

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761041Orig1s000

OTHER REVIEW(S)

PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # BLA 761041
Product Name: Tecentriq® (atezolizumab)

PMC Description: Submit the final report and datasets for clinical trial entitled “A Phase III, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer after Failure with Platinum-Containing Chemotherapy” [OAK (GO28915)].
PMC# 3133-2

PMC Schedule Milestones: Final Report Submission: 03/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Randomized, open-label, multicenter, multinational study of Tecentriq® versus docetaxel in patients with metastatic NSCLC have progressed on or after platinum-based doublet chemotherapy. Follow-up data to further describe safety and efficacy for the benefit-risk assessment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Randomized, open-label, multicenter, multinational study of Tecentriq® versus docetaxel in patients with metastatic NSCLC have progressed on or after platinum-based doublet chemotherapy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, open-label, multicenter, multinational study of Tecentriq® versus docetaxel in patients with metastatic NSCLC have progressed on or after platinum-based doublet chemotherapy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

Other
Follow-up to safety and efficacy of ongoing RCT.

5. Is the PMR/PMC clear, feasible, and appropriate?

6. <https://fda.webex.com/fda/j.php?MTID=m292a22df394929b54ed71c12fc1f98f9>

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 There is not enough existing information to assess these risks
 Information cannot be gained through a different kind of investigation
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

SAKAR M WAHBY
10/12/2016

KATHERINE M FEDENKO
10/13/2016

PMR Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

BLA # BLA 761041
Product Name: Tecentriq® (atezolizumab)

PMR Description: Conduct a randomized trial that will characterize the incidence, severity and response to treatment of Tecentriq® induced immune-mediated adverse reactions, including immune-mediated pneumonitis.
PMR #3133-1

PMR Schedule Milestones: Final Report Submission: 03/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Refractory metastatic non-small cell lung cancer (NSCLC) is a serious and life threatening condition with high unmet medical need. Tecentriq® demonstrated an overall survival (OS) benefit over standard therapy (docetaxel) and thus expeditious access to this agent through traditional approval is critical.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Patients with NSCLC may be at higher risk for immune-mediated pneumonitis as compared to patients with bladder cancer given the anatomic region of the malignancy, other co-morbidities, and prior radiotherapy to the thorax. Updated safety data from the randomized OAK study in refractory NSCLC is necessary to better characterize immune-mediated pneumonitis in this patient population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

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- Pediatric Research Equity Act
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, open-label, multicenter, multinational study of Tecentriq® versus docetaxel in patients with metastatic NSCLC who previously received platinum doublet-based chemotherapy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
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Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

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Nonclinical study, not safety-related (specify)

Other

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Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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PMR/PMC Development Coordinator:

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(signature line for BLAs)

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/s/

SAKAR M WAHBY
10/12/2016

KATHERINE M FEDENKO
10/13/2016

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

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

Memorandum

Date: 10/05/2016

To: Sakar Wahby, PharmD
Regulatory Health Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Tecentriq[®] (atezolizumab) injection, for intravenous use
BLA 761041

Office of Prescription Drug Promotion comments on proposed
prescribing information and medication guide

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) and medication guide (MG) for Tecentriq[®] (atezolizumab) injection, for intravenous use as requested in consult from DOP1 dated February 25, 2016. OPDP's review of the proposed PI is based on the draft PI titled, "10-3-16 Tecentriq FDA revised PI(7).docx" send via electronic mail on October 4, 2016 to OPDP (Nazia Fatima) from DOP1 (Sakar Wahby). OPDP reviewed the draft PI and has no comments at this time. Combined OPDP and DMPP comments on MG were provided on October 4, 2016 under a separate cover.

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NAZIA FATIMA
10/05/2016

**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: October 4, 2016

To: Geoffrey Kim, MD
Director
Division of Oncology Products 1 (DOP1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD, BCPS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): TECENTRIQ (atezolizumab)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761041

Applicant: Genentech, Inc.

1 INTRODUCTION

On November 19, 2015, Genentech, Inc. submitted for the Agency's review the first part of original Biologics License Application (BLA) 761041 for TECENTRIQ (atezolizumab) injection. The Applicant submitted the second and final part of the rolling submission on February 19, 2016. The proposed indication for TECENTRIQ (atezolizumab) injection is for the treatment of patients with metastatic non-small cell lung cancer 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 these aberrations prior to receiving TECENTRIQ.

TECENTRIQ (atezolizumab) injection was originally approved on May 18, 2016 under BLA 761034 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

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 Products 1 (DOP1) on February 25, 2016 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TECENTRIQ (atezolizumab) injection.

2 MATERIAL REVIEWED

- Draft TECENTRIQ (atezolizumab) injection MG received on June 15, 2016, and received by DMPP and OPDP on September 28, 2016.
- Draft TECENTRIQ (atezolizumab) injection Prescribing Information (PI) received on June 15, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 28, 2016.
- Approved TECENTRIQ (atezolizumab) injection labeling dated May 18, 2016.
- Approved OPDIVO (nivolumab) injection comparator labeling dated September 13, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB)

published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- 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/

ROWELL MEDINA
10/04/2016

NAZIA FATIMA
10/04/2016

BARBARA A FULLER
10/04/2016

LASHAWN M GRIFFITHS
10/04/2016

Clinical Inspection Summary

| | |
|-----------------------------------|---|
| Date | September 29, 2016 |
| From | Lauren Iacono-Connors, Reviewer |
| To | Sakar Wahby, Regulatory Project Manager Chana Weinstock, Clinical Reviewer Daniel Suzman, Clinical Reviewer Division of Oncology Products 1 |
| BLA # | 761041 |
| Applicant | Genentech, Inc. |
| Drug | Tecentriq (atezolizumab; MPDL3280A) |
| NME | Yes |
| Therapeutic Classification | Priority |
| Proposed Indication | Treatment of patients with advanced non-small cell lung cancer who have progressed on or after platinum-containing chemotherapy. |
| Consultation Request Date | Original: March 23, 2016 Updated: May 5, 2016 (DOP1 changed protocol for inspection from GO28754 to GO28753, cancelled the original clinical site inspections, and included two new clinical sites plus the sponsor) |
| Summary Goal Date | Original: July 10, 2016 Updated: August 15, 2016 Updated: September 19, 2016 Updated: September 29, 2016 |
| Action Goal Date | Original: August 19, 2016 Updated: October 19, 2016 |
| PDUFA Date | October 19, 2016 |

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study GO28753 was submitted to the Agency in support of BLA 761041. Two clinical sites, Dr. Aleksandra Szczesna, M.D. (Site 258690), Dr. Louis Fehrenbacher, M.D. (Site 258415), and the study sponsor, were selected for audit.

The primary efficacy endpoint, Overall Survival (OS), as reported in the application was verified with the source records generated at the inspected clinical sites. There were some significant deficiencies observed but these should not importantly impact study outcome or subject safety. The data from Study GO28753 submitted to the Agency in support of BLA 761041, appear reliable based on available information.

II. BACKGROUND

Genentech, Inc. seeks approval to market atezolizumab for the treatment of patients with Advanced Non-Small Cell Lung Cancer who have progressed on or after platinum-containing chemotherapy. The key study supporting this application is GO28753. The study enrolled 287 subjects (143 in the docetaxel arm and 144 in the atezolizumab arm) at 61 clinical centers in 13 countries.

Study GO28753: “A Phase II, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of MPDL3280A (Anti-PD-L1 Antibody) compared with Docetaxel in Patients with Non-Small Cell Lung Cancer after Platinum Failure.”

Number of subjects: 287 subjects were enrolled

Number of sites: 61

Number of countries where subjects were enrolled: 13

Study Period:

Study start date/first subject enrolled: August 5, 2013

Last subject enrolled: March 31, 2014

Primary outcome (OS) data cutoff date: May 8, 2015

Primary efficacy endpoint: OS

Sponsor’s interpretation of primary efficacy outcome: Time to event.

Objectives of Inspections:

- a. Verify primary efficacy endpoint of OS.
- b. Verify key secondary efficacy endpoints for a sample of enrolled subjects:
 - Progression Free Survival (PFS) per RECIST 1.1 and modified RECIST)
- c. Identification, documentation, and reporting of AEs for a sample of enrolled subjects.
- d. General compliance with the investigational plan.

III. RESULTS (by site):

| Name of CI, Site #, Address | Protocol # and # of Subjects | Inspection Date | Final Classification |
|---|--|------------------------------------|--|
| CI#1: Dr. Louis Fehrenbacher, M.D. Kaiser Permanente-Vallejo 975 Sereno Drive Vallejo, CA | Protocol: GO28753 Number of Subjects Enrolled: 16 | July 12, 2016 - August 11, 2016 | Pending Interim classification: VAI |
| CI#2: Aleksandra Szczesna, M.D. Mazowieckie Centrum Leczenia Chorob Pluc Reymonta 83/91, 05-400, Otwock, Poland | Protocol: GO28753 Number of Subjects Enrolled: 8 | July 18-21, 2016 | VAI |
| Sponsor: Genentech, Inc. 1 DNA Way, South San Francisco, California 94080 | Protocol: GO28753 | May 23, 2016 - June 1, 2016 | NAI |

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

1. Dr. Louis Fehrenbacher, M.D. (Site 258415)

The inspection reviewed the conduct of one clinical study (GO28753). The site screened 46 subjects and 16 were enrolled. Of the 16 subjects that were enrolled in the study, 13 completed treatment and three subjects did not complete treatment. Of the three subjects that did not complete treatment, one subject decided to withdraw from treatment due to a lower quality of life, and two subjects stopped treatment due to intolerable toxicities. Study records of 32 subjects (16 screen failures and 16 enrolled) were audited. Study source documents/records of 16 enrolled subjects were compared to the eCRF and data listings submitted to BLA 761041, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, and efficacy endpoint verification, as determined by the site investigator. Assessment of study oversight and conduct by Dr. Fehrenbacher included AE reporting practices, test article accountability, and general protocol compliance.

Generally, the investigator's execution of the protocol was found to be satisfactory. The inspection revealed numerous protocol deviations and GCP compliance deficiencies. A review of the AE master list found no significant deficiencies in AE reporting. The efficacy endpoint, OS, was verifiable. There were a number of inspectional observations related to drug accountability record keeping, documentation of vital signs (before, during and after infusions), documentation of infusion start and stop times, concomitant medication documentation, and two AEs where the start times were not clearly documented or were changed in the records without attribution. A summary of the key inspection observations is below.

The site pharmacy was unable to account for 8 IP vials (single dose equivalent). The consignment database showed 8 vials less than the inventory database, suggesting that the number of vials in the shipping container was different from the number of vials listed on the invoice. On April 29, 2014, the site's regional clinical trials research pharmacist discovered the 8-vial IP discrepancy which prompted a thorough investigation. The site could not reconcile the missing vials and reported the IP discrepancy to the sponsor and IRB. The IRB accepted the Corrective and Preventive Action Plan (CAPA) which was implemented in August 2014. This was an isolated incident of failure to maintain adequate records of drug disposition, but does not impact study outcome or subject safety.

For ten of the sixteen enrolled subjects there were a number of recordkeeping discrepancies between hand written source documents and electronic records/eCRFs regarding infusion start and stop times and pre- and post- infusion vital signs. For example, on November 11, 2013, Subject 213027's vital signs were recorded as taken at 1150 on the hand written source document, but the time was recorded as 1325 on the electronic progress note and the eCRF. Also, the 1150 vital signs were not the same as the 1325 vital signs between these source records. In Dr. Fehrenbacher's written response to the Form FDA 483, he explained that vital signs were taken at both 1150 and 1325. However, the vital signs taken at 1150 were recorded as observed on the hand written source document and only the vital signs taken at 1325 were recorded on the electronic medical record progress note source document as the pre-infusion vital signs. Infusion start time was at 1332, immediately following the second vital sign recorded. Pre-infusion times were appropriately and correctly reported on the eCRFs. He stated that all vital sign timepoints and infusion start and stop times should have been clearly captured on the hand written source document. The site conducted additional training of research staff addressing GCP documentation guidelines, including importance of consistent source data on August 23, 2016.

There were nine instances where the start or end dates of concomitant medications were recorded in the hand written source documents but not in the eCRF. Per Dr. Fehrenbacher's written response, those concomitant medications start dates were recorded as "taken prior to study" on the eCRF using the eCRF-provided check box.

The key inspectional observations summarized above are valid regulatory violations but should not importantly impact study outcomes, or have placed subjects at undue risk.

The data from Site 258415, associated with Study GO28753 appear reliable based on available information.

2. Dr. Aleksandra Szczesna, M.D. (Site 258690)

The inspection reviewed the conduct of one clinical study (GO28753). The site screened twelve subjects and eight were randomized. The study records of all enrolled subjects were reviewed. At the time of this inspection, all eight subjects were deceased. Study source documents/records of all subjects were compared to the CRF and data listings submitted to BLA 761041, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, and efficacy endpoint verification, as determined by the site investigator. Assessment of study oversight and conduct by Dr. Szczesna included AE reporting practices, test article accountability, and general protocol compliance.

The investigator's execution of the protocol was found to be adequate. The efficacy endpoint of OS was verified. There was no evidence of under-reporting of AEs. However, one observation was cited on a Form FDA 483, Inspectional Observations, regarding investigational drug disposition records; records were not adequate with respect to dates, quantity, and use by subjects. For example, the IP and diluent lot numbers were not always obtained by the pharmacist, through the subject specific electronic system, prior to IP infusion preparation. This led to the pharmacist preparing IP infusions using IP and diluent Lot Numbers that were not prespecified for use in the subject. While this is a regulatory violation, there was ample evidence in source documents at the site that the three subjects randomized to receive IP, Subjects 207009, 207019 and 207020, received a total of 32 infusions between Jan 2014 and Feb 2015, as specified in source records.

The receipt and inspection of investigational study drug was not always documented contemporaneously. However, there was ample evidence that the IP kits were received at the site, and used for IP infusions. Regarding the disposition of unused IP and diluent, there were not sufficient source records to verify IP and diluent destruction at the site. However, the site did have a note to file, dated July 9, 2014, that states that the IP was destroyed at this site.

The Pharmacy Instructions for Dose Preparation and Administration of MPDL3280A were not followed. Specifically, polyethylene bottles containing 0.9% sodium chloride solution instead of required saline IV bags were used to prepare study medication for infusions without prior Sponsor approval. In addition, the pharmacy used the gravimetric method for preparation of IP infusions prior to sponsor approval. The site reported the IP infusion preparation method used at this site to the sponsor on July 28, 2016. The sponsor has since confirmed that the method was acceptable.

Finally, the diluent lot numbers used in preparation of the IP for infusion were not consistently documented.

In a written response, dated August 10, 2016, to the Form FDA 483, Dr. Szczesna agreed with the observation and provided an explanation of the errors and, where appropriate, corrective/preventative actions. The clinical investigator confirmed that the drug accountability and use inspectional observations were largely pharmacy errors but that cited subjects were appropriately treated with IP.

In all other aspects, the site ran the study reasonably well. For reasons summarized above, the inspectional observations should not importantly impact study outcomes, or have placed subjects at undue risk.

The data from Site 258690, associated with Study GO28753 appear reliable based on available information.

3. Sponsor: Genentech, Inc.

The inspection focused on the sponsor's control, oversight, and management of Study GO28753. Monitoring records were reviewed from 4 clinical sites. Actions taken by the sponsor to bring non-compliant clinical sites into compliance were also assessed. Contract agreements and sponsor responsibility transfer agreements were reviewed as appropriate. Reporting practices for AEs, SAEs, and protocol deviations were reviewed these sites. An additional ten sites were reviewed for their oversight of significant adverse event and fourteen sites for protocol deviations. There were no major issues. Genentech maintained adequate oversight over the study. There was no evidence of under-reporting of AEs/SAEs.

{See appended electronic signature page }

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page }

Susan Thompson, M.D.
Team Leader
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Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm. BLA #761041
DOP1/Division Director/Geoffrey Kim
DOP1/Clinical Team Leader/Sean Khozin
DOP1/Project Manager/Sakar Wahby
DOP1/Medical Officer/Chana Weinstock
DOP1/Medical Officer/Daniel Suzman
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
09/29/2016

SUSAN D THOMPSON
09/30/2016

KASSA AYALEW
09/30/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: July 15, 2016
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: BLA 761041
Product Name and Strength: Tecentriq (atezolizumab) injection, 1200 mg/20 mL
Submission Date: July 8, 2016
Applicant/Sponsor Name: Genentech, Inc.
OSE RCM #: 2016-234-1
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

Division of Oncology Products 1 (DOP1) requested that we review the revised container label and carton labeling for Tecentriq (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 for Tecentriq are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Gao T. Label and Labeling Review for Tecentriq (BLA 761041). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUNE 23. 9 p. OSE RCM No.: 2016-234.

APPENDIX A. LABEL AND LABELING SUBMITTED ON JULY 8, 2016

(b) (4)

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/s/

TINGTING N GAO
07/15/2016

CHI-MING TU
07/15/2016

LABEL AND LABELING REVIEW

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

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

| | |
|---------------------------------------|---|
| Date of This Review: | June 23, 2016 |
| Requesting Office or Division: | Division of Oncology Products 1 (DOP1) |
| Application Type and Number: | BLA 761041 |
| Product Name and Strength: | Tecentriq (atezolizumab) Injection, 1200 mg/20 mL |
| Product Type: | Single ingredient product |
| Rx or OTC: | Rx |
| Applicant/Sponsor Name: | Genentech, Inc. |
| Submission Date: | February 19, 2016 and June 15, 2016 |
| OSE RCM #: | 2016-234 |
| DMEPA Primary Reviewer: | Tingting Gao, PharmD |
| DMEPA Team Leader: | Chi-Ming (Alice) Tu, PharmD |

1 REASON FOR REVIEW

Tecentriq (atezolizumab) injection is currently indicated for the treatment of patients with a locally advanced or metastatic urothelial carcinoma (BLA 761034).

Genentech, Inc. submitted Tecentriq (atezolizumab) injection container labels, carton labeling, and prescribing information (PI) for BLA 761041 with a proposed indication of treatment of patients with locally advanced or metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy.

The Division of Oncology Products 1 (DOP1) requested that we review the submitted container label, carton labeling, and PI for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B – N/A |
| 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 for 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 evaluate the proposed Tecentriq container labels and determine that the container labels can be improved by inserting adequate white space between the NDC number and the proprietary name to improve readability and to minimize information crowding. Additionally, we recommend replacing “Tradename” with the conditionally approved proprietary name, Tecentriq, for all container label and carton labeling.

Additionally, we noted the use of (b)(4) on the container label and carton labeling. We defer to Office of Pharmaceutical Quality (OPQ) for the determination of the appropriate package type term on labels and labeling.

The proposed PI is acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels and carton labeling for Tecentriq may be improved to promote the safe use of the product as described in Section 4.1. However, the proposed PI is acceptable from a medication error perspective, and we have no further recommendations for the proposed PI at this time.

4.1 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of BLA 761041:

- A. General recommendation
 - 1. Replace “Tradename” with the conditionally approved proprietary name, Tecentriq.
- B. Container labels
 - 1. On the principal display panel, ensure there is sufficient white space between the NDC number and the proprietary name to improve readability and to minimize information crowding.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tecentriq that Genentech, Inc. submitted on June 15, 2016.

| Table 2. Relevant Product Information for Tecentriq | |
|--|--|
| Initial Approval Date | May 18, 2016 |
| Active Ingredient | atezolizumab |
| Indication | <p>Current: treatment of patients with locally advanced or metastatic urothelial carcinoma who:</p> <ul style="list-style-type: none"> • have disease progression during or following platinum-containing chemotherapy. • have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. <p>Proposed: Treatment of patients with locally advanced or metastatic non-small cell lung cancer 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 these aberrations prior to receiving TECENTRIQ.</p> |
| Route of Administration | intravenous |
| Dosage Form | Solution for injection |
| Strength | 1200 mg/20 mL (60 mg/mL) |
| Dose and Frequency | Administer 1200 mg as an intravenous infusion over 60 minutes every 3 weeks. |
| How Supplied | single use 20 mL 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 | Consists of a USP/Ph. Eur./JP Type I glass vial sealed with a rubber stopper and crimped with an aluminum seal fitted with a plastic flip-off cap. |

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,¹ along with postmarket medication error data, we reviewed the following Tecentriq labels and labeling submitted by Genentech, Inc. on February 19, 2016 and June 15, 2016.

- Container labels
- Carton labeling
- Prescribing Information, including the Medication Guide

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

G.2 Label and Labeling Images

(b) (4)



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

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/s/

TINGTING N GAO
06/23/2016

CHI-MING TU
06/23/2016

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: May 4, 2016

To: Ni Aye, Khin, M.D., DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Kassa Ayalew, M.D.,M.P.H., Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Thompson, M.D. Team Leader, GCPAB
CDER OSI PM Track
Name of DSI Primary Reviewer (if known)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Medical Officers: Chana Weinstock, MD/ Division of Oncology Products 1 (DOP1)/ Daniel Suzman, MD/ DOP1
Clinical Team Leader: Sean Khozin, MD/ DOP2

From: Sakar Wahby, PharmD, Regulatory Project Manager/DOP1

Subject: Request for Clinical Site Inspections

I. General Information

Application#: BLA 761041

IND#:117296

Applicant/ Applicant contact information (to include phone/email): Genentech Inc./ Nitzan Sternheim, PhD, Regulatory Program Management, (Phone: (650) 270-0754, Email: sternheim.nitzan@gene.com)

Drug Proprietary Name: Tecentriq

Generic Drug Name: atezolizumab

NME or Original BLA: Yes

Application Submission Date: February 19, 2016

Review Priority: Priority

Study Population includes < 17 years of age: No

Is this for Pediatric Exclusivity: No

Proposed New Indication(s): Advanced Non-Small Cell Lung Cancer that has progressed on or after platinum-containing chemotherapy.

PDUFA: October 19, 2016

Action Goal Date: October 19, 2016

Inspection Summary Goal Date: August 15, 2016

OSI/DGCPC Consult
version: 09/12/2013

Reference ID: 3926887

Reference ID: 4006797

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

| Site # (Name,Address, Phone number, email, fax#) | Protocol ID | Number of Subjects | Indication/Primary endpoint and other endpoints for verification |
|---|---|--------------------------|---|
| Dr. Louis Fehrenbacher Kaiser Permanente- Vallejo 975 Sereno Drive Vallejo, CA | Protocol GO28753 – A Phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after platinum failure. | 16 | Indication: Treatment of non-small cell lung cancer after platinum failure. Endpoints: Primary: overall survival Secondary: PFS and ORR as per recist v1.1 criteria, also safety as measured in terms of AE reporting. |

III. Site Selection/Rationale

The review of efficacy for Atezolizumab in the proposed indication, which is for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or after platinum-containing chemotherapy, will be based data from the study POPLAR (GO28753). A total of 287 patients from 61 centers in 13 countries were randomized to either arm in the trial; 143 to Docetaxel and 144 to Atezolizumab. The highest-enrolling site within this primary efficacy analysis population is the site listed above, i.e. Kaiser Permanente in Vallejo, CA. This site enrolled 16 patients, making it the highest-enrolling site to POPLAR.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

Should you require any additional information, please contact *SakarWahby* at 240-402-5364 or *Chana Weinstock* at 240-402-2625

| Site # (Name,Address, Phone number, email, fax#) | Protocol ID | Number of Subjects | Indication/Primary endpoint and other endpoints for verification |
|---|---|--------------------------|---|
| Dr. Aleksandra Szczesna MAZOWIECKIE CENTRUM LECZENIA CHOROB PLUC I GRUZZLICY; ODDZIAŁ III, III Oddział Chorob Pluc z, pododdziałem Onkologicznym; ul. Reymonta 83/91, 05- 400, Otwock, POLAND | Protocol GO28753 – A Phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after platinum failure. | 6 | Indication: Treatment of non-small cell lung cancer after platinum failure. Endpoints: Primary: overall survival Secondary: PFS and ORR as per recist v1.1 criteria, also safety as measured in terms of AE reporting. |

IV. Site Selection/Rationale

The review of safety for Atezolizumab in the proposed indication, which is for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or after platinum-containing chemotherapy, will be based primarily on data from the study POPLAR (GO28753). A total of 287 patients from 61 centers in 13 countries were randomized to either arm in the trial; 143 to Docetaxel and 144 to Atezolizumab.

The site within this primary safety analysis population with the lowest number of treatment-emergent adverse events per subject (2.75 events/subject) is the site listed above, i.e. Mazowieckie Centrum Leczenia Chorob Pluc I Gruzlicy in Otwock, Poland.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Lowest number of treatment-emergent adverse events per subject (in sites enrolling at least 5 patients)

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/s/

SAKAR M WAHBY
05/05/2016

SEAN N KHOZIN
05/05/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

| Application Information | | |
|---|--|---|
| BLA# 761041 | NDA Supplement #: S- N/A BLA Supplement #: S- N/A | Efficacy Supplement Category: N/A <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10) |
| Proprietary Name: Tecentriq™ Established/Proper Name: atezolizumab Dosage Form: Injection Strengths: 1,200 mg/20 mL (60 mg/ mL) | | |
| Applicant: Genentech, Inc. Agent for Applicant (if applicable): N/A | | |
| Date of Application: February 19, 2016 Date of Receipt: February 19, 2016 Date clock started after UN: N/A | | |
| PDUFA/BsUFA Goal Date: October 19, 2016 | | Action Goal Date (if different): August 19, 2016 |
| Filing Date: April 19, 2016 | | Date of Filing Meeting: March 22, 2016 |
| Chemical Classification (original NDAs only) : N/A <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch | | |
| Proposed indication(s)/Proposed change(s): Non-Small Cell Lung Cancer | | |
| Type of Original NDA: N/A AND (if applicable) Type of NDA Supplement: | <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <hr/> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| <i>If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 . | | |

| | |
|--|---|
| Type of BLA | <input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k) |
| If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team | |
| Review Classification: | <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority |
| The application will be a priority review if: | <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher |
| <ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted | |
| Resubmission after withdrawal? <input type="checkbox"/> N/A | Resubmission after refuse to file? <input type="checkbox"/> N/A |
| Part 3 Combination Product? <input type="checkbox"/> | <input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) |
| If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults | |

| | |
|--|--|
| <input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |
|--|--|

Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 117296

| Goal Dates/Product Names/Classification Properties | YES | NO | NA | Comment |
|---|-------------------------------------|--------------------------|----|---------|
| PDUFA/BsUFA and Action Goal dates correct in tracking system? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates. | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Are the established/proper and applicant names correct in tracking system? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |

| | | | | |
|---|---|-------------------------------------|--------------------------|----------------|
| <i>to the supporting IND(s) if not already entered into tracking system.</i> | | | | |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| If yes, explain in comment column. | | | X | |
| If affected by AIP, has OC been notified of the submission? If yes, date notified: | <input type="checkbox"/> | <input type="checkbox"/> | X | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i> | Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required | | | |
| <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i> | Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears | | | |
| <u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf | Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | | | |
| 505(b)(2) (NDAs/NDA Efficacy Supplements only) | YES | NO | NA | Comment |
| Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i> | <input type="checkbox"/> | <input type="checkbox"/> | X | |

| | | | | | | | |
|--|--|-----------|--|--------------------------|-------------------------------------|--------------------------|----------------|
| cover letter, and annotated labeling). If yes , answer the bulleted questions below: | | | | | | | |
| <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | | | | <input type="checkbox"/> | <input type="checkbox"/> | X | |
| <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. | | | | <input type="checkbox"/> | <input type="checkbox"/> | X | |
| <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p> | | | | <input type="checkbox"/> | <input type="checkbox"/> | X | |
| <ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> | | | | <input type="checkbox"/> | <input type="checkbox"/> | X | |
| If yes , please list below: | | | | | | | |
| Application No. | | Drug Name | | Exclusivity Code | | Exclusivity Expiration | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| <p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p> | | | | | | | |
| Exclusivity | | | | YES | NO | NA | Comment |
| Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm | | | | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? | | | | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i> | | | | | | | |
| NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? | | | | <input type="checkbox"/> | <input type="checkbox"/> | | |
| If yes , # years requested: | | | | | | | |
| <i>Note: An applicant can receive exclusivity without requesting it;</i> | | | | | | | |

| | | | | |
|--|-------------------------------------|--------------------------|-------------------------------------|--|
| <i>therefore, requesting exclusivity is not required.</i> | | | | |
| NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

| Format and Content | | | | |
|---|---|--------------------------|--------------------------|--|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | |
| If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format? | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted). | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Index: Does the submission contain an accurate comprehensive index? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | Module 2.3, Module 3, and Module 4 Cross |

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

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|--|-------------------------------------|--------------------------|-------------------------------------|--|
| <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain. | | | | Referenced to the atezolizumab metastatic urothelial carcinoma (mUC) BLA 761034 |
| BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, PMA # P160006 | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | Device: VENTANA PD-L1 (SP142) CDx Assay Device Sponsor: Ventana Medical Systems, Inc. |
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| | | | | |
| Forms and Certifications | | | | |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> | | | | |
| Application Form | YES | NO | NA | Comment |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i> | | | | |
| Are all establishments and their registration numbers listed on the form/attached to the form? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Financial Disclosure | YES | NO | NA | Comment |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> | | | | |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> | | | | |
| Clinical Trials Database | YES | NO | NA | Comment |

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|--|-------------------------------------|--------------------------|-------------------------------------|----------------|
| <p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Debarment Certification | YES | NO | NA | Comment |
| <p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| <p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Controlled Substance/Product with Abuse Potential | YES | NO | NA | Comment |
| <p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i></p> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Pediatrics | YES | NO | NA | Comment |

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| <u>PREA</u> | | | | |
| Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | An agreed iPSP initial agreement letter for waiver of Pediatric Studies was issued on 5/8/2015 |
| If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| <u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | The proposed proprietary name, Tecentriq conditionally acceptable, Granted Letter issued on 3/8/2016 |
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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|--|---|---|---|---|---|--|----------------------------------|--|
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) | <input type="checkbox"/> Patient Package Insert (PPI) | <input type="checkbox"/> Instructions for Use (IFU) | <input checked="" type="checkbox"/> Medication Guide (MedGuide) | <input checked="" type="checkbox"/> Carton labels | <input checked="" type="checkbox"/> Immediate container labels | <input type="checkbox"/> Diluent | <input type="checkbox"/> Other (specify) |
| | YES | NO | NA | Comment | | | | |
| Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | | | | | |
| Is the PI submitted in PLR format? ⁴ | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | | | | | |
| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | | | | |
| For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵ | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | |
| Has a review of the available pregnancy and lactation data been included? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | |
| For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | | | | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | |
| OTC Labeling | <input checked="" type="checkbox"/> Not Applicable | | | | | | | |

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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|---|-------------------------------------|--------------------------|--------------------------|---------------------------|--------------------------|--------------|--------------------------|-----------------------|--------------------------|------------------------------------|--------------------------|------------------|--------------------------|-----------------|--------------------------|-----------------|
| Check all types of labeling submitted. | <input type="checkbox"/> | Outer carton label | <input type="checkbox"/> | Immediate container label | <input type="checkbox"/> | Blister card | <input type="checkbox"/> | Blister backing label | <input type="checkbox"/> | Consumer Information Leaflet (CIL) | <input type="checkbox"/> | Physician sample | <input type="checkbox"/> | Consumer sample | <input type="checkbox"/> | Other (specify) |
| | YES | NO | NA | Comment | | | | | | | | | | | | |
| Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | | |
| Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | |
| If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | |
| All labeling/packaging sent to OSE/DMEPA? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | |
| Other Consults | YES | NO | NA | Comment | | | | | | | | | | | | |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | CDRH DMPP | | | | | | | | | | | | |
| Meeting Minutes/SPAs | YES | NO | NA | Comment | | | | | | | | | | | | |
| End-of Phase 2 meeting(s)? Date(s): October 22, 2013 <i>If yes, distribute minutes before filing meeting</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): November 10, 2015 <i>If yes, distribute minutes before filing meeting</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | | |
| Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | <input type="checkbox"/> | X | | | | | | | | | | | | | | |
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MEMO OF FILING MEETING

DATE: March 22, 2016

BACKGROUND: Genentech, Inc. submitted an original Biologics License Application (BLA 761041) on February 19, 2016, for the use of Tecentriq™ (atezolizumab) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are PD-L1 selected, as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy. BLA 761034 from Genentech, Inc. is still pending with the Agency for the indication of locally advanced or metastatic urothelial carcinoma (mUC). The Action Goal date for BLA 761034 is May 18, 2016.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|---|----------------|--------------------------------------|--|
| Regulatory Project Management | RPM: | Sakar Wahby | Y |
| | CPMS/TL: | Alice Kacuba | N |
| Cross-Discipline Team Leader (CDTL) | Sean Khozin | | Y |
| Division Director/Deputy | Geoffrey Kim | | Y |
| | Amna Ibrahim | | N |
| Office Director/Deputy | Richard Pazdur | | N |
| Clinical | Reviewer: | Chana Weinstock Daniel Suzman | Y Y |
| | TL: | Sean Khozin | Y |
| Social Scientist Review (<i>for OTC products</i>) | Reviewer: | N/A | |
| | TL: | N/A | |
| Clinical Microbiology (<i>for antimicrobial products</i>) | Reviewer: | N/A | |
| | TL: | N/A | |
| Clinical Pharmacology | Reviewer: | Wentao Fu | Y |
| | TL: | Qi Liu | N |
| • Genomics | Reviewer: | Sarah Dorff Rosane Charlab-Orbach | N N |
| • Pharmacometrics | Reviewer: | Chao Liu | N |
| | | Jingyu Yu | N |
| Biostatistics | Reviewer: | Lijun Zhang | Y |
| | TL: | Shenghui Tang | N |

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|--|-----------|-------------------------|---|
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Tiffany Ricks | Y |
| | TL: | Todd Palmby | Y |
| Statistics (carcinogenicity) | Reviewer: | N/A | |
| | TL: | N/A | |
| Product Quality (CMC) Review Team: | ATL: | Joel Welch | N |
| | RBPM: | Andrew Shiber | N |
| • Product Quality | Reviewer: | Xiang Hong (Emily) Jing | Y |
| • Drug Substance | Reviewer: | | |
| • Drug Product | Reviewer: | | |
| • Process | Reviewer: | | |
| • Microbiology | Reviewer: | | |
| • Facility | Reviewer: | Wayne Seifert | N |
| • Biopharmaceutics | Reviewer: | | |
| • Immunogenicity | Reviewer: | | |
| • Labeling (BLAs only) | Reviewer: | | |
| • Other (e.g., Branch Chiefs, EA Reviewer) | | | |
| OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU) | Reviewer: | Rowe Medina | Y |
| | TL: | Barbara Fuller | N |
| OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels) | Reviewer: | Nazia Fatima | N |
| | TL: | Jessica Cleck Derenick | |
| OSE/DMEPA (proprietary name, carton/container labels) | Reviewer: | Tingting Gao | Y |
| | TL: | Chi-Ming (Alice) Tu | N |
| OSE/DRISK (REMS) | Reviewer: | Mona Patel | Y |
| | TL: | Naomi Redd | N |
| OC/OSI/DSC/PMSB (REMS) | Reviewer: | N/A | |
| | TL: | N/A | |

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|----------------------------------|-----------|--|---|
| Bioresearch Monitoring (OSI) | Reviewer: | Lauren Iacono-Connor | Y |
| | TL: | Susan Thompson | N |
| Controlled Substance Staff (CSS) | Reviewer: | N/A | |
| | TL: | N/A | |
| Other reviewers/disciplines | | | |
| CDRH | Reviewer: | Shyam Kalavar | Y |
| | TL: | Eunice Lee | Y |
| Other attendees | | | |
| | | | |
| | | | |
| | | *For additional lines, right click here and select "insert rows below" | |

FILING MEETING DISCUSSION:

| | |
|---|--|
| <p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments |

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|---|--|
| <p>CLINICAL</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: |
| <ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |

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|--|--|
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <p>BIOSTATISTICS</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments: Facility Inspections are cross referenced to BLA 761034 per Product Quality Team</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

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|--|---|
| <p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p> | <p>None</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? | <p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? | <p>CLINICAL- FDA agreed on the Sponsor’s submission of Study GO28915 (OAK) topline data approximately 30 days <u>prior</u> to the PDUFA date (10/19/2016) of the original application.</p> <p>90-Day Safety Update for BIRCH and POPLAR Studies for AESIs and imAEs</p> |
| <ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? Comments: Facility Inspections are cross referenced to BLA 761034 per Product Quality Team | <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |

| REGULATORY PROJECT MANAGEMENT | |
|---|---|
| Signatory Authority: Richard Pazdur, MD | |
| Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): June 9, 2016 | |
| 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): | |
| Comments: | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input checked="" type="checkbox"/> | The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review |
| ACTION ITEMS | |
| <input checked="" type="checkbox"/> | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug). |
| <input type="checkbox"/> | If RTF, notify everyone who already received a consult request, OSE PM, and RBPM |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input checked="" type="checkbox"/> | If priority review, notify applicant in writing by day 60 (see CST for choices) |
| <input checked="" type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input checked="" type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| <input checked="" type="checkbox"/> | Update the PDUFA V DARRTS page (for applications in the Program) |
| <input type="checkbox"/> | Other |

Annual review of template by OND ADRAAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAKAR M WAHBY
03/25/2016

ALICE KACUBA
03/25/2016

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: March 10, 2016

To: Ni Aye, Khin, M.D., DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Kassa Ayalew, M.D.,M.P.H., Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Thompson, M.D. Team Leader, GCPAB
CDER OSI PM Track
Name of DSI Primary Reviewer (if known)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Medical Officers: Chana Weinstock, MD/ Division of Oncology Products 1
(DOP1)/ Daniel Suzman, MD/ DOP1
Clinical Team Leader: Sean Khozin, MD/ DOP2

From: Sakar Wahby, PharmD, Regulatory Project Manager/DOP1

Subject: Request for Clinical Site Inspections

I. General Information

Application#: BLA 761041

IND#:117296

Applicant/ Applicant contact information (to include phone/email): Genentech Inc./ Nitzan Sternheim, PhD, Regulatory Program Management, (Phone: (650) 270-0754, Email: sternheim.nitzan@gene.com)

Drug Proprietary Name: Tecentriq

Generic Drug Name: atezolizumab

NME or Original BLA (Yes/No/Not Applicable*): Yes

Application Submission Date: February 19, 2016

Review Priority (Standard or Priority or Not Applicable*): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

OSI/DGCPC Consult
version: 09/12/2013

Reference ID: 3906951

Reference ID: 4006797

Proposed New Indication(s): Advanced Non-Small Cell Lung Cancer that is PD-L1 selected, as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy.

PDUFA: October 19, 2016

Action Goal Date: August 19, 2016

Inspection Summary Goal Date: July 10, 2016

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

| Site # (Name,Address, Phone number, email, fax#) | Protocol ID | Number of Subjects | Indication/Primary endpoint and other endpoints for verification |
|--|---|--------------------|--|
| Site # 264392 Besse, Benjamin, MD Institut Gustave Roussy Departement Oncologie Medicale 114 Rue Edouard Vaillant Cedex, 94805 Villejuif, France Phone- 33142114322 Fax- 33142115219 benjamin.besse@gustaverou ssy.fr | GO28754 A Phase II, Multicenter, Single-Arm Study of MPDL3280A in Patients with PD-L1-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer. | 24 | High enroller; large number of observed protocol violations overall. Primary endpoint of overall response rate for verification. |
| Site # 263886 Janne, Pasi, M.D. Dana Farber Cancer Institute, 450 Brookline Ave., Boston, MA, 02215, United States Phone- 16176326076 Fax- 16176325786 pjanne@partners.org | GO28754 A Phase II, Multicenter, Single-Arm Study of MPDL3280A in Patients with PD-L1-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer. | 18 | High enroller. Primary endpoint of overall response rate for verification. |

III. Site Selection/Rationale

Rationale for OSI Audits

The review of efficacy for Atezolizumab in the proposed indication, which is for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are PD-L1 selected, as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy, will be based on a small subset of patients from the single-arm study BIRCH (GO28754). Overall, this multi-center, multi-cohort, international, biomarker-enriched, single-arm trial enrolled 667 patients; however, the subgroup to be evaluated for the primary efficacy endpoint is 139 patients. Only 32 of these patients were from the USA, and the highest-enrolling site in the USA will be chosen for inspection since there were 6 patients enrolled from that site in the primary efficacy analysis subset. The investigator who enrolled these 6 patients was Dr. Pasi Janne of Site # 263886, who also enrolled a large number of patients overall onto the greater BIRCH trial (18 patients in total). The next-highest enrolling site in the USA enrolled only 3 patients into the primary efficacy analysis subset, so it was felt that a non-USA, high-enrolling site was needed to ensure good study conduct and compliance overall.

The highest-enrolling sites within the primary efficacy analysis subset of 139 patients were two non-USA sites, both of whom enrolled 7 patients overall. However, the site chosen for inspection- Site # 264392 (Dr. Bess, France)- was responsible for more enrollment into the overall BIRCH protocol than any other investigator, with 24 patients overall enrolled. Additionally, this one site in particular was found to have 22 protocol violations overall in 16 of these patients enrolled in BIRCH, so there is concern with overall conduct of the trial in this site. Additionally, in the primary efficacy analysis population of 139 patients, 4 of the 7 patients enrolled at the site had major protocol violations that were considered procedural, so there is concern that conduct of the study at this site could compromise overall efficacy results.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other - Enrollment of large numbers of study subjects and site specific protocol violations. Additionally, this would be the first approval of this drug in the indication of NSCLC and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *SakarWahby* at 240-402-5364 or *Chana Weinstock* at 240-402-2625.

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/s/

SAKAR M WAHBY
03/23/2016

GEOFFREY S KIM
03/23/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761041

Application Type: Original BLA

Drug Name(s)/Dosage Form(s): Tecentriq™ (atezolizumab) Injection for intravenous use

Applicant: Genentech, Inc.

Receipt Date: February 19, 2016

Goal Date: October 19, 2016

1. Regulatory History and Applicant's Main Proposals

- April 11, 2013, IND 117296 was cleared safe to proceed by the FDA
- January 28, 2015, Breakthrough Therapy Designation was granted for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are PD-L1 selected, as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy
- October 22, 2013, a Type B End-of-Phase 2 Meeting was held to discuss the proposed phase 2 study (Study GO28754), intended to support accelerated approval and the proposed phase 3 study (Study GO28915), intended to support conversion to full approval
- June 26, 2015, a Type B Content & Format Pre-BLA Teleconference was held to discuss the proposed content and format of the planned Non-Small Cell Lung Cancer submission
- November 10, 2015, a Type B Clinical Pre-BLA Meeting was held to discuss the clinical trial results to support the Non-Small Cell Lung Cancer indication

Genentech, Inc. submitted an original Biologics License Application (BLA 761041) for the use of atezolizumab (MPDL3280A) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are PD-L1 selected, as determined by an FDA-approved test, and who have progressed on or after platinum-containing chemotherapy.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

Selected Requirements of Prescribing Information

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 13, 2016. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- NO** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment: *There is no horizontal line separating TOC from the FPI.*

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *There is no white space before each major heading in HL.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Selected Requirements of Prescribing Information

| Heading | Required/Optional |
|---|---|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a BOXED WARNING is in the FPI |
| • Recent Major Changes | Required for only certain changes to PI* |
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state "None.") |
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

N/A

Selected Requirements of Prescribing Information

13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- NO** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**

Comment: *Since this product will have FDA-approved patient labeling (Medication Guide), the statement should read "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"*

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

| |
|---|
| BOXED WARNING |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery") |
| 8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers") |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

SAKAR M WAHBY
03/22/2016

ALICE KACUBA
03/22/2016