CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761347Orig1s000

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:	September 3, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761347
Product Name, Dosage Form, and Strength:	Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) Injection, 1,875 mg and 30,000 units/15 mL (125 mg and 2,000 units/mL)
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Genentech Inc.
FDA Received Date:	November 15, 2023 and August 30, 2024
TTT ID #:	2022-2208-2
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Acting Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

As part of the approval process for Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) Injection, the Division of Oncology 2 (DO2) requested that we review the proposed Tecentriq Hybreza Prescribing Information (PI), Medication Guide (MG), container label(s), and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Genentech Inc. previously submitted BLA 761347 on November 15, 2022. Genentech subsequently withdrew the application on August 31, 2023 (b) (4) .[a]

Thus, Genentech Inc. resubmitted BLA 761347 on November 15, 2023.[b]

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761347.

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

3 CONCLUSION

Our evaluation of the proposed Tecentriq Hybreza Prescribing Information (PI), Medication Guide (MG), container label(s), and carton labeling did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

[a] Request for Withdrawal of BLA 761347. South San Francisco (CA): Genentech Inc.; 2023 AUG 31. Available from: \\CDSESUB1\EVSPROD\bla761347\0029\m1\us\cover.pdf

[b] Cover Letter. South San Francisco (CA): Genentech Inc.; 2023 NOV 15. Available from: \\CDSESUB1\EVSPROD\bla761347\0030\m1\us\cover.pdf .

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Tecentriq Hybreza received on August 30, 2024 from Genentech Inc.

Table 2. Relevant Product Information for Tecentriq Hybreza	
Initial Approval Date	N/A
Nonproprietary Name	atezolizumab and hyaluronidase-tqjs
Indication	• Non-small cell lung cancer (NSCLC) • Small-cell lung cancer (SCLC) • Hepatocellular carcinoma (HCC) • Melanoma • Alveolar soft Part Sarcoma (ASPS)
Route of Administration	Subcutaneous Injection (thigh)
Dosage Form	Injection
Strength	1,875 mg and 30,000 units/15 mL (125 mg and 2,000 units/mL)
Dose and Frequency	1,875 mg/30,000 units (1,875 mg atezolizumab and 30,000 units hyaluronidase) administered subcutaneously in the thigh over approximately 7 minutes every 3 weeks.
How Supplied	Carton containing 1 single-dose vial
Storage	Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
Container Closure	20 mL colorless (b) (4) glass vial sealed with a 20 mm rubber stopper and crimped with a 20 mm aluminum seal fitted with a plastic flip-off cap

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Tecentriq Hybreza labels and labeling submitted by Genentech Inc..

- Prescribing Information received on August 30, 2024, available from \\CDSESUB1\EVSPROD\bla761347\0047\m1\us\clean-label-text.docx
- Medication Guide received on August 30, 2024, available from \\CDSESUB1\EVSPROD\bla761347\0047\m1\us\medguide-clean.docx
- Container label(s) received on November 15, 2023
- Carton labeling received on November 15, 2023

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

Container label(s)

(b) (4)

[redacted]

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

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX C. PREVIOUS DMEPA REVIEWS

On August 30, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, Tecentriq Hybreza. Our search identified 2 previous review(s)[d,e] and we considered our previous recommendations to see if they are applicable for this current review.

[d] Stewart, J. Label and Labeling Review for Tecentriq Hybreza (BLA 761347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 AUG 16. TTT ID No.: 2022-2208-1.

[e] Stewart, J. Label and Labeling Review for Tecentriq Hybreza (BLA 761347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 23. TTT ID No.: 2022-2208.

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/s/

JANINE A STEWART
09/03/2024 05:04:03 PM

TINGTING GAO
09/04/2024 12:56:09 PM

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

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

Memorandum

Date: July 23, 2024

To: Jeffrey Ingalls, PharmD, Regulatory Project Manager
Division of Oncology 2 (DO2)

From: Jeena Sun, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for TECENTRIQ HYBREZA™ (atezolizumab and hyaluronidase-tqjs) injection, for subcutaneous use

BLA: 761347

Background:
In response to DO2's consult request dated November 28, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for the original BLA submission for TECENTRIQ HYBREZA™ (atezolizumab and hyaluronidase-tqjs) injection, for subcutaneous use.

PI/Medication Guide
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 12, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on July 22, 2024.

Thank you for your consult. If you have any questions, please contact Jeena Sun at (301) 796-9699 or jeena.sun@fda.hhs.gov.

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/s/

JEENA L SUN
07/23/2024 01:48:44 PM

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:	July 22, 2024
To:	Jeffrey Ingalls, PharmD Regulatory Health Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, WOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jeena Sun, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761347
Applicant:	Genentech, Inc.

1 INTRODUCTION

On November 15, 2023, Genentech, Inc. submitted for the Agency's review a resubmission after withdrawal of their original Biologics License Application (BLA) 761347 for TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection. The proposed indications for TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection are:

Non-Small Cell Lung Cancer (NSCLC)

- as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.
- for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
- in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
- for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ HYBREZA.

Small Cell Lung Cancer (SCLC)

- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Hepatocellular Carcinoma (HCC)

- in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.

Melanoma

- in combination with cobimetinib and vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Alveolar Soft Part Sarcoma (ASPS)

- for the treatment of adult patients with unresectable or metastatic ASPS.

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 II (DO2) on November 28, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection.

2 MATERIAL REVIEWED

- Draft TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection MG received on November 15, 2023, and received by DMPP and OPDP on July 12, 2024.
- Draft TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection Prescribing Information (PI) received on November 15, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 12, 2024.
- Approved TECENTRIQ (atezolizumab) injection, BLA 761034 labeling dated April 22, 2024.
- DMPP-OPDP collaborative review of TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection MG dated August 11, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
07/22/2024 12:47:01 PM

JEENA L SUN
07/22/2024 03:22:16 PM

BARBARA A FULLER
07/22/2024 03:35:52 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:	August 16, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761347
Product Name, Dosage Form, and Strength:	Tecentriq Hybreza (atezolizumab and hyaluronidase-xxxx)[a] Injection, 1,875 mg and 30,000 units/15 mL (125 mg and 2,000 units/mL)
Applicant/Sponsor Name:	Genentech Inc.
TTT ID #:	2022-2208-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 12, 2023 for Tecentriq Hybreza. The Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Tecentriq Hybreza (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b] We note the Applicant responded they intend to have a expiration date format of MM YYYY (e.g.: 05 2025). (b) (4) .

2 CONCLUSION

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

[a] The proposed nonproprietary name has not yet been conditionally accepted. We therefore refer to the proposed product as "atezolizumab and hyaluronidase-xxxx" throughout this review in place of the nonproprietary name for this product.

[b] Stewart, J., Label and Labeling Review for Tecentriq Hybreza (BLA 761347). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 23. TTT ID No.: 2022-2208.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 12, 2023

Container labels

Carton labeling

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/s/

JANINE A STEWART
08/16/2023 03:56:22 PM

ASHLEIGH V LOWERY
08/17/2023 01:52:11 PM

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:	August 11, 2023
To:	Jeffrey Ingalls, PharmD Regulatory Project Manager **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Dvorsky, PharmD Team Leader **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761347
Applicant:	Genentech, Inc.

1 INTRODUCTION

On November 15, 2022, Genentech Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761347 for TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection. The proposed indications for TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection are the following:

Non-Small Cell Lung Cancer

- as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.
- for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
- in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- in combination with paclitaxel protein-bound and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.

Small Cell Lung Cancer

- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Hepatocellular Carcinoma

- in combination with bevacizumab, for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

Melanoma

- in combination with cobimetinib and vemurafenib, for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Alveolar Soft Part Sarcoma

- for the treatment of adults with unresectable or metastatic alveolar soft part sarcoma (ASPS).

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 2 (DO2) on December 30, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection.

2 MATERIAL REVIEWED

- Draft TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection MG received on November 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 31, 2023.
- Draft TECENTRIQ HYBREZA (atezolizumab and hyaluronidase-tqjs) injection Prescribing Information (PI) received on November 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 31, 2023.
- Approved TECENTRIQ (atezolizumab) injection, BLA 761034 labeling dated May 12, 2023.

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)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
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EMILY M DVORSKY
08/11/2023 10:56:06 AM

BARBARA A FULLER
08/11/2023 11:08:07 AM

LASHAWN M GRIFFITHS
08/11/2023 12:25:55 PM

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

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

Memorandum

Date: August 11, 2023

To: Jeffrey Ingalls, PharmD, Regulatory Project Manager, DO2

From: Emily Dvorsky, PharmD, RAC, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for TRADENAME (atezolizumab and hyaluronidase-xxxx) injection, for subcutaneous use

BLA: 761347

Background:

In response to DO2's consult request dated December 30, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA submission for TRADENAME (atezolizumab and hyaluronidase-xxxx) injection, for subcutaneous use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 31, 2023, and our comments are provided below.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on June 12, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at Emily.Dvorsky@fda.hhs.gov.

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/s/

EMILY M DVORSKY
08/11/2023 08:36:54 AM

Clinical Inspection Summary

Date	August 7, 2023
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Katie Chon, Clinical Analyst Satinder (Mona) Choudhary, Clinical Analyst Paz Vellanki, MD, Team Leader Division of Oncology 2 (DO2), Office of Oncology Products
NDA/BLA #	BLA 761347
Applicant	Genentech, Inc.
Drug	Atezolizumab and Hyaluronidase
NME (Yes/No)	No
Therapeutic Classification	Anti-PD-L1 monoclonal antibody; endoglycosidase
Proposed Indication(s)	Atezolizumab Subcutaneous (atezolizumab and hyaluronidase (rHuPH20) co-formulation) for Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Hepatocellular Cancer, Melanoma, and Alveolar Soft Part Sarcoma
Consultation Request Date	January 6th, 2023
Summary Goal Date	August 11, 2023
Action Goal Date	September 13, 2023
PDUFA Date	September 15, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study BP40657 were submitted to the Agency in support of Biologic License Application (BLA 761347) for atezolizumab and hyaluronidase (rHuPH20) for the treatment of patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC), small cell lung cancer, hepatocellular cancer, melanoma, and alveolar soft part sarcoma. Two clinical investigators, Dr. Mehmet Ali Sendur (site #328478), and Dr. Yotsawaj Vajiira Runglodvatana (site # 328384), were inspected.

Despite two protocol deviations at Dr. Runglodvatana's site which did not appear to have significant impact on the safety or efficacy data generated from the site, Study BP40657 appears to have been conducted adequately. The data generated by the inspected clinical investigators and submitted by the Sponsor appear acceptable in support of the proposed indication.

II. BACKGROUND

Genentech Inc. submitted efficacy and safety data from Study BP40657 seeking approval for atezolizumab and hyaluronidase subcutaneous (SC) injection (rHuPH20) for use in the treatment of patients with NSCLC, small cell lung cancer, hepatocellular cancer, melanoma, and alveolar soft part sarcoma.

Study BP40657 (IMscin001) is a two-part, randomized, open-label, multicenter Phase Ib/III study designed to investigate the pharmacokinetics (PK), efficacy, safety, and immunogenicity of subcutaneous (SC) atezolizumab in comparison with intravenous (IV) atezolizumab in patients with previously treated locally advanced or metastatic NSCLC who were cancer immunotherapy (CIT)-naive and for whom prior platinum therapy had failed.

- Part 1 of the study consisted of three single-arm cohorts and determined the dose of atezolizumab SC that yields comparable exposure to atezolizumab IV on the basis of serum C_{trough} at Cycle 1 (pre-dose Cycle 2). Atezolizumab SC co-mix was used for Part 1 (Cohorts 1, 2, and 3). Atezolizumab SC co-mix was prepared from atezolizumab SC drug product and rHuPH20 drug product, which were manually mixed at the clinical sites.

- Part 2 of the study consisted of a two-arm, randomized, multicenter study of atezolizumab SC compared with atezolizumab IV. The aim of Part 2 was to demonstrate non-inferiority of PK exposure of the SC formulation versus the IV formulation. A ready-to-use SC formulation of atezolizumab co-formulated with rHuPH20 (atezolizumab SC) was used in Part 2 and was provided as a sterile liquid at a concentration of 125 mg/mL atezolizumab and 2000 U/mL rhuPH20 with no manual mixing required.

The primary endpoint of BP40657 study was to demonstrate noninferiority of exposure to atezolizumab SC compared with atezolizumab IV. Key secondary efficacy endpoints were objective response rate (ORR) as determined by the investigator according to RECIST v1.1, progression-free survival (PFS), overall survival (OS), and duration of response (DOR)

Safety, efficacy, and PK data from 371 subjects previously treated locally advanced or metastatic NSCLC enrolled in Part 2 of Study BP40657 were submitted to support the proposed indication. Subjects were to sign the informed consent form before any study-specific procedures were to be performed. Serum and plasma samples for PK and ADA were to be obtained on Cycle 1, Day 1, and every cycle thereafter, and upon treatment discontinuation. Patients were to undergo tumor assessments at baseline, every 6 weeks for the first 36 weeks, and every 9 weeks thereafter, until disease progression per RECIST v1.1.

Study BP40657 was ongoing at the time of BLA submission. The first subject was enrolled on December 2, 2020. The data cut-off date for BP40657 was April 26, 2022. Subjects were randomized across 68 clinical sites across 19 countries in East Asia, Eastern Europe, South America, Africa, and New Zealand. The study did not enroll subjects in the US.

Drs. Mehmet Ali Sendur (site #328478), and Yotsawaj Vajiira Runglodvatana (site # 328384), were inspected.

III. RESULTS (by site):

1. **Dr. Mehmet Ali Sendur (Site # 328478)**
   Nahit Ankara City Hospital
   Dumlupnar Bulvar 6001. Cadde No-3
   Cankaya Ankara, 6490
   Turkey

   Inspection dates: June 5 – June 9, 2023

   Dr. Sendur was inspected as a routine PDUFA inspection for Study BP40657. This was the first FDA inspection of this investigator.

   At the time of the inspection, the site screened 44 subjects and enrolled 29 subjects in the study, of which, 5 are still active in the study and receiving study medication; 12 had discontinued due to disease progression, 9 subjects died, and 3 were discontinued due to symptomatic progression.

   Source records for all subjects were reviewed. Records reviewed included, informed consent forms, inclusion and exclusion criteria, pathology reports, EGFR and EML4-mutation status, PD-L1status, previous chemotherapies, genetic testing report, treatment randomization documents, investigational drug dosing, protocol deviations, adverse events reporting, concomitant medications, and subject dispositions. Source records were compared with data listing tables submitted to the BLA.

   The inspection verified that serum and plasma samples were drawn, processed, and shipped according to protocol specified time points and procedures for assessment of primary study endpoint.

   Secondary efficacy variables of tumor response and progression were verifiable by source records and no discrepancies were observed. The inspection verified that all imaging scans were performed at protocol specified timepoints. Tumor measurements at baseline and follow-up scans, disease progression and survival status were verified and found to be consistent with line listings submitted to the BLA.

   As previously communicated to the Division, by email on July 21, 2023, discrepancies concerning disease staging at diagnosis was incorrectly recorded in 2 subjects:
   - Subject SCR# (b) (6): staging at diagnosis was incorrectly reported as IIA, according to source records, the staging at diagnosis was IIIA.
   - Subject SCR# (b) (6)'s staging at diagnosis was incorrectly reported as IIB, according to source record, the staging at diagnosis was IVA.

   Reviewer's comment: The above data entry errors appear to be isolated incidents. It is noted that the errors would not impact the efficacy result because both subjects had confirmed stage IV disease at the time of the study enrollment, as required by protocol.

Additional records reviewed included, but were not limited to, investigational product shipping, dispensing, storage, and accountability records, biological sample collection and storage records, subject and study related correspondence between the sponsor, the site, and the ethics committee. monitoring reports, financial disclosure reports, electronic case report forms, site staff training records and delegation log.

Based on the results of the inspection, data generated at Dr. Sendur's site appear acceptable in support of the proposed indication in the BLA.

2. Dr. Yotsawaj Vajiira Runglodvatana (Site # 328384)
Hospital 681 Samsen Road Dusit
Bangkok, 10300
Thailand

Inspection dates: March 20 thru March 24, 2023

Dr. Runglodvatana was inspected as a routine PDUFA inspection for Study BP40657. This was the first FDA inspection of this investigator.

At the time of the inspection, the site had screened 20 and enrolled 13 subjects in the study. At the time of the data cut-off date, 5 subjects were on active treatment, 5 subjects had died, 1 was transferred to another hospital and 2 subjects were on survival follow-up phase.

Source records for all 13 subjects were reviewed and compared with line listings submitted to the BLA. Records reviewed for informed consent documents, inclusion and exclusion criteria, adverse events reporting, investigational drug administration records, protocol deviations, laboratory reports, and concomitant medications.

Source records verified that serum and plasma samples were collected according to protocol specified time points and procedures and shipped for processing for assessment of primary study PK endpoint.

Secondary efficacy endpoint variables were verifiable by source records. The inspection verified that imaging scans were performed according to the protocol specified timepoints and tumor measurements and assessment by the investigator were consistent with the information contained in the BLA.

As previously communicated to the Division by email on April 20, 2023, the following subjects were enrolled despite having met exclusion criteria:

- Six of 13 subjects (ID # (b) (6)) had positive HBcAb test at screening and were randomized into the study before the results of the HBV DNA test became available. Per inclusion criterion 4.1.1.1.

– 10, subject with HBcAb positive must be followed by a negative HBV DNA test at screening.

Reviewer's comment: Although the subjects were enrolled/randomized before results were available, HBV DNA tests were drawn, and results were reported to be <20 IU/mL for all 6 subjects. There is no evidence of subject harm related to the described protocol deviation. The investigator stated that he misread the criterion requirement regarding the need to wait for HBV DNA test result prior to enrollment. Dr. Runglodvatana provided a corrective action plan that was reviewed and found to be adequate.

- Subject ID # (b) (6) did not meet inclusion criterion 4.1.1.1. – 7, which required a baseline lymphocyte count ≥ 0.5 x 10^9/L (500µ/L). The subject signed informed consent on (b) (6). Baseline (screening) laboratory test on (b) (6) reported an absolute lymphocyte count of 361.24/µL. The subject was enrolled in the study and randomized on the same day to receive atezolizumab IV. Source record indicate that subsequent follow-up absolute lymphocyte count on (b) (6), four days after receiving cycle 1 atezolizumab IV, was 1599/*µL*.

  Reviewer's comment: Although the lymphocyte count at the screening (baseline) was below the eligibility requirement, there was no evidence of subject harm given the normal lymphocyte count in the subsequent follow-up. Dr. Runglodvatana provided a corrective action plan that was reviewed and found to be adequate.

Based on the results of the inspection, the BP40657 study data generated at Dr. Runglodvatana's site appear acceptable in support of the proposed indication in the BLA.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
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Office of Scientific Investigations

CC:

DARRTS: BLA 761347
Review Division /Project Manager/Jeffrey Ingalls and Idara Ojofeitimi (Supervisor)
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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08/07/2023 06:35:32 PM

M E M O R A N D U M

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

DATE: July 27, 2023

TO: Harpreet Singh, MD
Director
Division of Oncology II
Office of Oncologic Diseases
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Division Director
DNDSI/OSIS

SUBJECT: Routine inspection of two clinical sites involved with study BP40657 submitted in support of BLA 761347 (Atezolizumab and recombinant human hyaluronidase).

1. Inspection Summary

OSIS arranged an inspection of the clinical portion of study BP40657 (BLA 761347, Atezolizumab and recombinant human hyaluronidase) conducted at 1. Vajira Hospital, Bangkok, Thailand, and 2. Ankara City Hospital, Ankara, Turkey.

Objectionable conditions were observed and Form FDA 483 was issued to Vajira Hospital. Based on the inspectional observations, exhibits, and Vajira Hospital's response to Form FDA 483, the clinical data from Vajira Hospital are reliable. However, I recommend that the Division of Oncology II should consider excluding Subject (b) (6) from study data analyses because the subject did not meet inclusion criteria for lymphocytes.

No objectionable conditions were observed at Ankara City Hospital. However, based on the review of the establishment inspection report and exhibits, the initial diagnosis stage of cancer for Subjects (b) (6) was reported incorrectly to the Agency. The correct stage of cancer is IIIA and IVB for Subjects (b) (6), respectively. Despite the reporting error, both subjects were still eligible for enrollment based on the review of source documents and eligibility criterion of the

clinical protocol. Therefore, the finding has no impact on the reliability of clinical data from these two subjects and I recommend Subjects (b) (6) to be included in the study data analyses.

2. Inspected Study

BLA 761347

Study Number: BP40657 (IMscin001)
Study Title: "A randomized, multicenter, Phase Ib/III study to investigate the pharmacokinetics, efficacy, and safety of atezolizumab subcutaneous compared with atezolizumab intravenous in patients with previously treated locally advanced or metastatic non-small cell lung cancer."
Dates of study conduct: December 2, 2020 to April 26, 2022.

3. Inspectional Findings

Clinical Site ID #: 328384
Clinical Investigator: Yotsawaj Runglodvatana, MD (FEI # 3025879450)
Clinical site: Vajira Hospital (FEI # 3004545855)
Address: 681 Samsen Road Dusit, Wachira Phayaban, Dusit District Bangkok, 10300, Thailand.

ORA investigator Rebecca T. Davis (OBIMO/DBIMOII) inspected Vajira Hospital, Bangkok, Thailand from March 20 to 24, 2023.

3.1 Previous Inspection

This was the first inspection of Vajira Hospital under the bioavailability/bioequivalence (BA/BE) program.

3.2. Current Inspection

The current inspection included auditing the following items:

-Case report forms.
-Informed consent process.
-Protocol deviations.
-Subject eligibility.
-Subjects records.
-Study staff qualifications and training.
-Laboratory results.
-Independent ethics committee approvals.

-Investigational medicinal products.
-Randomization.
-Adverse events.
-Concomitant medications.

3.3.1. FDA 483 Observations

At the conclusion of the inspection, Investigator Davis observed objectionable conditions and Form FDA 483 was issued to the clinical site. The Form FDA 483 observations (**Attachment-1**), the site's response dated April 12, 2023 (**Attachment-2**), and my evaluation are presented below.

Observation 1 (1): Subject (b) (6) did not meet inclusion criteria # I-7 Adequate hematologic and end-organ function including lymphocyte count ≥ 0.5 X 10^9/L (500/µL). At screening, subject absolute lymphocyte count was 361.24/µL and was enrolled into the clinical study.

OSIS Evaluation of the Finding: The finding is accurate based on the review of evidence collected for Subject (b) (6) with lymphocyte count of 361.24/µL (**Attachment-3**) which is below the lymphocyte count of ≥ 500/µL specified in the inclusion criterion of the clinical protocol (**Attachment-4**). The lymphocyte count of Subject (b) (6) was below the level of lymphocyte count mentioned in the clinical protocol; therefore, the subject did not meet the inclusion criterion for enrollment. However, the principal investigator (PI), Dr. Runglodvatana, enrolled Subject (b) (6) in the study, which is a protocol violation. I recommend that the Division of Oncology II should consider excluding Subject (b) (6) from study data analyses because the subject did not meet all inclusion criteria.

Site's Response: Dr. Runglodvatana acknowledged and responded to the finding. He misread the absolute lymphocyte count, and although the misread value from screening was outside of the normal range, Dr. Runglodvatana considered the value was not clinically significant and he enrolled the subject.

As a proposed corrective action, the site implemented additional review processes on March 1, 2023 (**Attachment-5**) for eligibility assessment of screening participants before randomization and enrollment. The protocol deviation for the subject was documented in the subject records and the protocol deviation was reported to Ethics Committee on March 3, 2023 (**Attachment-6**).

The site's corrective actions are adequate to prevent similar findings in future studies.

Observation 1 (2): Six of 13 subjects were enrolled/randomized into the clinical study without HBV DNA test to confirm undetectable levels for subjects with positive HBcAb. Inclusion criteria # I-10 requires performing HBV DNA test for subjects who have a positive total HBcAb test.

Subject ID	Screened (Date)	Enrolled/ Randomized (Date)	HBcAb Test Result	HBV DNA Test
(b) (6)			Positive	Not Performed
			Positive	Not Performed
			Positive	Not Performed
			Positive	Not Performed
			Positive	Not Performed
			Positive	Not Performed

OSIS Evaluation: The finding is accurate based on the review of inclusion criteria of clinical protocol (**Attachment-4**) which specifically states that during screening if a subject tested positive for hepatitis B core antibody (HBcAb), hepatitis B virus (HBV) DNA test should be performed and tested negative. This finding is a protocol violation. The table in the above observation indicates that HBV DNA test was "Not Performed" for all six subjects tested positive for HBcAb. On the contrary, the evidence collected during the inspection by Investigator Davis shows that HBV DNA test was performed before enrollment for Subjects (b) (6) (**Attachment-7**) and on the day of enrollment for Subjects (b) (6) (**Attachment-8**); however, the results for the HBV DNA test were received after the enrollment date for all six subjects.

Although the finding is a protocol violation, HBV DNA test was performed for all six subjects and their HBV DNA test results were negative for HBV (**Attachment-9**). Therefore, the finding has no impact on the reliability of clinical data from these subjects.

Site's Response: Dr. Runglodvatana acknowledged and responded to the finding. Dr. Runglodvatana stated that there was misinterpretation of the protocol requirements for conducting HBV DNA test. As a proposed corrective action, the site implemented additional review processes on March 1, 2023 (**Attachment-5**) for eligibility assessment of screening participants before randomization and enrollment. The protocol deviation for these subjects was documented in respective subject records and the protocol deviations were reported to Ethics Committee on March 3, 2023 (**Attachment-10**). On March 1, 2023, Clinical Research Associate (CRA) discussed with Dr. Runglodvatana the requirement of conducting and reviewing HBV

DNA test for the subjects positive with HBcAb prior to randomization and enrollment in the study (**Attachment-11**).

The site's corrective actions are adequate to prevent similar findings in future studies.

Observation 1 (3): Review of temperature records during the study noted that on 30-Nov-2022, 16 IMPs were stored at 1.5°C (0.5 Celsius below lower limit) for approximately 30 minutes, which is not within the required temperature storage at 2°-8°C. The IMPs were not quarantined and were administered to six subjects.

LOT NO. 117615-Atezolizumab IV 1200 mg/20 mL (8 IMP Kits)		
Subject ID	**Enrolled/ Randomized (Date)**	**Cycle No. Visit/Infusion Date**
(b) (6)		Cycle 16-18; (b) (6)
		Cycle 21-23
		Cycle 26; (b) (6)
LOT NO. 1170891-Atezolizumab SC 1875 mg/25 mL (8 IMP Kits)		
(b) (6)		Cycle 20-21; (b) (6)
		Cycle 19-21; (b) (6)
		Cycle 15-18;

OSIS Evaluation of the finding: The finding is accurate based on the review of evidence collected during inspection that the investigational medicinal products (IMP) were stored at 1.5°C for 30 minutes below the required storage temperature of 2°-8°C (**Attachment-12**). Although there was a recorded temperature excursion at the lower limit of storage temperature (2°C) (**Attachment-13**), the drug products were stored at colder temperature (1.5°C) for a short period of time (30 minutes). I could not find data to evaluate whether the stability of the IMP was compromised when stored at a lower temperature, but it may be safe to assume that the drug product remains stable when stored for such a short time at 0.5°C colder temperature. Therefore, I believe that the finding has no impact on the reliability of clinical data from affected subjects.

Site's Response: Dr. Runglodvatana acknowledged and responded to the finding. The pharmacist at the site stated that the observed temperature excursion was due to the close contact of temperature data logger to the cooling unit inside the refrigerator and there was no alarm during the temperature excursion. The clinical site received information from sponsor's Pharma Technical Quality Team that the observed temperature excursion had no impact on the stability of drug products by

reviewing the SOP 017470 titled Temperature Excursions Management (**Attachment-14**).

As a proposed corrective action, the site installed a new temperature data logger with alarm notification system on April 24, 2023 (**Attachment-15**) and added CRA and PI to the temperature excursion alarm notification list. On April 5, 2023, the site also implemented a procedure for IMP storage and temperature excursion management (**Attachment-16**).

The site's corrective actions are adequate to prevent similar findings in future studies.

Clinical Site ID #: 328478
Clinical Investigator: Mehmet Ali Nahit Sendur, MD (FEI # 3025881916)
Clinical site: Ankara City Hospital (FEI # 3026311521)
Address: Ankara Sehir Hastanesi Universiteler Mahallesi
Dumlupnar Bulvar 6001, Cadde # 3
Nahit Ankara City
Cankaya Ankara, 6490, Turkey.

ORA investigator Gene R. Gunn (OBIMO/BMFC) inspected Ankara City Hospital, Ankara, Turkey from June 5 to 9, 2023.

3.4. Previous Inspection

This was the first inspection of Ankara City Hospital under the BA/BE program.

3.5. Current Inspection

The current inspection included auditing the following items:

-Case report forms.
-Informed consent process.
-Tumor scans.
-Response Evaluation Criteria in Solid Tumors (RECIST) determinations.
-ECHO and pathology reports.
-Electro cardio grams.
-Laboratory results.
-Protocol deviations.
-Inclusion and exclusion criteria.
-Subject records.
-Randomization.
-Adverse events.
-Training records of study personnel.

-Previous chemotherapies.
-Concomitant medications.
-Independent ethics committee approvals.
-Investigational drug product shipping, dispensing, storage, and accountability records.
-Biological sample collection and storage records.

3.6. Inspectional findings

At the conclusion of the inspection, Investigator Gunn observed no objectionable conditions and no Form FDA 483 was issued to the clinical site. However, he observed that two subjects had initial diagnosis stage of cancer that was not consistent with data reported to the Agency. The finding, site's response during the inspection and my evaluation are presented below.

Finding # 1: The electronic case report form (eCRF) of Subject (b) (6) and Subject (b) (6) had initial diagnosis of cancer with IIA stage and IIB stage, respectively; however, the source records of these subjects indicate that the stage of cancer was IIIA and IVB, respectively.

OSIS Evaluation of the finding: The finding is accurate based on the review of source documents collected from the site for Subjects (b) (6) (**Attachment-17**) and (b) (6) (**Attachment-18**). The source documents indicate the initial diagnosis stage of cancer was IIIA and IVB for Subjects (b) (6), respectively. However, it was incorrectly reported to the Agency as IIA for Subject (b) (6) (**Attachment-19**) and IIB for Subject (b) (6) (**Attachment-20**). Although eCRFs with incorrect information were submitted to the Agency for Subjects (b) (6), subjects were still eligible for enrollment based on the review of source documents and eligibility criterion of the clinical protocol. Therefore, the finding has no impact on the reliability of clinical data from these two subjects and I recommend Subjects (b) (6) to be included in the study data analyses.

Site's Response: Dr. Sendur acknowledged and promised to correct eCRF of Subjects (b) (6) for the initial diagnosis stage of cancer.

The site did not propose any corrective actions during the inspection to prevent similar findings in future studies.

Draft: GM 07/24/2023; 7/27/2023; 7/27/2023
Edit: RCA 07/25/2023, 7/27/2023; AD 07/25/2023, 7/27/2023

OSIS File BE #: 9793

eNSpect Assignment ID: 218928
eNSpect Op IDs: 247325 (Ankara City Hospital)
247326 (Vajira Hospital)

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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:	May 23, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761347
Product Name, Dosage Form, and Strength:	Tecentriq Hybreza (atezolizumab and hyaluronidase-xxxx)[a] Injection, 1,875 mg and 30,000 units/15 mL (125 mg and 2,000 units/mL)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech Inc.
FDA Received Date:	November 15, 2022, February 17, 2023
TTT ID #:	2022-2208
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

[a] The proposed nonproprietary name has not yet been conditionally accepted. We therefore refer to the proposed product as "atezolizumab and hyaluronidase-xxxx" throughout this review in place of the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for Tecentriq Hybreza (atezolizumab and hyaluronidase-xxxx) Injection, the Division of Oncology 2 (DO2) requested that we review the proposed Tecentriq Hybreza prescribing information, 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– N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E– N/A
Labels and Labeling	F

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 performed a risk assessment of the Tecentriq Hybreza container label, carton labeling, PI, and MG to identify areas of vulnerability that may lead to medication errors and other areas of improvement. The MG is acceptable from a medication error perspective. However, we note an instance of lack of continuity of product information between the labeling components, ambiguous administration instructions, and the information for how the product is supplied can be revised for completeness and clarity. Thus, the labeling components can be revised to support the safe and effective use of the product.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Tecentriq Hybreza PI, container label, and carton labeling can be improved to promote the safe and effective use of the product. We provide recommendations for DO2 in Section 4.1 and recommendations for Genentech Inc. in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. It is recommended to revise the phrase [redacted] (b) (4) to read "priming volume", which is the term that many infusion sets are labeled with.

b. The proposed information for how to store a prepared syringe that is not for immediate use appeared can be revised to eliminate redundancy and to improve clarity. Consider revising the section as follows:

Storage of the Syringe

- If the prepared syringe containing TECENTRIQ HYBREZA is not for immediate use, DO NOT attach a SC infusion set. The capped syringe can be stored at ambient temperature [≤25°C (77°F)] in ambient room lighting for up to 8 hours or in the refrigerator [2°C to 8°C (36°F to 46°F)] for up to 72 hours. Do not shake or freeze.
- If the prepared syringe is stored at 2 to 8°C (36°F to 46°F), allow the syringe to reach room temperature prior to administration.

2. How Supplied/Storage and Handling Section

a. Consider revising the information in Section 16 for improved clarity to read as follows:

TRADENAME (atezolizumab and hyaluronidase-xxxx) injection for subcutaneous use is a sterile, preservative-free, and colorless to slightly yellow solution. It is supplied in a carton containing:

- 1,875 mg and 30,000 units/15 mL (125 mg and 2,000 units/mL)in a single-dose vial (NDC 50242-933-01).

Store vials under refrigeration 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.

4.2 RECOMMENDATIONS FOR GENENTECH INC.

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

A. General Comments (Container labels & Carton Labeling)

1. Please replace "TRADENAME" with the conditionally approved proprietary name, "Tecentriq Hybreza" on the container label and carton labeling.

2. 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.
3. Revise the statement that reads (b) (4) to read "For subcutaneous use only". We recommend this revision for greater clarity regarding the route of administration to minimize the risk of confusion between Tecentriq Hybreza and the Tecentriq intravenous formulation.

B. Carton Labeling
1. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tecentriq Hybreza received on November 15, 2022 from Genentech Inc..

Table 2. Relevant Product Information for Tecentriq Hybreza	
Initial Approval Date	N/A
Nonproprietary Name	atezolizumab and hyaluronidase-xxxx
Indication	o Non-small cell lung cancer (NSCLC) o Small-cell lung cancer (SCLC) o Hepatocellular carcinoma (HCC) o Melanoma o Alveolar soft Part Sarcoma (ASPS)
Route of Administration	Subcutaneous Injection (thigh)
Dosage Form	Injection
Strength	1,875 mg and 30,000 units/15 mL (125 mg and 2,000 units/mL)
Dose and Frequency	1,875 mg/30,000 units (1,875 mg atezolizumab and 30,000 units hyaluronidase) administered subcutaneously in the thigh over approximately 7 minutes every 3 weeks.
How Supplied	Carton containing 1 single-dose vial
Storage	Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
Container Closure	20 mL colorless (b) (4) glass vial sealed with a 20 mm rubber stopper and crimped with a 20 mm aluminum seal fitted with a plastic flip-off cap

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Tecentriq Hybreza labels and labeling submitted by Genentech Inc..

- Container label received on November 15, 2022
- Carton labeling received on November 15, 2022
- Prescribing Information with Medication Guide (Image not shown) received on November 15, 2022, available from \\CDSESUB1\EVSPROD\bla761347\0001\m1\us\clean-label-text.docx

F.2 Label and Labeling Images

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

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M E M O R A N D U M

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

DATE: 2/3/2023

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

FROM: Office of Study Integrity and Surveillance (OSIS)

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

RE: BLA 761347

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

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4). The RRA was conducted under the following submission: Non-responsive

The following objectionable conditions were observed:

(b) (4)

After review of the observations, OSIS concluded that data from the reviewed studies were reliable. (OSIS Final Review – (b) (4) RRR).

Site

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

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