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 30. RCM No.: 2021-1435.

(b) (4) We find their proposal and rationale acceptable.

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

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SARAH E THOMAS
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JANINE A STEWART
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