

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761232Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary Addendum

Date	February 6, 2024
From	Michele Fedowitz, MD (Clinical Reviewer and Team Leader) Jenn Sellers, MD, Ph.D., (Branch Chief) Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Sandra Casak MD, Clinical Team Leader Rebecca Cohen, Regulatory Project Manager Steven Lemery MF Division Director Division of Oncology 3/ Office of Oncologic Products
BLA #	761232
Applicant	BeiGene Inc.
Drug	Tevimbra (tislelizumab-jsgr)
NME	Yes
Therapeutic Classification	Programmed death receptor-1 (PD-1) blocking antibody
Proposed Indication(s)	Treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy
Submission Date	07/12/2021
Consultation Request Date	08/05/2021
Summary Goal Date	05/01/2022
CIS Filed in DARRTs	04/26/2022
Action / PDUFA Date	07/05/2022 Action deferred due to inability to inspect manufacturing and clinical sites in China due to COVID-19 pandemic

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This addendum is a correction to the CIS addendum filed into DARRTs on 2/5/2024. The inspection results of Dr. Zhao (Site #086003) are based on the final FDA Establishment Inspection Report (EIR).

This is an Addendum to the Clinical Inspection Summary (CIS) filed in DARRTs on 04/26/2022 and 02/05/2024.

Clinical data from Study BGB-A317-302 (NCT 03430843) were submitted to the Agency in support of a New Biologics Application (BLA 761232) for tislelizumab for the treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy.

Three clinical investigators, Drs. Shen (Site #086001), Yu (Site #086027), and Zhao (Site

#086003), as well as the Sponsor, BeiGene USA, Inc., were selected for clinical inspections. Please refer to the CIS dated April 26, 2022, which detailed the inspection findings for Dr. Shen and the Sponsor. Inspections of Drs. Yu and Zhao had been delayed due to ongoing travel restrictions related to the COVID-19 pandemic in China, however, they were recently completed.

The conducted inspections of Drs. Yu and Zhao did not find significant concerns regarding the oversight of the clinical trial, GCP or regulatory compliance, or the data generated.

II. BACKGROUND

The Applicant submitted clinical data from Study BGB-A317-302 to support approval of an indication for tislelizumab for the treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) who progressed on or after prior systemic treatment.

Study BGB-A317-302 is a multicenter, open-label, randomized, controlled, Phase 3 study comparing tislelizumab (BGB-A317) versus investigator's choice chemotherapy (ICC) in adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) who have progressed on or after prior systemic treatment.

The primary objective was to compare the overall survival (OS) in tislelizumab versus Investigator's choice chemotherapy, when given as second-line treatment in patients with advanced unresectable or metastatic ESCC. The primary endpoint is OS, in the intent to treat (ITT) Analysis Set.

The key secondary endpoint is OS in the PD-L1-Positive Analysis Set (PD-L1 expression status of visually estimated Combined Positive Score [vCPS] $\geq 10\%$). Additional secondary endpoints include objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR) between tislelizumab, and investigator's choice chemotherapy (ICC) as assessed by the investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

Subjects were to be randomized 1:1 to receive either tislelizumab or investigator's choice chemotherapy.

- Arm 1, Tislelizumab 200 mg every 3 weeks
- Arm 2, Investigator's Choice Chemotherapy (pembrolizumab, ipilimumab, or dacarbazine) were given on Day 1 of each 3-week cycle:
 - Paclitaxel (135 to 175 mg/m² every 3 weeks starting on Day 1)
 - Docetaxel (75 mg/m² every 3 weeks starting on Day 1)
 - Irinotecan (125 mg/m² on Days 1 and 8, given every 3 weeks)

Treatment was to be continued until disease progression, unacceptable toxicity, or other treatment discontinuation criteria were met. All subjects who discontinued treatment before disease progression were to be followed for disease progression and were to continue to undergo

tumor assessments as scheduled until they began a new anticancer treatment, experienced disease progression, withdrew consent, died, were lost to follow-up, or the study completed.

Subjects were to be followed for survival status beginning approximately 1 month (4 weeks $\pm$ 7 days) after the Safety Follow-up Visit (which was to be conducted within 30 days ($\pm$ 7 days) after the last study treatment) and approximately monthly thereafter or as directed by the sponsor. Information on survival follow-up and the subsequent anticancer treatment was to be collected every month until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. Imaging assessments for the imaging secondary endpoints were to be performed at screening and then every 6 weeks ($\pm$ 7 days) for 6 months, then every 9 weeks ($\pm$ 7 days) and were to be performed on schedule *regardless* of whether study treatment had been administered or held. Tumor response was to be assessed by the investigator using RECIST v1.1.

This study was conducted at 132 study centers in 11 countries/regions globally. Patients were enrolled in Belgium; France; Germany; Italy; Japan; Korea; Spain; Taiwan, China; the United Kingdom; and the United States (US). A total of 392 subjects were enrolled in Asia/Pacific with 286 subjects enrolled in China. 101 subjects were enrolled in Western Europe. Two subjects were enrolled in the US. The data cutoff for the current submission was December 1, 2020.

Please refer to the initial CIS dated April 26, 2022, for a complete summary of the inspection results for Dr. Shen and the Sponsor. This CIS summarizes the inspection findings for Drs. Yu and Zhao.

III. RESULTS (by site):

1. Dr Xinmin Yu (Site #086027)

No 1 East Banshan Bridge Road, Gongshu District
Hangzhou, Zhejiang, 310022
CHINA

Inspection dates: September 11-15, 2023

Dr. Yu was inspected as a routine PDUFA inspection for Study BGB-A317-302. This was the first FDA inspection of this investigator.

At the time of the inspection, the site had enrolled 15 subjects and the inspection verified source records for all 15 subjects. Documents reviewed include informed consent forms, inclusion/exclusion criteria, adverse events, medical records including medical history, subject visits, concomitant medications, vital signs, laboratory results, imaging and imaging reports/interpretations, physical exams, IP accountability, and protocol deviations. No significant discrepancies were found.

Additional records reviewed during the inspection included, but were not limited to, financial disclosures, FDA Form 1572s, site training, electronic case report forms and audit trails, protocols and amendments, EC approvals, study monitoring reports, and Sponsor

communications. No issues were identified.

Efficacy endpoint assessment consisted of verification of subject's survival status in the source records comparing with the data submitted to the BLA. No discrepancies were found.

Based on the results of the inspection, the study was conducted in accordance with the investigational plan and the data generated at Dr. Yu's site appear acceptable in support of the proposed indication in the BLA.

2. Dr. Kuaile Zhao (Site # 086003)

No. 270 Dongan Road
Shanghai, Shanghai 200032
CHINA

Inspection dates: October 31 – November 3, 2023

Dr. Zhao was inspected as a routine PDUFA inspection for Study BGB-A317-302. This was the first FDA inspection of this investigator.

At the time of the inspection, the site had screened 49 and enrolled and treated 41 subjects in the study. There were 33 subjects who had completed the study and 8 had discontinued from study treatment.

Source records for 12 of 41 subjects enrolled at the site were reviewed and compared with data submitted to the BLA. Records reviewed included informed consent documents, AE and SAE reports, protocol deviations, concomitant medications, and eligibility criteria. No significant discrepancies were found. There was no evidence of under-reporting of AEs or unreported protocol violations. The subjects' survival status for the efficacy endpoint data in the source records were compared with the data submitted to the BLA. No discrepancies were found.

Additional records reviewed during the inspection included, but were not limited to, FDA Form 1572s, site training, protocols and amendments, EC approvals, study monitoring reports and communications, investigational products records, investigational product storage and shipment. No issues were identified.

Based on the results of the inspection, the study was conducted in accordance with the investigational plan and the data generated at Dr. Zhao's site appear acceptable in support of the proposed indication in the BLA.

{ See appended electronic signature page }

Michele Fedowitz, MD
OSI Reviewer and Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Jenn Sellers, MD, PhD
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DARRTS: BLA 761232
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OOP/ DO3/Regulatory Project Manager/Rebecca Cohen

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/

MICHELE B FEDOWITZ
02/06/2024 01:22:51 PM

JENN W SELLERS
02/06/2024 01:34:05 PM

February 6th, 2024

The inspection results of Dr. Zhao (Site #086003) are based on the final FDA Establishment Inspection Report (EIR).

Clinical Inspection Summary Addendum

Date	February 5, 2024
From	Michele Fedowitz, MD (Clinical Reviewer and Team Leader) Jenn Sellers, MD, Ph.D., (Branch Chief) Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Sandra Casak MD, Clinical Team Leader Rebecca Cohen, Regulatory Project Manager Steven Lemery MF Division Director Division of Oncology 3/ Office of Oncologic Products
BLA #	761232
Applicant	BeiGene Inc.
Drug	Tevimbra (tislelizumab-jsgr)
NME	Yes
Therapeutic Classification	Programmed death receptor-1 (PD-1) blocking antibody
Proposed Indication(s)	Treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy
Submission Date	07/12/2021
Consultation Request Date	08/05/2021
Summary Goal Date	05/01/2022
CIS Filed in DARRTs	04/26/2022
Action / PDUFA Date	07/05/2022 Action deferred due to inability to inspect manufacturing and clinical sites in China due to COVID-19 pandemic

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This is an Addendum to the Clinical Inspection Summary (CIS) filed in DARRTs on 04/26/2022.

Clinical data from Study BGB-A317-302 (NCT 03430843) were submitted to the Agency in support of a New Biologics Application (BLA 761232) for tislelizumab for the treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy.

Three clinical investigators, Drs. Shen (Site #086001), Yu (Site #086027), and Zhao (Site #086003), as well as the Sponsor, BeiGene USA, Inc., were selected for clinical inspections. Please refer to the CIS dated April 26, 2022, which detailed the inspection findings for Dr. Shen and the Sponsor. Inspections of Drs. Yu and Zhao had been delayed due to ongoing travel restrictions related to the COVID-19 pandemic in China, however, they were recently completed.

The conducted inspections of Drs. Yu and Zhao did not find significant concerns regarding the oversight of the clinical trial, GCP or regulatory compliance, or the data generated.

Of note, the inspection results of Dr. Zhao (Site #086003) are based on a summary provided by the FDA field. If significantly new or different information is contained in the final FDA Establishment Inspection Report (EIR), another addendum to this clinical inspection summary addendum will be filed.

II. BACKGROUND

The Applicant submitted clinical data from Study BGB-A317-302 to support approval of an indication for tislelizumab for the treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) who progressed on or after prior systemic treatment.

Study BGB-A317-302 is a multicenter, open-label, randomized, controlled, Phase 3 study comparing tislelizumab (BGB-A317) versus investigator's choice chemotherapy (ICC) in adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) who have progressed on or after prior systemic treatment.

The primary objective was to compare the overall survival (OS) in tislelizumab versus Investigator's choice chemotherapy, when given as second-line treatment in patients with advanced unresectable or metastatic ESCC. The primary endpoint is OS, in the intent to treat (ITT) Analysis Set.

The key secondary endpoint is OS in the PD-L1-Positive Analysis Set (PD-L1 expression status of visually estimated Combined Positive Score [vCPS] $\geq$ 10%). Additional secondary endpoints include objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR) between tislelizumab, and investigator's choice chemotherapy (ICC) as assessed by the investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

Subjects were to be randomized 1:1 to receive either tislelizumab or investigator's choice chemotherapy.

- Arm 1, Tislelizumab 200 mg every 3 weeks
- Arm 2, Investigator's Choice Chemotherapy (pembrolizumab, ipilimumab, or dacarbazine) were given on Day 1 of each 3-week cycle:
 - Paclitaxel (135 to 175 mg/m² every 3 weeks starting on Day 1)
 - Docetaxel (75 mg/m² every 3 weeks starting on Day 1)
 - Irinotecan (125 mg/m² on Days 1 and 8, given every 3 weeks)

Treatment was to be continued until disease progression, unacceptable toxicity, or other treatment discontinuation criteria were met. All subjects who discontinued treatment before disease progression were to be followed for disease progression and were to continue to undergo

tumor assessments as scheduled until they began a new anticancer treatment, experienced disease progression, withdrew consent, died, were lost to follow-up, or the study completed.

Subjects were to be followed for survival status beginning approximately 1 month (4 weeks $\pm$ 7 days) after the Safety Follow-up Visit (which was to be conducted within 30 days ($\pm$ 7 days) after the last study treatment) and approximately monthly thereafter or as directed by the sponsor. Information on survival follow-up and the subsequent anticancer treatment was to be collected every month until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor. Imaging assessments for the imaging secondary endpoints were to be performed at screening and then every 6 weeks ($\pm$ 7 days) for 6 months, then every 9 weeks ($\pm$ 7 days) and were to be performed on schedule *regardless* of whether study treatment had been administered or held. Tumor response was to be assessed by the investigator using RECIST v1.1.

This study was conducted at 132 study centers in 11 countries/regions globally. Patients were enrolled in Belgium; France; Germany; Italy; Japan; Korea; Spain; Taiwan, China; the United Kingdom; and the United States (US). A total of 392 subjects were enrolled in Asia/Pacific with 286 subjects enrolled in China. 101 subjects were enrolled in Western Europe. Two subjects were enrolled in the US. The data cutoff for the current submission was December 1, 2020.

Please refer to the initial CIS dated April 26, 2022, for a complete summary of the inspection results for Dr. Shen and the Sponsor. This CIS summarizes the inspection findings for Drs. Yu and Zhao.

III. RESULTS (by site):

1. Dr Xinmin Yu (Site #086027)

No 1 East Banshan Bridge Road, Gongshu District
Hangzhou, Zhejiang, 310022
CHINA

Inspection dates: September 11-15, 2023

Dr. Yu was inspected as a routine PDUFA inspection for Study BGB-A317-302. This was the first FDA inspection of this investigator.

At the time of the inspection, the site had enrolled 15 subjects and the inspection verified source records for all 15 subjects. Documents reviewed include informed consent forms, inclusion/exclusion criteria, adverse events, medical records including medical history, subject visits, concomitant medications, vital signs, laboratory results, imaging and imaging reports/interpretations, physical exams, IP accountability, and protocol deviations. No significant discrepancies were found.

Additional records reviewed during the inspection included, but were not limited to, financial disclosures, FDA Form 1572s, site training, electronic case report forms and audit trails, protocols and amendments, EC approvals, study monitoring reports, and Sponsor

communications. No issues were identified.

Efficacy endpoint assessment consisted of verification of subject's survival status in the source records comparing with the data submitted to the BLA. No discrepancies were found.

Based on the results of the inspection, the study was conducted in accordance with the investigational plan and the data generated at Dr. Yu's site appear acceptable in support of the proposed indication in the BLA.

2. Dr. Kuaile Zhao (Site # 086003)

No. 270 Dongan Road
Shanghai, Shanghai 200032
CHINA

Inspection dates: October 31 – November 3, 2023

The official establishment inspection report (EIR) is pending. The review below is from the summary close out email and communications with the inspector during the inspection. This report will be updated after review of the official EIR, if relevant additional information is included.

Dr. Zhao was inspected as a routine PDUFA inspection for Study BGB-A317-302. This was the first FDA inspection of this investigator.

At the time of the inspection, the site had screened 49 and enrolled and treated 41 subjects in the study. There were 33 subjects who had completed the study and 8 had discontinued from study treatment.

Source records for 12 of 41 subjects enrolled at the site were reviewed and compared with data submitted to the BLA. Records reviewed included informed consent documents, AE and SAE reports, protocol deviations, concomitant medications, and eligibility criteria. No significant discrepancies were found. There was no evidence of under-reporting of AEs or unreported protocol violations. The subjects' survival status for the efficacy endpoint data in the source records were compared with the data submitted to the BLA. No discrepancies were found.

Additional records reviewed during the inspection included, but were not limited to, FDA Form 1572s, site training, protocols and amendments, EC approvals, study monitoring reports and communications, investigational products records, investigational product storage and shipment. No issues were identified.

Based on the results of the inspection, the study was conducted in accordance with the investigational plan and the data generated at Dr. Zhao's site appear acceptable in support of the proposed indication in the BLA.

{ See appended electronic signature page }

Michele Fedowitz, MD
OSI Reviewer and Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Jenn Sellers, MD, PhD
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DARRTS: BLA 761232
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OOP/ DO3/Regulatory Project Manager/Rebecca Cohen

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/

MICHELE B FEDOWITZ
02/05/2024 03:39:37 PM

JENN W SELLERS
02/05/2024 04:02:26 PM

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 Memorandum:	January 19, 2024
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761232
Product Name, Dosage Form, and Strength:	Tevimbra (tislelizumab -jsgr) injection, 100 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	BeiGene, USA Inc.
FDA Received Date:	January 11, 2024
OSE RCM #:	2021-1363-3
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 11, 2024 for Tevimbra. Division of Oncology 3 (DO3) requested that we review the revised container label and carton labeling for Tevimbra (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

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

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

¹ Mahmoud, S. Label and Labeling Review for tislelizumab (BLA 761232). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JAN 5. RCM No.: 2021-1363-2.

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/

SALI MAHMOUD
01/19/2024 03:58:04 PM

ASHLEIGH V LOWERY
01/22/2024 08:50:10 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 Memorandum:	January 5, 2024
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761232
Product Name, Dosage Form, and Strength:	Tevimbra (tislelizumab -jsgr) injection, 100 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	BeiGene, USA Inc.
FDA Received Date:	November 30, 2023
OSE RCM #:	2021-1363-2
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 30, 2023 for Tevimbra. Division of Oncology 3 (DO3) requested that we review the revised container label and carton labeling for Tevimbra (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container label and carton labeling can be improved from a medication error perspective. We provide our recommendations to improve formatting and display required information in Section 3.

3 RECOMMENDATIONS FOR BEIGENE, USA INC.

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

- A. Confirm that expiration date MM/YYYY will use numerical characters only².
- B. To improve readability- add spaces and change dash to "to" in the temperature statement as follows "Refrigerate at 2 °C to 8 °C (36 °F to 46 °F)"
- C. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.²

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

¹ Mahmoud, S. Label and Labeling Review for tislelizumab (BLA 761232). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 DEC 20. RCM No.: 2021-1363.

² [Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers, June 2021](#)

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/

SALI MAHMOUD
01/05/2024 03:44:28 PM

ASHLEIGH V LOWERY
01/05/2024 04:02:36 PM

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: July 15, 2022
Requesting Office or Division: Division of Oncology 3 (DO3)
Application Type and Number: BLA 761232
Product Name and Strength: Tevimbra (tislelizumab) injection, 100 mg/10mL
Applicant/Sponsor Name: BeiGene USA, Inc
OSE RCM #: 2021-1363-1
DMEPA 2 Safety Evaluator: Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader: Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 11, 2022 for Tevimbra. Division of Oncology 3 (DO3) requested that we review the revised container label and carton labeling for Tevimbra (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

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

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

^a Mahmoud, S. Label and Labeling Review for tislelizumab (BLA 761232). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 DEC 20. RCM No.: 2021-1363.

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/

SALI MAHMOUD
07/15/2022 05:12:37 PM

ASHLEIGH V LOWERY
07/18/2022 01:48:02 PM

Clinical Inspection Summary

Date	4/21/2022
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	Lorraine Pelosof MD, Clinical Reviewer Sandra Casek MD, Clinical Team Leader Rebecca Cohen, Regulatory Project Manager Division of Oncology 3 (DO3)
BLA #	761232
Applicant	BeiGene USA Inc.
Drug	Tislelizumab
NME (Yes/No)	Yes
Therapeutic Classification	Programmed death receptor-1 (PD-1) blocking antibody
Proposed Indication	Treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy
Consultation Request Date	08/05/2021
Summary Goal Date	05/01/2022
Action Goal Date	07/08/2022
PDUFA Date	07/08/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study BGB-A317-302 (NCT 03430843) were submitted to the Agency in support of a New Biologics Application (BLA 761232) for tislelizumab (also known as BGB-A317) for the treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy.

Three clinical investigators, Drs Shen (Site 086001), Yu (Site 086027), and Zhao (Site 086003) were selected for clinical inspections as they were top enrolling sites, with Site 086003 as the top enrolling site. The Sponsor, BeiGene USA, Inc., was inspected as it is a new molecular entity. Inspections of Dr. Yu and Zhao, have been delayed due to ongoing travel restrictions related to the COVID-19 pandemic in China. The outstanding inspections will not be completed prior to the PDUFA date and an addendum will be generated when they are completed.

The conducted inspections of Dr. Shen clinical site #086001 and the sponsor did not find significant concerns regarding the management of the clinical trial, GCP compliance, or the data generated.

II. BACKGROUND

BeiGene USA, Inc., seeks approval of Tislelizumab for the proposed indication. In support of the BLA, the Applicant submitted clinical data from Study BGB-A317-302, a multicenter, open-label, randomized, controlled, Phase 3 study in comparing tislelizumab (BGB-A317) versus investigator's choice chemotherapy (ICC) in adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) who progressed on or after prior systemic treatment.

The primary objective is to compare the overall survival (OS) in tislelizumab versus Investigator's choice chemotherapy, when given as second-line treatment in patients with advanced unresectable or metastatic ESCC. The primary endpoint is OS, in the intent to treat (ITT) Analysis Set.

The key secondary endpoint is OS in the PD-L1-Positive Analysis Set (PD-L1 expression status of visually-estimated Combined Positive Score [vCPS] $\geq 10\%$). Additional secondary endpoints include objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR) between tislelizumab and investigator's choice chemotherapy (ICC) as assessed by the investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

Key Inclusion Criteria - Subjects were required to have:

- Histologically confirmed esophageal squamous cell carcinoma (ESCC),
- Tumor progression during or after first-line systemic treatment for advanced unresectable metastatic ESCC,
- At least one measurable lesion according to RECIST v1.1 as determined by local site, investigator within 28 days before randomization,
- ECOG performance status of 0 or 1 at screening.

Key Exclusion Criteria - Subjects could not have:

- Active brain or leptomeningeal metastases,
- Active autoimmune disease,
- Tumor invasion of organs adjacent to the esophageal site,
- A history of prior PD-1 or PD-L1 targeting therapies,
- A condition requiring systemic treatment with either corticosteroids or immunosuppressants.

Subjects were stratified by region (Asia [excluding Japan] versus Japan versus US/EU), ECOG performance status score (0 versus 1), and ICC option (paclitaxel versus docetaxel versus irinotecan).

Subjects were randomized 1:1 to receive either tislelizumab or investigator's choice chemotherapy.

- Arm 1, Tislelizumab 200 mg every 3 weeks

- Arm 2, Investigator's Choice Chemotherapy (pembrolizumab, ipilimumab, or dacarbazine) were given on Day 1 of each 3-week cycle:
 - Paclitaxel (135 to 175 mg/m² every 3 weeks starting on Day 1)
 - Docetaxel (75 mg/m² every 3 weeks starting on Day 1)
 - Irinotecan (125 mg/m² on Days 1 and 8, given every 3 weeks)

Treatment was to be continued until disease progression, unacceptable toxicity, or other treatment discontinuation criteria were met. All subjects who discontinued treatment before disease progression were to be followed for disease progression and were to continue to undergo tumor assessments as scheduled until they began a new anticancer treatment, experienced disease progression, withdrew consent, died, were lost to follow-up, or the study completed.

Subjects were to be followed for survival status beginning approximately 1 month (4 weeks $\pm$ 7 days) after the Safety Follow-up Visit (which was to be conducted within 30 days ($\pm$ 7 days) after the last study treatment) and approximately monthly thereafter or as directed by the sponsor. Information on survival follow-up and the subsequent anticancer treatment was to be collected every month until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor.

Imaging assessments for the imaging secondary endpoints were to be performed at screening and then every 6 weeks ($\pm$ 7 days) for 6 months, then every 9 weeks ($\pm$ 7 days) and required to be performed on schedule regardless of whether study treatment had been administered or held. Tumor response will be assessed by the investigator using RECIST v1.1.

This study was conducted at 132 study centers in 11 countries/regions globally. Patients were enrolled in Belgium; France; Germany; Italy; Japan; Korea; Spain; Taiwan, China; the United Kingdom; and the United States (US). A total of 392 subjects were enrolled in Asia/Pacific with 286 subjects enrolled in China. 101 subjects were enrolled in Western Europe. Two subjects were enrolled in the US.

By the data cutoff, 495 patients were enrolled and randomized in a 1:1 ratio to receive either tislelizumab (Tislelizumab Arm) or the investigator's choice treatment (ICC Arm: choice of paclitaxel, docetaxel, or irinotecan). The data cutoff for the current submission was December 1, 2020.

III. RESULTS

1. Dr. Lin Shen, (Site 086001)

No.52 Fu Cheng Road Haidian District
Beijing, Beijing 100142
CHN Asia/Pacific

Inspection Dates: November 16-19 and 23-24, 2021

This investigator was inspected as an onsite surveillance inspection for Study BGB-A317-302. This was the first FDA inspection for this investigator.

At the time of data cutoff, there were 34 subjects screened and 24 subjects enrolled and treated at the site. Of the 24 subjects enrolled in the study at Dr. Shen's site, 17 subjects completed the study due to radiographic disease progression and seven subjects discontinued due to clinical progression ((b) (6) adverse event (subject (b) (6)), or physician decision (subject (b) (6)). At the time of the inspection, 21 subjects had died and 3 subjects were in survival follow up (Subjects (b) (6)).

The source documents for eligibility were reviewed for all 34 screened subjects. All 24 enrolled subjects were reviewed regarding treatment assignment and efficacy. Twelve subject records were reviewed for adverse events and eight subject records were reviewed for investigational product administration, concomitant medication, and adherence to study procedures (see below). The reviewed subject records included medical records, informed consent, eligibility criteria, concomitant medications and safety evaluations, including assessments of adverse events, serious adverse events, and laboratory parameters. Study related documents were also reviewed including Form FDA 1572s, delegation of responsibilities log, training records, site monitoring log, IRB communications/approvals, investigational test article accountability records, and the site protocol with amendments.

The source records for survival follow-up, subject disposition, and the tumor assessment data used to generate the key secondary endpoints of PFS, ORR, and DOR were reviewed for all subjects by comparison with the data listings. There were no discrepancies, however, it was noted that the survival follow up documentation was not contemporaneous and/or detailed. The follow up consisted of monthly phone calls that were documented later the same day in a progress note. The date was documented, but not the time of the phone call or the contact person providing the information. Additionally, a medical death certificate or any record documenting an attempt to obtain a death certificate was not obtained. The CI explained that death certificates were not requested due to sensitivity and respect for local cultural preferences.

Twelve subject records were reviewed for adverse events (Subjects (b) (6)). Of the records reviewed, there were three subjects with one adverse event each (anemia, leukopenia, and hypokalemia – all grade 1) that were in the source documents but not in the eCRF submitted to the Sponsor.

Subject (treatment assigned)	Adverse Event	Start - end dates	Grade
(b) (6) (Irinotecan)	Anemia	(b) (6)	1
(tislelizumab)	Leukopenia		1
(tislelizumab)	Hypokalemia		1

Reviewer's Comments: The unreported adverse events are minor (grade 1) and do not affect the safety profile of the drug, as they are already known adverse reactions. The lab abnormalities were included in the submission in the data listings for safety monitoring labs.

Eight subject records were reviewed for investigational product administration, concomitant medication, and adherence to study procedures (Subjects (b) (6)). There were 2 instances of concomitant medications (Subject (b) (6)) that were observed in the source documents but were not in the eCRF submitted to the Sponsor.

Subject (Treatment assigned)	Concomitant medications	Start - end dates	Reason for medication
(b) (6) (tislelizumab)	Kang fuxin (Periplaneta Americana, 10ml three times daily)	(b) (6)	Ulcers
(b) (6) (tislelizumab)	Tai Le Ning (Oxycodone: Paracetamol, dose unknown)		Upper abdominal (stomach) pain

Reviewer's Comments: The unreported medications were not prohibited by the protocol. For Subject (b) (6) the medication was given for abdominal pain, a known adverse event, and was reported on 3/1/2020-4/30/2020.

The investigator reported the root cause of the unreported adverse events and concomitant medications was to human error (transcription from source records to eCRF). The clinical investigator's CAPA was acceptable and all unreported adverse events and medications were reported by December 17, 2021.

No unreported protocol deviations were identified.

2. BeiGene USA, Inc. (Sponsor)

2955 Campus Drive, Suite 200
San Mateo, CA 94403

Inspection dates: October 18-22, 2021.

BeiGene USA was inspected as a surveillance inspection for Study BGB-A317-302. This is the fourth FDA inspection for the firm, previous inspections (6/2021, 9/2019, 10/2021) all had a

regulatory classification of NAI.

BeiGene USA is the sponsor for this regulatory submission in the US. BeiGene, Ltd., is located in the Cayman Islands and oversees all global BeiGene operations. The study data is produced by and the clinical sites work under global BeiGene, Ltd. All vendors and CROs have contracts with BeiGene, Ltd. BeiGene, Ltd. has an agreement in place with BeiGene USA to act as sponsor for all USA regulatory submissions and with BeiGene China to act as sponsor for all China regulatory submissions.

Records reviewed included organizational charts and personnel, monitors and site personnel job qualifications, clinical investigators selection and monitoring, standard operating procedures (SOPs), service contractual agreements, transfer of regulatory obligation (TORO) agreements, Quality Assurance (QA), clinicaltrials.gov study submissions, monitoring procedures and monitor visit logs and reports for sites 086001, 086003, 086027, safety/adverse event reporting, data collection management/ electronic records, financial disclosure forms, FDA 1572s, and Investigational Medicinal Product (IMP) integrity and accountability.

Monitoring responsibility was transferred to (b) (4) CRO) and the TORO was reviewed. None of the sites appear to have had investigators with multiple unchecked protocol violations or non-compliance. No significant issues were noted during monitoring visits and protocol deviations were addressed, documented and reported adequately. In general, monitors performed study visits as per the SOPs and monitoring plan.

The sponsor appeared to follow their SOPs and had control of the conduct of the study.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Director
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Division Director/Steve Lemery, MD
Review Division /Project Manager/ Rebecca Cohen
Review Division/Cross Discipline Team Lead/Sandra Casek, MD
Review Division/Clinical Reviewer/ Lorraine Pelosof, MD
OSI/Office Director/Dave Burrow
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/

MICHELE B FEDOWITZ
04/25/2022 09:04:05 AM

KAREN B BLEICH
04/25/2022 09:30:16 AM

KASSA AYALEW
04/26/2022 03:27:24 PM

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

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

Memorandum

Date: April 5, 2022

To: Rebecca Cohen, RN, MPH, OCN, Regulatory Project Manager,
Division of Oncology 3 (DO3)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (tislelizumab-xxxx) injection,
for intravenous use

BLA: 761232

In response to DO3's consult request dated July 16, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG), and carton and container labeling for the original BLA submission for TRADENAME (tislelizumab-xxxx) injection, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Rebecca Cohen) on March 28, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed MG were sent under separate cover on April 4, 2022.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 10, 2021 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

21 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

REBECCA A FALTER
04/05/2022 10:33:44 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: April 4, 2022

To: Rebecca Cohen, RN, MPH, OCN
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)
Rebecca Falter, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TEVIMBRA (tislelizumab-jsgr)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761232

Applicant: BeiGene U.S.A., Inc

1 INTRODUCTION

On July 12, 2021, BeiGene USA, Inc submitted for the Agency's review an original Biologics License Application (BLA) 761232 for TRADENAME (tislelizumab-jsgr) injection. The proposed indication for TRADENAME (tislelizumab-jsgr) is for the treatment of adult patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy.

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 July 16, 2021 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (tislelizumab-jsgr) injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (tislelizumab-jsgr) injection MG received on July 12, 2021, and received by DMPP on July 27, 2021.
- Draft TRADENAME (tislelizumab-jsgr) injection Prescribing Information (PI) received on July 12, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on March 28, 2022.
- JEMPERLI (dostarlimab-gxly) injection approved labeling dated August 17, 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.

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.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/

SHARON R MILLS
04/04/2022 02:39:22 PM

REBECCA A FALTER
04/04/2022 03:13:15 PM

BARBARA A FULLER
04/04/2022 03:18:43 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:	December 20, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761232
Product Name, Dosage Form, and Strength:	tislelizumab injection, 100 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	BeiGene, USA Inc.
FDA Received Date:	July 12, 2021
OSE RCM #:	2021-1363
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for tislelizumab injection, the Division of Oncology 3 (DO3) requested that we review the proposed prescribing information (PI), Medication Guide, 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– N/A
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

We reviewed the proposed PI, medication guide, and container labels and determined that they may be improved to ensure safe product use.

4 CONCLUSION & RECOMMENDATIONS

The proposed PI, medication guide, and container label may be improved to ensure safe product use. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Dosage and Administration Section

- a. We recommend ordering preparation instructions in numerical fashion.

B. Medication Guide

1. Use active, neutral language in the introduction. Delete (b) (4) and change (b) (4) to “side effects.”

4.2 RECOMMENDATIONS FOR BEIGENE, USA INC.

A. Container Label

1. 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 forward slash or a hyphen be used to separate the portions of the expiration date.
2. Change statement (b) (4) to “For Intravenous Infusion After Dilution” for consistency with the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for tislelizumab received on July 12, 2021 from BeiGene, USA Inc..

Table 2. Relevant Product Information for tislelizumab	
Initial Approval Date	NA
Nonproprietary Name	tislelizumab
Indication	Treatment of patients with unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma after prior systemic therapy.
Route of Administration	Intravenous
Dosage Form	injection
Strength	100 mg/10 mL
Dose and Frequency	200 mg as an intravenous infusion once every 3 weeks
How Supplied	100 mg/10 mL (10mg/mL) solution in a single-dose vial.
Storage	Store 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. Do not shake.
Container Closure	20 mm rubber stopper with aluminum flip-off seal

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 29, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, tislelizumab. Our search identified no previous reviews.

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,^a along with postmarket medication error data, we reviewed the following tislelizumab labels and labeling submitted by BeiGene, USA Inc..

- Container label received on July 12, 2021
- Carton labeling received on July 12, 2021
- Prescribing Information (Image not shown) received on July 12, 2021, available from <\\CDSESUB1\evsprod\bla761232\0001\m1\us\draft-labeling-text.doc>
- Medication Guide received on July 12, 2021, available from <\\CDSESUB1\evsprod\bla761232\0001\m1\us\medication-guide.pdf>

G.2 Label and Labeling Images

Container label



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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

/s/

SALI MAHMOUD
12/20/2021 05:53:31 PM

ASHLEIGH V LOWERY
12/22/2021 09:59:33 AM