CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s000

<u>OTHER REVIEW(S)</u>

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Conduct a clinical trial to evaluate the effect of atezolizumab on thyroid function tests and clincial thyroid disease. Submit the completed report, datasets, and revised labeling

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	05/31/2016
	Study/Clinical trial Completion Date:	08/31/2020
	Final Report Submission Date:	02/28/2021
	Other:	MM/DD/YYYY

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

   This study will provide information concerning the incidence of thyroid function test abnormalities and clinical hypo/hyperthyroidism. Immune-mediated thyroid disease is a known adverse event with this class of drugs and the submission contains preliminary evidence that this is an issue with atezolizumab.

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."

   To accurately describe the incidence, treatment, and outcome of thryoid disease in patients receiving atezolizumab.

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.

(b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☒ 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
- ☐ 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

_____

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

- ☒ 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?

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.*

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(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Conduct "GO29294: A Phase III, Open-label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab Compared with Chemotherapy in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer After Failure with Platinum-containing Chemotherapy" and provide a study report, datasets, and, if appropriate, revised labeling.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	09/12/2014
	Study/Clinical trial Completion Date:	08/31/2017
	Final Report Submission Date:	12/31/2017
	Other:	MM/DD/YYYY

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

   This is a confirmatory, randomized study with a primary endpoint of OS. Atezolizumab will received accelerated approval based on a durable response rate.

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."

   Establish the clinical benefit of atezolizumab in a randomized trial with a primary endpoint of overall survival.

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.

A randomized trial of atezolizumab versus Investigator's choice of chemotherapy in patients with second-line bladder cancer. The primary endpoint is overall survival. It is hoped that this study will establish the clinical benefit of atezolizumab. The accelerate approval of atezolizumab is based on response rate and duration of response in a single arm trial.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

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

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

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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

_____

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

   - ☒ 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?

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.*

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(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # 761034
Product Name: Tecentriq (atezolizumab)

PMR/PMC Description: Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against atezolizumab in the presence of atezolizumab levels that are expected to be present in samples at the time of patient sampling.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

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

   The safety profile observed in clinical studies indicates that the presence of anti-drug antibodies does not appear to be a significant safety issue. The development and implementation of a more sensitive assay for detecting neutralizing anti-drug-antibodies (ADAs) would provide better assessment and characterization of the patients' ADA response to atezolizumab.

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."

   The current methods for detecting neutralizing anti-drug antibody (ADA) are not tolerant to the presence of drug at the levels expected to be in some patients' serum at the time of sampling, leading to a reduced capability of detecting ADA.

   The goal of the study is to develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against atezolizumab in the presence of atezolizumab levels that are expected to be present in samples at the time of patient sampling.

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
     - x☐ 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?
     - x☐ 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

     - x☐ 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.

Development and validation of sensitive and drug tolerant methods to detect binding antibodies and neutralizing antibodies to atezolizumab in patients' serum samples.

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

x☐ 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
x☐ 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)

x☐ Other
develop and validate a method to detect neutralizing antibodies in patient serum to better assess the clinical outcome of atezolizumab

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

x☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
x☐ Are the objectives clear from the description of the PMR/PMC?
x☐ Has the applicant adequately justified the choice of schedule milestone dates?
x☐ 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

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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)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Submit the median duration of response for all patients, all PD-L1 positive patients (IC 2/3), and all PD-L1 negative patients (IC 0/1) who responded to atezolizumab on IMvigor 210. Submit datasets and revised labeling concerning the median duration of response.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	01/06/2014
	Study/Clinical trial Completion Date:	08/31/2016
	Final Report Submission Date:	04/30/2017
	Other:	MM/DD/YYYY

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

   Information concerning the response rate to atezolizumab in patients with urothelial cancer who have received prior platinum-based therapy is included in the current submission. Patient follow up is insufficient to determine the median duration of response. This PMC will include that information.

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."

   To fully characterize patient response to atezolizumab, it is necessary to include the median duration of response in the product label.

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.

IMvigor has already been initiated and the primary analysis is complete. Additional follow up information is needed to obtain the median duration of response.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ 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
- ☐ 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

_____

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

   - ☒ 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?

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.*

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(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # Product Name:	761034/Tecentriq
PMC #1 Description:	Perform supplemental characterization of the MCB to provide additional assurance that the cell bank was [redacted] (b) (4). These data should include the evaluation of [redacted] (b) (4) and analysis with respect to growth characteristics and product quality.

PMC Schedule Milestones:	Final Protocol Submission:		
	Study/Trial Completion:		
	Final Report Submission: By end of Q2 2017		Genentech to provide date
	Other:		

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

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

   - ☐ Need for drug (unmet need/life-threatening condition)
   - ☐ Long-term data needed (e.g., stability data)
   - ☐ Only feasible to conduct post-approval
   - ☐ Improvements to methods
   - ☐ Theoretical concern
   - ☐ Manufacturing process analysis
   - ☒ Other

   Data provided in the BLA suggest atezolizumab MCB [redacted] (b) (4) [redacted] (b) (4) Additional characterization of the MCB will aid in the understanding of [redacted] (b) (4) [redacted] (b) (4).

2. Describe the particular review issue and the goal of the study.

The goal of this PMC study is to further characterize the atezolizumab MCB to [redacted] (b) (4) (b) (4) (b) (4). Understanding the risk of [redacted] (b) (4) (b) (4) will aid in the assessment of [redacted] (b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   - ☐ Dissolution testing
   - ☐ Assay
   - ☐ Sterility
   - ☐ Potency
   - ☐ Product delivery
   - ☐ Drug substance characterization
   - ☐ Intermediates characterization
   - ☐ Impurity characterization
   - ☐ Reformulation
   - ☐ Manufacturing process issues
   - ☒ Other

   Describe the agreed-upon study:

   Perform additional characterization to assure [redacted] (b) (4) of the MCB for atezolizumab. This data should include evaluation of [redacted] (b) (4) with respect to growth characteristics and product quality.

5. To be completed by ONDQA/OBP Manager:

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

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.*

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(signature line for BLAs only)

PMR/PMC Development Template

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

NDA/BLA # 761034
Product Name: TECENTRIQ (atezolizumab)

PMR/PMC Description: A pharmacology study to further characterize the effect of atezolizumab on the immune response

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

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

   To further characterize the effect of atezolizumab on the immune response

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."

   The PMC is to conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate timepoints.

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.

The animal study will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate timepoints.

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)
Study to further characterize the effect of atezolizumab on the immune response
☐ Other

_____

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

☒ 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

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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)

FINAL LABEL AND LABELING REVIEW

Date:	May 3, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad -S Digitally signed by Jibril Abdus-samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S Date: 2016.05.03 15:25:13 -04'00'
Through:	Xianghong Jing, PhD, Product Quality Reviewer Division of Biotechnology Review and Research II Xianghong Jing -S Digitally signed by Xianghong Jing -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xianghong Jing -S 0.9.2342.19200300.100.1.1=2000380094 Date: 2016.05.03 17:58:41 -04'00'
Application:	BLA 761034/0
Product:	Tecentriq (atezolizumab)
Applicant:	Genentech, Inc.
Submission Dates:	January 12; April 20, 2016

Executive Summary:

The container labels and carton labeling for Tecentriq (atezolizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 38/NF 33 December 1, 2015 to April 30, 2016]. Labeling deficiencies were identified and resolved. The container labels and carton labeling submitted on April 20, 2016 are acceptable.

Background and Summary Description:

The Applicant submitted BLA 761034 Tecentriq (atezolizumab) as a rolling submission with the final component submitted on January 12, 2016. Table 1 lists the proposed characteristics of Tecentriq (atezolizumab).

Table 1: Proposed Product Characteristics of Tecentriq (atezolizumab).

Proprietary Name:	Tecentriq
Proper Name:	atezolizumab
Indication:	programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who: • Have disease progression during or following platinum-containing chemotherapy [redacted] (b) (4) • Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (1)
Dose:	1200 mg as an intravenous infusion over 60 minutes every 3 weeks
Route of Administration:	intravenous infusion
Dosage Form:	injection
Strength and Container-Closure:	1200 mg/20 mL in a single-dose vial
Storage and Handling:	Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Materials Reviewed:

- Container Labels
- Carton Labeling

Start of Sponsor Material

(b) (4)

End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label: *This product has a partial label (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label*.

(1) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

(2) The name, address, and license number of manufacturer; *conforms*. *However OBP recommends standard labeling format for Country of Origin*.

OBP Request: Revise "[redacted] (b) (4)" to "Product of Switzerland". This is our current labeling practice utilized when Applicants propose to label the Country of Origin. *Applicant revised as requested*.

(3) The lot number or other lot identification; *conforms*.

(4) The expiration date; *conforms*.

(5) The recommended individual dose, for multiple dose containers; *not applicable*.

(6) The statement: "'Rx only'" for prescription biologicals. *conforms*.

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label; *not applicable because label is a partial label*.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label; *not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label; *not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *insufficient data to support*.

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e). *The Applicant provided photos that illustrate there is adequate visual areas for inspections*.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*. However, we requested revision of the package type-term.

OBP Request: Revise "(b) (4)" to "Single-dose vial." *Applicant revised as requested*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; *conforms*.

I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

K. 21 CFR 201.55 Statement of dosage; *Not applicable as this appears on the carton labeling*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

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II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

b) The name, addresses, and license number of manufacturer; *conforms. However OBP recommends standard labeling format for Country of Origin*.

> OBP Request: Revise "[redacted] (b) (4)" to "Product of Switzerland". This is our current labeling practice utilized when Applicants propose to label the Country of Origin. Applicant revised as requested.

c) The lot number or other lot identification; *conforms*.

d) The expiration date; *conforms*.

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.

f) The number of containers, if more than one; *not applicable*.

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms*.

h) The recommended storage temperature; *conforms*.

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable*.

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

o) The adjuvant, if present; *not applicable*.

p) The source of the product when a factor in safe administration; *not applicable*.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels; *conforms*.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Tecentriq (atezolizumab) is a monoclonal antibody.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *not applicable*.

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

> Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*. *However, we requested revision of the package type-term*.

> OBP Request: Revise "(b) (4)" to "Single-dose vial." Applicant revised as requested.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*. *However the list of ingredients requires revisions.*

OBP Request: Revise the list of inactive ingredients to alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients. For example:

Vial contains in 20 mL: atezolizumab (1200 mg), glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg) and sucrose (821.6 mg).

Note deletion of the trailing zeros (62.0 mg to 62 mg and 8.0 mg to 8 mg).

Conclusions:

The container labels and carton labeling for Tecentriq (atezolizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 38/NF 33 December 1, 2015 to April 30, 2016]. Labeling deficiencies were identified and resolved. The container labels and carton labeling submitted on April 20, 2016 are acceptable (see below).

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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:	April 27, 2016
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761034
Product Name and Strength:	Tecentriq (atezolizumab) injection, 60 mg/mL
Submission Date:	April 20, 2016
Applicant/Sponsor Name:	Genentech, Inc.
OSE RCM #:	2015-2684-1
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 761034). 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 MAR 22. 6 p. OSE RCM No.: 2015-2684.

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/s/

TINGTING N GAO
04/27/2016

CHI-MING TU
04/27/2016

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

****Pre-decisional Agency Information

Memorandum

Date: 04/20/2016

To: Kim J. Robertson
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products

From: Nazia Fatima, Pharm.D, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: Tecentriq (atezolizumab)
BLA 761034

Office of Prescription Drug Promotion Comments on proposed labeling (PI), Medication Guide (MG) and Carton/Container Labeling

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Office of Prescription Drug Promotion (OPDP) has reviewed the package insert (PI), Medication Guide (MG) and the Carton/Container Labeling for Tecentriq (atezolizumab) intravenous infusion as requested in consult from Division of Oncology Products (DOP1) dated January 19, 2016.

OPDP's review of the proposed PI is based on the substantially completed draft labeling titled, "Proposed Tecentriq (atezolizumab) USPI-complementary_4.19.2016" send via electronic mail (link to the share drive) on April 19, 2016 to OPDP (Nazia Fatima) from DOP1 (Kim Robertson). OPDP's comments are provided directly on the marked-up version of the label attached below. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed medication guide were provided under a separate cover and entered in DARRTs on 4/19/2016. OPDP has reviewed the Carton/Container Labeling titled, "Tecentriq draft-carton-container-labels" accessed via link to the share drive and has no comments.

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
04/20/2016

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:	April 19, 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 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 761034
Applicant:	Genentech, Inc.

1 INTRODUCTION

On October 23, 2015, Genentech, Inc. submitted for the Agency's review initial portions of original Biologics License Application (BLA) 761034 TECENTRIQ (atezolizumab) injection. The Applicant submitted the final portion of the rolling submission on January 12, 2016. The proposed indication for TECENTRIQ (atezolizumab) injection is for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy (b) (4)
- 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 January 15, 2016 and January 19, 2016, respectively, 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 January 12, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 13, 2016.
- Draft TECENTRIQ (atezolizumab) injection Prescribing Information (PI) received on January 12, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 13, 2016.
- Approved KEYTRUDA (pembrolizumab) injection comparator labeling dated December 18, 2015.

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 have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
04/19/2016

NAZIA FATIMA
04/19/2016

BARBARA A FULLER
04/19/2016

LASHAWN M GRIFFITHS
04/19/2016

Clinical Inspection Summary

Date	March 31, 2016
From	Lauren Iacono-Connors, Reviewer
To	Kim Robertson, Regulatory Project Manager Yangmin (Max) Ning, Clinical Reviewer Division of Oncology Products 1
BLA #	761034
Applicant	Hoffmann-La Roche, Inc./Genentech, Inc.
Drug	Tencentriq (atezolizumab)
NME	Yes
Therapeutic Classification	Priority
Proposed Indication	Treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) [redacted]
Consultation Request Date	January 27, 2016
Summary Goal Date	April 16, 2016
Action Goal Date	May 18, 2016
PDUFA Date	September 12, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study IMvigor210 (GO29293) was submitted to the Agency in support of BLA 761034. Three clinical sites, Dr. Jonathan Rosenberg, M.D. (Site 268278), Dr. Ani Balmanoukian, M.D. (Site 268794), Dr. Richard Joseph, M.D. (Site 268646), and the study sponsor were selected for audit.

The primary efficacy endpoint is Objective Response Rate (ORR), the proportion of subjects that had an objective response. Objective Response, as determined by the clinical investigators, per Modified RECIST, was verified for a subset of study subjects. There were no significant deficiencies.

There were no significant inspectional findings for clinical investigators Dr. Jonathan Rosenberg, M.D., Dr. Ani Balmanoukian, M.D., Dr. Richard Joseph, M.D., and the study sponsor Genentech. The data from IMvigor210 (GO29293) submitted to the Agency in support of BLA 761034, appear reliable based on available information.

II. BACKGROUND

Hoffmann-La Roche, Inc./Genentech, Inc. seeks approval to market Tencentriq (atezolizumab) for the treatment of patients with locally advanced or metastatic urothelial carcinoma (b) (4) [redacted] Study IMvigor210 (GO29293), the key study supporting this application, enrolled a total of 438 subjects into one of two cohorts; Cohort 1 (cisplatin-ineligible treatment-naïve) and 311 patients in Cohort 2 (previously treated with platinum-containing chemotherapy). Relevant to the proposed indication are those subjects enrolled into Cohort 2 in the current submission.

Study GO29293: "A Phase II, Multicenter, Single-arm Study of Atezolizumab in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer."

Number of subjects: 311 subjects were enrolled into Cohort 2
Number of sites: 62
Number of countries where subjects were enrolled: 8
Study Period:

- Study start date: May 2014
- Data cut-off date: May 5, 2015 [BIMO Datalistings]
- Primary efficacy endpoint:
  - (1) Independent review facility (IRF)-assessed objective response (OR; defined as a confirmed partial response (PR) or complete response (CR)) per RECIST v1.1 and
  - (2) Investigator-assessed OR per modified RECIST (immune-related criteria). Modified RECIST outcomes incorporate the measurement of new lesions.
- Sponsor's interpretation of primary efficacy outcome: The OR Rate (ORR), the proportion of patients whose confirmed best overall response is either a PR or a CR.

Objectives of Inspections:

a. Verify primary efficacy endpoint of OR, as determined by the clinical investigator, for a sample of enrolled subjects.
b. Verify secondary efficacy endpoint, progression-free survival (PFS) and duration of response (DOR) according to RECIST v1.1 as assessed by the clinical investigator, for a sample of enrolled subjects.
c. Identification, documentation, and reporting of AEs for all enrolled subjects.
d. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Jonathan Rosenberg, M.D. Memorial Sloan-Kettering Cancer Center 1275 York Avenue, Box 344 New York, NY 10065	Protocol: IMvigor210 (GO29293) Site Number: 268278 Number of Subjects Enrolled: 30	March 10-15, 2016	Pending Interim classification: NAI
CI#2: Ani Balmanoukian, M.D. The Angeles Clinic and Research Institute – W. LA Office 11818 Wilshire Blvd., Suite 200 Los Angeles CA 90025	Protocol: IMvigor210 (GO29293) Site Number: 268794 Number of Subjects Enrolled: 12	March 22-24, 2016	Pending Interim classification: NAI
CI#3: Richard Joseph, M.D. Mayo Clinic Cancer Center 4500 San Pablo Road Jacksonville FL 32224	Protocol: IMvigor210 (GO29293) Site Number: 268646 Number of Subjects Enrolled: 12	February 23-29, 2016	Pending Interim classification: VAI
Sponsor: Hoffmann-La Roche, Inc./Genentech, Inc. 1 DNA Way South San Francisco, California 94080-499	Protocol: IMvigor210 (GO29293) Number of Sites: 26	March 9-16, 2016	Pending Interim classification: 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. Jonathan Rosenberg, M.D. (Site 268278)

This inspection was performed as a data audit for BLA #761034. The inspection reviewed the conduct of one clinical study (IMvigor210 (GO29293)). The site screened 42 subjects and 30 were enrolled. At the time of this inspection no subjects had completed the study; seven remain on study treatment, and 20 subjects have died. Study source documents/records of 30 enrolled subjects were compared to the eCRF and data listings submitted to BLA 761034, 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. Rosenberg included AE reporting practices, test article accountability, and general protocol compliance.

The inspection found no significant deficiencies. The efficacy endpoint, as determined by the investigator, and OS, was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 268278, associated with Study IMvigor210 (GO29293), submitted to the Agency in support of BLA 761034, appear reliable based on available information.

2. Dr. Ani Balmanoukian, M.D. (Site 268794)

This inspection was performed as a data audit for BLA #761034. The inspection reviewed the conduct of one clinical study (IMvigor210 (GO29293)). The site screened 13 subjects and 12 were enrolled and treated. At the time of this inspection no subjects had completed the study. One subject remains on study treatment and one subject (1165) went into follow up prior to study completion. Subject 1165 was treated with investigational product from September 2014 until September 2015 when the subject voluntarily withdrew from the study to return to their home in (b) (6) . The site remains in contact with Subject 1165 and their local oncologist to collect follow up information. Ten subjects have died due to progressive disease. Study source documents/records of all enrolled subjects were compared to the eCRF and data listings submitted to BLA 761034, focusing on informed consent, protocol procedure compliance, and adverse events. Assessment of study oversight and conduct by Dr. Balmanoukian included IRB approvals, AE reporting practices, test article accountability, and general protocol compliance.

The inspection found no significant deficiencies. The efficacy endpoint, as determined by the investigator, and OS, was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 268794, associated with Study IMvigor210 (GO29293), submitted to the Agency in support of BLA 761034, appear reliable based on available information.

3. Dr. Richard Joseph, M.D. (Site 268646)

This inspection was performed as a data audit for BLA #761034. The inspection reviewed the conduct of one clinical study (IMvigor210 (GO29293)). The site screened 20 subjects and 12 were enrolled. At the time of this inspection five subjects had completed the study and are in follow up. Six subjects have died due to progressive disease and one subject was discontinued due to treatment noncompliance. Specifically, this subject was off treatment for more than 42 days due to adverse events, and therefore was discontinued. Study source documents/records of 10 enrolled subjects were compared to the eCRF and data listings submitted to BLA 761034, 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. Joseph included AE reporting practices, test article accountability, and general protocol compliance.

The efficacy endpoint data, OR, as determined by the investigator, and OS, was verifiable. There was no evidence of under-reporting of AEs. The inspection found no significant deficiencies. However, there were several protocol compliance observations. For example, Subject 1132 was enrolled into the study and received investigational product prior to a screening MRI/CT brain scan to rule out CNS metastasis, an exclusion criteria. Subject 1153 was enrolled into the study prior to confirmation of adequate organ function. Pre- and post- infusion vital signs were not always completed per protocol. For example, Subject 1176 did not have post-infusion vital signs taken at treatment Cycle 13. There were several laboratory assessments missed during study conduct. Such as, Subject 1132 had no urinalysis at treatment Cycle 3 Day 1 or at the end of treatment.

The inspectional observations summarized above represent exceptions to the overall conduct of the study at this site and should not importantly impact study outcomes, or have placed subjects at undue risk. The data from Site 268646, associated with Study IMvigor210 (GO29293), submitted to the Agency in support of BLA 761034, appear reliable based on available information.

4. Sponsor: Hoffmann-La Roche, Inc./Genentech, Inc. [Genentech]

This sponsor inspection assignment was issued to review the conduct of one clinical study (IMvigor210 (GO29293)), performed in support of BLA 761034. The inspection focused on the sponsor's control, oversight and management of Study IMvigor210 (GO29293). Monitoring records were reviewed from 26 clinical sites. Actions taken by the sponsor to bring non-compliant clinical sites into compliance were also assessed. All contract agreements and sponsor responsibility transfer agreements were reviewed as appropriate. Reporting practices for AEs and SAEs were also reviewed.

Genentech maintained adequate oversight over the study. There was no evidence of under-reporting of AEs/SAEs. The primary efficacy endpoint, ORR, was a derived

efficacy outcome measure, based upon tumor response per RECIST1.1 as determined by an Independent Radiology Review, CRO (b) (4). Compliance with the investigational plan appeared to be adequate. Monitoring appeared adequate.

The data from this sponsor submitted to the Agency associated with Study IMvigor210 (GO29293) submitted to the Agency in support of BLA 761034, appear reliable based on available information.

{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:

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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
03/31/2016

KASSA AYALEW
03/31/2016

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	761034
Brand Name	Tecentriq®
Generic Name	Atezolizumab (injection, solution)
Sponsor	Genentech, Inc.
Indication	Treatment of locally advanced or metastatic urothelial carcinoma (mUC) (b) (4)
Dosage Form	Liquid Single-Use Vial
Drug Class	Programmed death-ligand 1 (PD-L1) blocking antibody
Therapeutic Dosing Regimen	1200 mg/20 mL (60 mg/mL) intravenous infusion over 60 minutes every 3 weeks (q3w)
Duration of Therapeutic Use	Acute or chronic depending on treatment outcome
Maximum Tolerated Dose	MTD has not been reached, highest dose administered 20 mg/kg q3w
Submission Number and Date	002 / 1/12/2016 (Kim Robertson)
Review Division	DOP1

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 Overall Summary of Findings

Atezolizumab as a large targeted protein has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical data to suggest that atezolizumab has the potential to delay ventricular repolarization.

In this open-label, phase Ia study, a total of 417 patients was dosed with atezolizumab at 10 mg/kg (n=29), 15 mg/kg (n=227), 20 mg/kg (n=129) and 1200 mg (n=32). The 1200 mg q3w dosing is considered to represent a fixed dose equivalent of 15 mg/kg q3w dosing. But, in this particular study the exposures due to 1200 mg q3w dosing were

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closer to 20 mg/kg than 15 mg/kg q3w dosing. There was no clinically important difference in clearance of atezolizumab with renal impairment or mild hepatic impairment. There is no data available for exposure changes in patients with moderate or severe hepatic impairment. Given that the clearance pathway for monoclonal antibodies is through proteolytic degradation, it is less likely that hepatic impairment and drug-drug interaction would lead to considerable increases in drug exposure.

2 PROPOSED LABEL

No labeling information is included by the Applicant in the currently submitted label.

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Atezolizumab is an Fc-engineered, humanized immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumor immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in an increased frequency of activated cytotoxic T cells and decreased tumor growth.

3.2 MARKET APPROVAL STATUS

Atezolizumab is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of atezolizumab's clinical pharmacology.

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4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT previously reviewed the QT waiver request for this product under IND (b) (4) and agreed that adequate QT assessment has been conducted. The sponsor submitted the study report 1066934 and data from the study PCD4989g, including electronic datasets and waveforms to the ECG warehouse.

4.1 QT STUDY

4.1.1 Title

Concentration-QTc Analysis for Atezolizumab Based on Data from study PCD4989g (GO27831)

4.1.2 Protocol Number

1066934 - Concentration QT study report

4.1.3 Study Dates

Cutoff date: 12/ 02/2014.

4.1.4 Objectives

To construct a quantitative model describing the relationship, if any, between observed atezolizumab concentrations and the change from baseline QTc interval (ΔQTc) in study PCD4989g.

4.1.5 Study Description

4.1.5.1 Design

This is an open-label, Phase Ia study of atezolizumab designed to assess the safety, tolerability, pharmacokinetics, immunogenicity, exploratory pharmacodynamics, and preliminary evidence of biologic activity in patients with locally advanced or metastatic solid tumors or hematologic malignancies. The collection of 12-lead ECGs in triplicate via digital capture at specified time points that were matched with pharmacokinetic (PK) sample collection in the dose expansion cohorts of the PCD4989g study allow for an evaluation of the relationship between atezolizumab exposure and changes in QT/QTc interval.

4.1.5.2 Controls

Neither placebo nor positive (moxifloxacin) control was included.

4.1.5.3 Blinding

The treatment administrated in an open-label manner.

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4.1.6 Treatment Regimen

4.1.6.1 Treatment Arms

Atezolizumab was administered at doses of 10 mg/kg, 15 mg/kg, or 20 mg/kg or at 1200 mg (fixed dose equivalent of 15 mg/kg) as a single agent by i.v. infusion to patients once every three weeks (21 [±2] days).

4.1.6.2 Sponsor's Justification for Doses

The evaluation of the concentration- QT/QTc interval relationship included ECG-PK measurements from patients receiving atezolizumab every 3 weeks at doses of 10 mg/kg, 15 mg/kg, 20 mg/kg or 1200 mg; the 1200 mg dose level is the fixed dose equivalent of 15 mg/kg, and this is the dose level investigated in Phase II studies including PCD4989g in urothelial bladder cancer and PCD4989g in non-small cell lung cancer, respectively.

Therefore, the range of dose levels entered into this investigation includes the 1200 mg Phase II dose, and the highest dose level of 20 mg/kg included in this investigation exceeds the Phase II dose. Accordingly, the Cycle 1 Cmax 30 minute concentration for the 1200 mg dose of 455 µg/mL was in between the Cycle 1 Cmax 30 minute concentrations for the 15 mg/kg (344 µg/mL) and 20 mg/kg (491 µg/mL) dose levels, respectively. No time-matched PK-ΔQTcF observations at Cmax 30 minutes after end of infusion in Cycle 4 were collected for the 1200 mg dose cohort. However, as described above, the available Cycle 4 Cmax 30 minute concentration data obtained up to the 20 mg/kg is expected to surpass the Cycle 4 Cmax 30 minute concentration following administration of 1200 mg atezolizumab.

Based on the final model the predicted QTcF interval prolongation (upper bound of two-sided 90% CI) at the Cycle 4 Cmax 30 minute concentration after 10 mg/kg, 15 mg/kg and 20 mg/kg dosing was 0.71 (1.75), 1.14 (2.33) and 2.57 (4.68) milliseconds, respectively. Thus, the upper bound of the 90% CI of the predicted QTc interval prolongation is well below the threshold of regulatory concern of 10 milliseconds for the 10 mg/kg, 15 mg/kg and 20 mg/kg dosing cohorts.

Reviewer's Comment: The exposures (C_{max}) with highest studied dose of 20 mg/kg cover the range of exposures (C_{max}) expected with the therapeutic dose of 1200 mg q3w. There was no significant concentration-QT relationship with the dose ranging design upto a maximum dose of 20 mg/kg and thus the ΔQTcF changes expected with concentrations produced by 1200 mg q3w dosing will not be clinically meaningful. There was no clinically important difference in clearance of atezolizumab with renal impairment or mild hepatic impairment. There is no data available for exposure changes expected in patients with moderate or severe hepatic impairment. Also no drug-drug interaction studies were carried out to explore these scenarios as potential high clinical exposure scenario.

4.1.6.3 Instructions with Regard to Meals

Reviewer's Comment: Acceptable. Atezolizumab is administered as an i.v. infusion. Food is not expected to affect atezolizumab's exposure.

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4.1.6.4 ECG and PK Assessments

Digitized 12-lead ECGs were collected in triplicate for patients enrolled in the dose-expansion cohorts at screening, 30 (± 15) minutes before and after end of infusion on Day 1 of Cycle 1, 30 (± 15) minutes before and after end of infusion on Day 1 of Cycle 4, and at the treatment discontinuation visit not more than 30 days after the last atezolizumab dose was received. Concurrent PK samples for the assessment of atezolizumab serum concentrations were obtained at the same nominal time points (except for the screening assessment), i.e., predose and 30 (± 10) minutes after end of atezolizumab infusion on Day 1 of Cycle 1, predose and 30 (± 10) minutes after end of atezolizumab infusion on Day 1 of Cycle 4, and at the treatment discontinuation visit.

Reviewer's Comment: Since the drug has long half-life, *the timing of ECGs is adequate to capture potential effects near T_{max}. There are no ECG measurements to capture potential delayed effects (although being a mAb, atezolizumab is not expected to interact directly with hERG channel).*

4.1.6.5 Baseline

The Applicant used the individual pre-dose QTc value on Cycle 1 Day 1 as the baseline.

4.1.7 Sponsor's Results

4.1.7.1 Study Subjects

A total of 811 ΔQTcF, 858 ΔQTcB and 593 ΔRR observations with time matched PK samples from 417 patients exposed to atezolizumab were included in the analysis set. The subsequent analysis was performed on QTcF because QTcF minimized the effect of heart rate on the estimation of QTc interval prolongation.

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Table 4 Number of patients with time-matched ECG parameters and PK samples by cohort, nominal time point and ECG parameter (Study PCD4989g).

Cohort	Nominal time point	Number of patients		
		ΔQTcF	ΔQTcB	ΔRR
10 mg/kg	30 min after end of infusion on Day 1 Cycle 1	26	26	4
	30 min before infusion on Day 1 Cycle 4	18	19	1
	30 min after end of infusion on Day 1 Cycle 4	15	16	0
	Treatment discontinuation	10	14	3
15 mg/kg	30 min after end of infusion on Day 1 Cycle 1	194	206	167
	30 min before infusion on Day 1 Cycle 4	120	126	98
	30 min after end of infusion on Day 1 Cycle 4	27	28	0
	Treatment discontinuation	81	88	73
	Unscheduled	1	1	1
20 mg/kg	30 min after end of infusion on Day 1 Cycle 1	115	119	92
	30 min before infusion on Day 1 Cycle 4	78	82	62
	30 min after end of infusion on Day 1 Cycle 4	17	19	0
	Treatment discontinuation	74	79	62
1200 mg	30 min after end of infusion on Day 1 Cycle 1	26	26	22
	30 min before infusion on Day 1 Cycle 4	5	5	4
	Treatment discontinuation	4	4	4

Source: Disposition_subjects.sas (analysis), Disposition_subjects_bycohort.rtf (output).
Δ = Change from baseline, with baseline defined as nominal time point 30 minutes before infusion on Day 1 of Cycle 1.

4.1.7.2 Statistical Analyses

4.1.7.2.1 Central Tendency Analysis

Not provided.

Reviewer's Comments: We will provide our independent analysis result in Section 5.2.

4.1.7.2.2 Assay Sensitivity

No assay sensitivity analysis is performed.

4.1.7.2.3 Categorical Analysis

4.1.7.3 Not provided.Safety Analysis

The most commonly reported adverse events (> 10%) in urothelial carcinoma (UC) and non-small cell lung cancer (NSCLC) combined populations were fatigue, decreased appetite, nausea, dyspnea, cough, diarrhea, pyrexia, constipation, vomiting, back pain, arthralgia, anemia, pruritus and asthenia. Respiratory symptoms were more commonly observed in the NSCLC population.

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Immune mediated adverse events were reported in 405/1547 (26%) of patients. The most commonly reported were dermatologic reactions, changes in liver function tests and thyroid disorders in both populations. Pneumonitis was reported in 3.4% of NSCLC patients and 1.2% of UC patients.

No dose limiting adverse events were observed in any population.

4.1.7.4 Clinical Pharmacology

4.1.7.4.1 Pharmacokinetic Analysis

The PK results for atezolizumab are presented in Table 1. C_{max} values in cycle 1 were 1.1-fold higher following administration of 20 mg/kg of atezolizumab compared with 1200 mg of atezolizumab, the intended clinical dose.

Table 1: Sponsor's Results for Serum Concentrations of Atezolizumab (µg/mL) at C_{max} 30 minutes after End of Infusion in Cycle 1 and Cycle 4 in Patients

C_{max} 30 minutes after end of infusion		Dose cohort			
		10 mg/kg	15 mg/kg	20 mg/kg	1200 mg
Day 1 of Cycle 1	n	26	194	115	26
	Mean (SD)	255 (51)	380 (207)	504 (119)	470 (128)
	Geomean (%CV)	249 (24)	344 (72)	491 (24)	455 (26)
	Range	107-343	0-2850	267-908	275-824
Day 1 of Cycle 4	n	15	27	17	-
	Mean (SD)	381 (73)	477 (158)	668 (229)	-
	Geomean (%CV)	374 (21)	430 (66)	625 (42)	-
	Range	242-490	31-834	207-1090	-

Source: Table 7 of Applicant's study report

4.1.7.4.2 Exposure-Response Analysis

The Applicant used a linear mixed effects model with intercept as a random variable and concentration as a fixed-effect variable to quantify the relationship between serum concentrations of atezolizumab and ΔQTcF. Reduced linear mixed effects model with intercept fixed to 0 (with IIV) is also explored. The model-estimated intercept and slope were not statistically significantly different from zero, meaning that there was no significant relationship between atezolizumab concentrations and ΔQTcF in this study. The model with intercept fixed to zero, also concluded that the slope was not statistically significantly different from zero. The final model with intercept as a random variable was used to predict the expected ΔQTcF over the range of administered doses (10 mg/kg, 15 mg/kg, 20 mg/kg) at the geometric mean C_{max} 30 minutes after end of atezolizumab infusion in Cycle 4. The parameter estimates of the models are displayed in Table 2 and the predicted ΔQTcF at C_{max} for different dosing scenarios with these models are displayed in Table 3.

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The predicted ΔQTcF and associated 90% CI for the entire atezolizumab concentration range using the model with random intercept (Model 1) is displayed in Figure 1.

Table 2: Parameter Estimates from Linear Mixed Effects Model

Model	Parameter (unit)	Estimate (90% CI)	*P*-value	IIV (%RSE)	AIC
1	Intercept (ms)	-1.49 (-3.99 to 1.02)	0.33	199 (13.0)	7356
	Slope (ms/µg·mL)	0.0056 (-0.0006 to 0.0118)	0.14	na	
2	Intercept (ms)	0[a]	na	197 (13.1)	7359
	Slope (ms/µg·mL)	0.0028 (-0.0012 to 0.0069)	0.25	na	

[a]: fixed at 0.

Source: Table 6 of Applicant's study report

Table 3: Predicted ΔQTcF (90% CI) at Serum Concentrations of Atezolizumab (µg/mL) at C_{max} 30 minutes after End of Infusion in Cycle 4 in Patients

Dose cohort (mg/kg)	Geometric mean C_{max} (µg/mL)[a]	Predicted ΔQTcF (90% CI)[b] in milliseconds at geometric mean C_{max}	
		Model 1	Model 2
10	374	0.71 (-0.36 to 1.75)	1.53 (0.27 to 2.97)
15	430	1.14 (-0.09 to 2.33)	1.76 (0.31 to 3.41)
20	625	2.57 (0.51 to 4.68)	2.56 (0.45 to 4.96)

[a]: Observed geometric mean serum concentration atezolizumab at C_{max} 30 minutes after end of infusion in Cycle 4.
[b]: Calculated as the median and 5th and 95th percentile of ΔQTcF predictions from 1000 bootstrap samples from the primary analysis set.

Source: Table 8 of Applicant's study report

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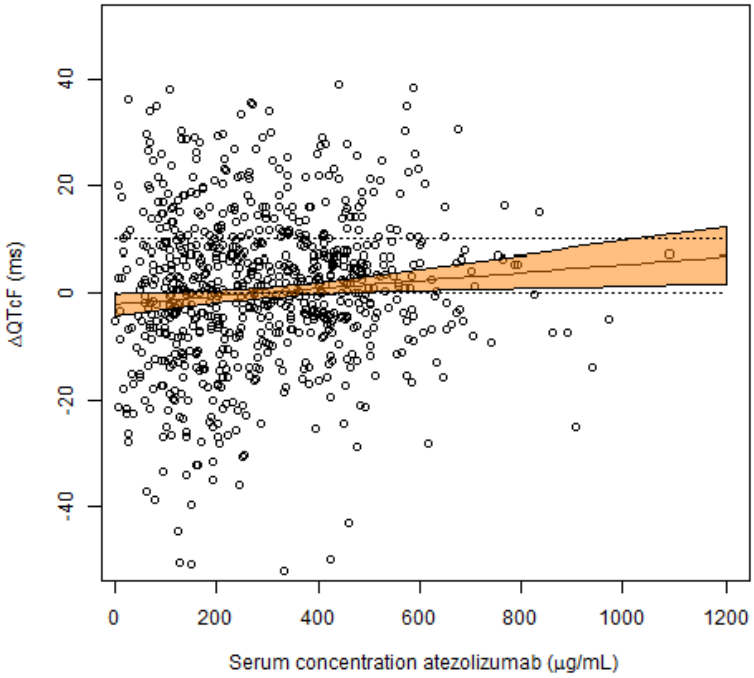
Figure 1: ΔQTcF versus Serum Concentrations of Atezolizumab (Solid Line Depicts Predicted Population Mean and Orange Shaded Area Depicts Associated 90% CI Based on the Model with Random Intercept)



Source: Figure S1 of Applicant's study report

Reviewer's Analysis: A plot of ΔQTcF vs. atezolizumab concentrations is presented in Figure 3. Consistent with the sponsor's results, no evident relationship between ΔQTcF and atezolizumab concentrations was observed.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcF is better than QTcB.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcB		QTcF	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**
MPDL3280A 10MG/KG Q3W IV	13	0.01569	13	0.01699
MPDL3280A 15MG/KG Q3W IV	183	0.30770	183	0.29337
MPDL3280A 20MG/KG Q3W IV	98	0.13741	98	0.12392

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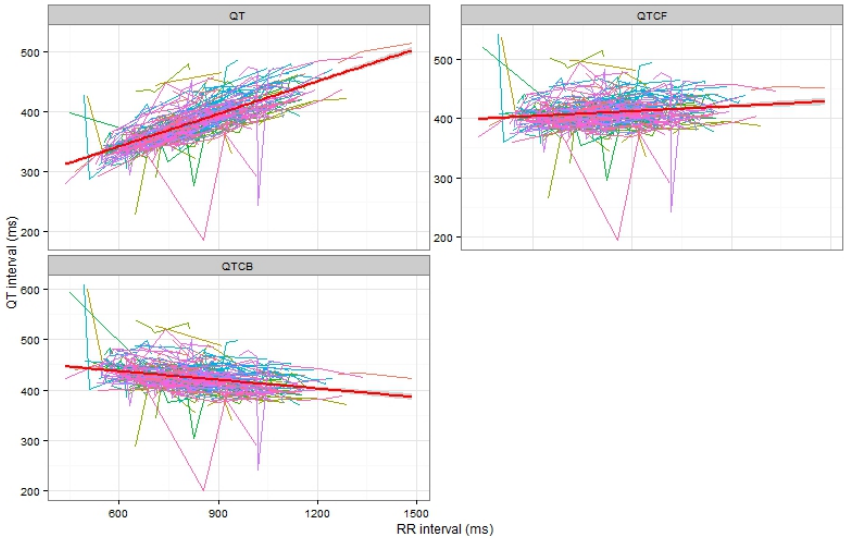
	QTcB		QTcF	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**
MPDL3280A 1200MG Q3W IV	22	0.16332	22	0.11727
All	316	0.23283	316	0.21719

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Central Tendency Analysis for the Study Drug

The primary endpoint is the change from baseline of QTcF. The descriptive statistics are listed in Table 5. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean stratified by 30 minutes before and after infusion on Day 1 of Cycle 1, 30 minutes before infusion on Day 1 of Cycle 4.

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Table 5: Descriptive Statistics Results of ΔQTcF for MPDL3280A Doses 10 mg/kg up up to 20 mg/kg once every 3 Weeks, and 1200 mg (by Cycle and Time)

Treatment	Cycle	Time (h)	N	Mean	Std Dev	90% CI for Mean
MPDL3280A 10 mg/kg q3w i.v.	1	30 min after end of infusion on Day 1	27	4.0	17.8	(-1.9, 9.8)
	4	30 min before infusion on Day 1	19	15.2	25.2	(5.2, 25.2)
		30 min after end of infusion on Day 1	15	20.3	30.6	(6.4, 34.2)
MPDL3280A 15 mg/kg q3w i.v	1	30 min after end of infusion on Day 1	195	2.6	16.1	(0.7, 4.5)
	4	30 min before infusion on Day 1	120	-1.5	25.9	(-5.4, 2.5)
		30 min after end of infusion on Day 1	27	3.8	20.0	(-2.7, 10.4)
MPDL3280A 20 mg/kg q3w i.v	1	30 min after end of infusion on Day 1	113	-0.3	22.0	(-3.7, 3.1)
	4	30 min before infusion on Day 1	77	-4.6	22.3	(-8.9, -0.4)
		30 min after end of infusion on Day 1	17	-0.6	15.8	(-7.2, 6.1)
MPDL3280A 1200 mg q3w i.v	1	30 min after end of infusion on Day 1	26	-0.1	11.0	(-3.8, 3.6)
	4	30 min after end of infusion on Day 1	5	10.9	26.2	(-14.1, 35.9)

5.2.1.1 Assay Sensitivity Analysis

No assay sensitivity analysis performed in this study because no positive control arm included.

5.2.1.2 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms between 480 ms and 500 ms and >500. One subject's QTcF is above 500 ms.

Table 6: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value> 500
MPDL3280A 10 mg/kg q3w i.v.	30	27 (90.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)
MPDL3280A 15 mg/kg q3w i.v.	211	199 (94.3%)	9 (4.3%)	3 (1.4%)	0 (0.0%)
MPDL3280A 20 mg/kg q3w i.v.	117	101 (86.3%)	14 (12.0%)	1 (0.8%)	1 (0.8%)

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Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value> 500
MPDL3280A 1200 mg q3w i.v.	26	20 (76.9%)	5 (19.2%)	0 (0.0%)	0 (0.0%)

Table 7 lists the categorical analysis results for ΔQTcF. Six subjects' changes from baseline are above 60 ms.

Table 7: Categorical Analysis of ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	Value>60 ms
MPDL3280A 10 mg/kg q3w i.v.	21	18 (85.7%)	1 (4.0%)	2 (9.5%)
MPDL3280A 15 mg/kg q3w i.v.	128	117 (91.4%)	8 (6.3%)	3 (2.3%)
MPDL3280A 20 mg/kg q3w i.v.	73	71 (97.3%)	2 (2.7%)	0 (0.0%)
MPDL3280A 1200 mg q3w i.v.	12	10 (83.3%)	1 (8.3%)	1 (8.3%)

5.2.2 HR Analysis

The primary endpoint is the change from baseline of HR. The descriptive statistics are listed in Table 8. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean stratified by 30 minutes before and after infusion on Day 1 of Cycle 1, 30 minutes before infusion on Day 1 of Cycle 4. Table 9 presents the categorical analysis of HR. Three hundred and twenty-eight subjects who experienced HR intervals greater than 100 bpm are in MPDL3280A group.

Table 8: Descriptive Statistics Results of ΔHR and ΔΔHR for MPDL3280A Doses 10 mg/kg up to 20 mg/kg Once Every 3 Weeks, and MPDL3280A 1200 mg

Treatment	Cycle	N	Mean	Std Dev	90% CI for Mean
MPDL3280A 10 mg/kg q3w i.v.	1	8	0.4	6.4	(-4.0, 4.7)
	4	4	-2.5	3.4	(-6.5, 1.4)
MPDL3280A 15 mg/kg q3w i.v.	1	179	-1.4	6.5	(-2.2, -0.6)
	4	103	1.2	11.3	(-0.6, 3.1)
MPDL3280A 20 mg/kg q3w i.v.	1	94	-1.6	9.1	(-3.2, -0.1)
	4	64	-1.7	13.0	(-4.4, 1.0)
MPDL3280A 1200 mg q3w i.v.	1	22	-1.3	12.8	(-6.0, 3.4)
	4	4	-8.6	6.9	(-16.7, -0.5)

Table 9: The Category Analysis of HR

Treatment Group	Total N	HR <= 100 ms	HR >100 ms
MPDL3280A 10 mg/kg q3w i.v.	14	3 (21.4%)	11 (78.6%)
MPDL3280A 15 mg/kg q3w i.v.	194	6 (3.1%)	188 (96.9%)

Reference ID: 3904726

Treatment Group	Total N	HR <= 100 ms	HR >100 ms
MPDL3280A 20 mg/kg q3w i.v.	103	1 (1.0%)	102 (99.0%)
MPDL3280A 1200 mg q3w i.v.	22	0 (0.0%)	22 (100%)

5.2.3 PR Analysis

The primary endpoint is the change from baseline of PR. The descriptive statistics are listed in Table 10. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean stratified by 30 minutes before and after infusion on Day 1 of Cycle 1, 30 minutes before infusion on Day 1 of Cycle 4. Table 11 presents the categorical analysis of PR. Two hundred and eighty-six subjects who experienced PR interval greater than 200 ms are in MPDL3280A group.

Table 10: Descriptive Satistics Results of ΔPR and ΔΔPR for MPDL3280A Doses 10 mg/kg up to 20 mg/kg Once Every 3 Weeks, and 1200 mg

Treatment	Cycle	N	Mean	Std Dev	90% CI for Mean
MPDL3280A 10 mg/kg q3w i.v.	1	8	5.6	7.8	(0.4, 10.8)
	4	4	7.9	10.4	(-4.3, 20.2)
MPDL3280A 15 mg/kg q3w i.v.	1	172	3.9	12.2	(2.4, 5.4)
	4	99	-0.5	15.6	(-3.1, 2.1)
MPDL3280A 20 mg/kg q3w i.v.	1	90	3.3	11.0	(1.3, 5.2)
	4	62	-0.2	17.6	(-3.9, 3.5)
MPDL3280A 1200 mg q3w i.v.	1	21	1.7	9.4	(-1.9, 5.2)
	4	4	5.2	17.5	(-15.4, 25.9)

Table 11: Categorical Analysis for PR

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
MPDL3280A 10 mg/kg q3w i.v.	13	4 (30.8%)	9 (69.2%)
MPDL3280A 15 mg/kg q3w i.v.	188	19 (10.1%)	169 (89.9%)
MPDL3280A 20 mg/kg q3w i.v.	100	7 (7.0%)	93 (93.0%)
MPDL3280A 1200 mg q3w i.v.	22	1 (4.5%)	21 (95.5%)

5.2.4 QRS Analysis

The primary endpoint is the change from baseline of QRS. The descriptive statistics are listed in Table 12. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean stratified by 30 minutes before and after infusion on Day 1 of Cycle 1, 30 minutes before infusion on Day 1 of Cycle 4. Table 13

Reference ID: 3904726

presents the categorical analysis of QRS. Three hundred and twenty subjects who experienced QRS interval greater than 110 ms are in MPDL3280A group.

Table 12: Descriptive Statistics Results of ΔQRS and ΔΔQRS for MPDL3280A Doses 10 mg/kg up to 20 mg/kg Once Every 3 Weeks, and 1200 mg

Treatment	Cycle	N	Mean	Std Dev	90% CI for Mean
MPDL3280A 10 mg/kg q3w i.v.	1	8	0.0	3.7	(-2.4, 2.5)
	4	4	0.9	4.6	(-4.5, 6.3)
MPDL3280A 15 mg/kg q3w i.v.	1	179	0.1	4.5	(-0.4, 0.7)
	4	103	0.1	7.4	(-1.2, 1.3)
MPDL3280A 20 mg/kg q3w i.v.	1	94	0.1	5.1	(-0.8, 1.0)
	4	64	-0.8	6.2	(-2.1, 0.5)
MPDL3280A 1200 mg q3w i.v.	1	22	-0.1	5.2	(-2.0, 1.8)
	4	4	3.3	8.9	(-7.1, 13.8)

Table 13: Categorical Analysis for QRS

Treatment Group	Total N	QRS <= 110 ms	QRS > 110 ms
MPDL3280A 10 mg/kg q3w i.v.	14	3 (21.4%)	11 (78.6%)
MPDL3280A 15 mg/kg q3w i.v.	194	8 (4.1%)	186 (95.9%)
MPDL3280A 20 mg/kg q3w i.v.	103	2 (1.9%)	101 (98.1%)
MPDL3280A 1200 mg q3w i.v.	22	0 (0.0%)	22 (100%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔQTcF and atezolizumab serum concentrations is visualized in Figure 3. The linear mixed effects model with (between-subject variability on intercept and slope) showed that both the model-estimated intercept (Estimate [95% CI]= 0.47 [-3.46,4.39]) and slope (Estimate [95% CI]= 0.00274 [-0.00662,0.01210]) were not statistically significantly different from zero (p=0.82 and 0.57 respectively for intercept and slope estimate), meaning that there was no significant relationship between atezolizumab concentrations and ΔQTcF in this study.

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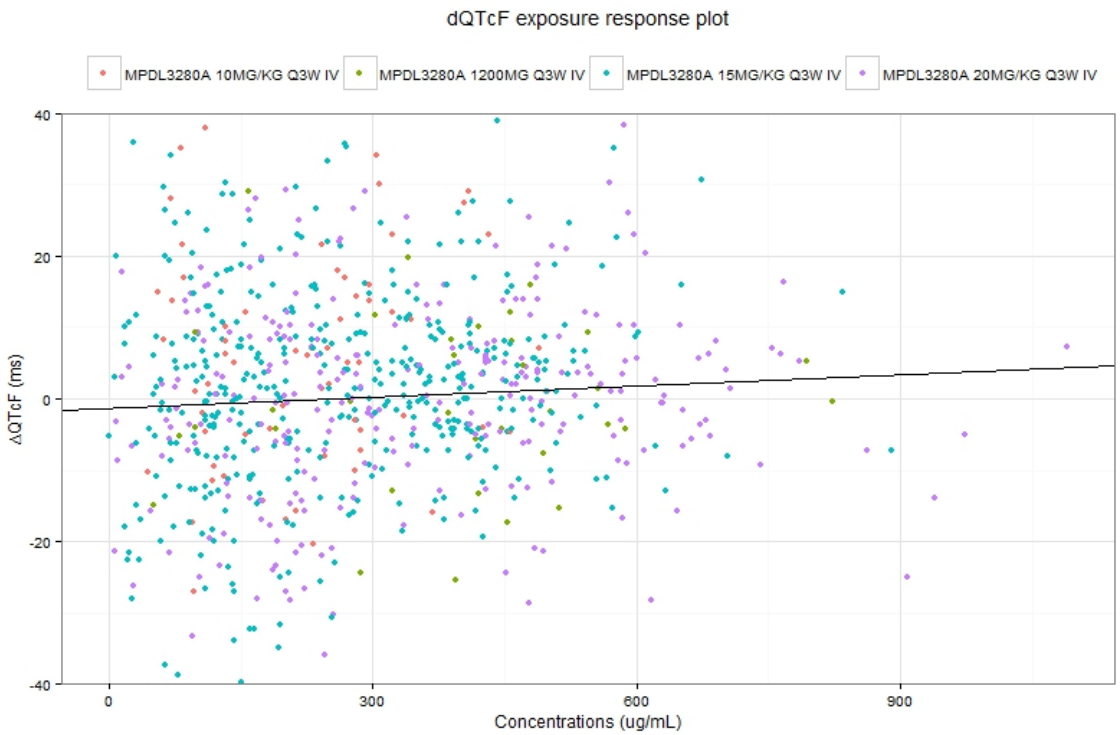
Figure 3: ΔQTcF vs. Atezolizumab concentration together with the Population Predictions (solid line)



Note: One data point with concentration of 2850 µg/mL was removed from the plot for better visual representation of x-axis range and relationship trends

5.4 Clinical Assessments

5.4.1 ECG assessments

ECG waveforms have no annotations. Random samples of short, normal, long QT intervals are reviewed and measured. Some of the shorter reported values are erroneous, majority QT values agree. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.2 ECG Parameters

There was no clinically relevant effect on heart rate, PR or QRS intervals.

Reference ID: 3904726

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Atezolizumab 1200 mg q3w	
Maximum tolerated dose (MTD): Study PCD4989g[1]	MTD has not been reached, highest dose administered 20 mg/kg	
Principal adverse events	The most commonly reported adverse events (≥ 10%) in urothelial carcinoma (UC) and non-small cell lung cancer (NSCLC) combined populations were fatigue, decreased appetite, nausea, dyspnea, cough, diarrhea, pyrexia, constipation, vomiting, back pain, arthralgia, anemia, pruritus and asthenia. Respiratory symptoms were more commonly observed in the NSCLC population. Immune mediated adverse events were reported in 405/1547 (26%) of patients. The most commonly reported were dermatologic reactions, changes in liver function tests and thyroid disorders in both populations. Pneumonitis was reported in 3.4% of NSCLC patients and 1.2% of UC patients. No dose limiting adverse events were observed in any population.	
Maximum dose tested (Study PCD4989g[1])	Single Dose	20 mg/kg
	Multiple Dose	20 mg/kg every 3 weeks. Patients were initially offered atezolizumab treatment beyond Cycle 1 for up to 16 cycles or 1 year (whichever occurred first). Subsequently, atezolizumab treatment could be continued as long as patients were experiencing clinical benefit as assessed by the investigator.
Exposures achieved at maximum tested dose (Population PK[2]):	Single Dose (Cycle 1) GM (%CV)	C_{max} 488 (19.5%) µg/mL C_{min} 75.0 (23.5%) µg/mL AUC 3749 (22.2%) day*µg/mL
	Multiple Dose (Steady-state) GM (%CV)	$C_{max,ss}$ 715 (21.7%) µg/mL $C_{min,ss}$ 213 (48.5%) µg/mL AUC_{ss} 7206 (32.9%) day*µg/mL
Range of linear PK (Study PCD4989g[1]):	1 mg/kg to 20 mg/kg q3w	
Accumulation ratio (AR) at steady state (Population PK[2]):	Dose range: 1 mg/kg to 20 mg/kg (AR; GM (%CV)) C_{max} 1.46 C_{min} 2.75 AUC 1.91	
Metabolites	The metabolism of atezolizumab has not been directly studied, however antibodies are cleared primarily via proteolytic degradation	
Absorption	Absolute/Relative Bioavailability	NA- atezolizumab is administered as an IV infusion
	T_{max}	NA- atezolizumab is administered as an IV infusion
Distribution	V_{ss} Population PK	6.91 L
	% bound	NA

Reference ID: 3904726

Elimination	Route	Predominantly non-specific IgG clearance at doses 1 to 20 mg/kg
	Terminal t½ Population PK[2]	27 days
	CL Population PK[2]	0.200 L/day

Intrinsic Factors	Age Population PK[2]	No clinically important difference was observed in the pharmacokinetics of atezolizumab among patients < 65 years (n = 274), patients between 65 - 75 years (n = 152), and patients > 75 years (n = 46)
	Gender Population PK[2]	Gender was identified as a statistically significant covariate on both V1 and V2, but not CL, based upon a dataset including 276 men (58.5%) and 196 women (41.5%). In females, volumes are 13% and 27% lower than males for V1 and V2, respectively. For a typical female patient (weight normalized to 77 kg), there would be a maximum 8 % increase in AUC_{ss}, $C_{max,ss}$ or $C_{min,ss}$ of atezolizumab compared to a typical male[3].
	Race Population PK[2]	After adjusting for covariate effects in the final population PK model, race (Asian n = 17, Black n = 15, and White n = 375) was not a significant covariate on the pharmacokinetics of atezolizumab.
	Renal Impairment Population PK[2]	No clinically important differences in the clearance of atezolizumab were found in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2; n = 208), or moderate (eGFR 30 to 59 mL/min/1.73 m^2; n = 116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n = 140) renal function. Few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n = 8). No dose adjustment in patients with renal impairment is required.
	Hepatic Impairment: Population PK[2]	There were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin < ULN and AST > ULN or bilirubin < 1.0 to 1.5 ´ ULN and any AST; n = 71) and normal hepatic function (bilirubin and AST less than or equal to ULN; n = 401). No dose adjustment in patients with mild hepatic function impairment is required. No data are available in patients with either moderate or severe hepatic impairment.

Reference ID: 3904726

	Body weight Albumin Tumor burden Anti-therapeutic antibody (ATA): Population PK[2]	Based on a population PK analysis, there were no clinically important differences in atezolizumab exposure based on albumin, ATA, body weight, gender and tumor burden. Patients with body weight lower than 54 kg would have up to a 32%, 28%, 40% higher AUC_{ss}, $C_{max,ss}$ or $C_{min,ss}$, respectively, than the typical patient[3].
Extrinsic Factors	Drug Interactions	No formal drug-drug interaction studies have been conducted at this time
	Food Effects	NA - atezolizumab is administered as an IV infusion
Expected High Clinical Exposure Scenario	No exposure beyond highest dose tested (20 mg/kg) anticipated	

Pre-Clinical Cardiac Safety	Although a dedicated safety pharmacology study of atezolizumab has not been performed, central nervous system, cardiovascular (telemetry and/or surface leads), and respiratory safety pharmacology parameters were evaluated in GLP cynomolgus monkey toxicology studies (and No atezolizumab-related electrocardiographic findings were observed; all electrocardiograms evaluated in these studies were qualitatively and quantitatively within normal limits. There were no changes in mean arterial blood pressure, heart rate, body temperature, respiratory rate, oxygen saturation, or neurological parameters observed at doses up to 50 mg/kg given intravenously weekly for up to 26 weeks (27 total doses).
Clinical Cardiac Safety[4]	An analysis of the relationship between atezolizumab concentration and change from baseline QTc interval (delta QTcF) suggests no clinically meaningful change in delta QTcF at atezolizumab concentrations up to the geometric mean C_{max} following 4 doses of atezolizumab 20 mg/kg administered once q3w.

Abbreviations: AESI, adverse events of special interest; AR, accumulation ratio; AST, aspartate aminotransferase; ATA, anti-therapeutic antibody; AUC, area under the curve at Cycle 1; AUC_{ss}, area under the curve at steady-state; %CV, geometric mean coefficient of variation; C_{max}, maximum concentration; C_{min}, minimum concentration; $C_{max,ss}$, maximum concentration at steady-state ; $C_{min,ss}$, minimum concentration at steady-state; CL, clearance; eGFR, estimated glomerular filtration rate; GLP, good laboratory practice; GM, geometric mean; IgG, immunoglobulin G; MTD, maximum tolerated dose; NA, not applicable; n, number of subjects; NR, not reported; q3w every three weeks; QTc, corrected QT interval; QTcF, QTc-correct using Fridericia's formula; ORR, overall response rate; PK, pharmacokinetic; T_{max}, maximum concentration; V1, volume of the central compartment; V2, volume of the peripheral compartment; V_{ss}, volume at steady-state; t½, elimination half-life; ULN, upper limit of normal

[1] Study PCD4989g (GO27831): A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously as a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies. 2015. Report No. 1064914

[2] Population PK report (N=472): Pharmacokinetics of Atezolizumab (PD-L1 inhibitor) Administered as a Single Agent in Patients (N= 472) with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies (Based on Studies PCD4989g and JO28944). 2015. Report No. 1066935.

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[3] Typical patient in the population PK model is a male without positive ATA, weighing 77 kg, with an albumin level of 40 g/L and a tumor burden of 63 mm

[4] Concentration-QTc Analysis for Atezolizumab Based on Data from Study PCD4989g (GO27831) 2015, Report No. 1066934

Reference ID: 3904726

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/s/

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03/22/2016

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:	March 22, 2016
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761034
Product Name and Strength:	Tecentriq (atezolizumab) injection, 60 mg/mL
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genentech, Inc.
Submission Date:	January 12, 2016 and March 16, 2016
OSE RCM #:	2015-2684
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Reference ID: 3905774

1 REASON FOR REVIEW

Genentech, Inc. submitted Tecentriq (atezolizumab) injection container label, carton labeling, and prescribing information (PI) for BLA 761034. 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.

Table 1. Materials Considered for this Label and Labeling Review

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 container label and determine that the container label 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.

We evaluated the proposed prescribing information and recommend revising the statement "(b) (4)" with "storage of the infusion solution in the infusion bag" for clarity.

Reference ID: 3905774

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label and PI labeling for Tecentriq may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   a. In the Dosage and Administration Section, replace the statement (b) (4) ” with “…storage of the infusion solution in the infusion bag” for clarity.

4.2 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of BLA 761034:

A. General recommendation
   a. Replace “Tradename” with the conditionally approved proprietary name, Tecentriq.
B. Container label
   a. 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.

Reference ID: 3905774

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 January 12, 2016.

Table 2. Relevant Product Information for Tecentriq	
Initial Approval Date	N/A
Active Ingredient	atezolizumab
Indication	Treatment of patients with locally advanced or metastatic urothelial carcinoma [redacted] (b) (4)
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.

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

Reference ID: 3905774

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/s/

TINGTING N GAO
03/22/2016

CHI-MING TU
03/22/2016

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# 761034

Application Type: Original BLA

Drug Name(s)/Dosage Form(s): Tecentriq® (atezolizumab) Infusion: 60 mg/mL solution in a single use 20 mL vial

Applicant: Genentech, Inc.

Receipt Dates: January 12, 2016

Goal Date: September 12, 2016

1. Regulatory History and Applicant's Main Proposals

- February 7, 2014, IND 120827 was cleared by the FDA
- May 22, 2014, Breakthrough Therapy Designation was granted for the treatment of patients with locally advanced or metastatic UBC that are PD-L1 positive
- June 12, 2014, a Type B Pre-Phase III Meeting was held to discuss the acceptability of Phase II Study IMvigor210 (GO29293) and Phase III Study IMvigor211 (GO29294) to support accelerated approval
- May 11, 2015, a Type B Content & Format Pre-BLA Teleconference was held to discuss the proposed content and format of the planned mUC BLA submission
- September 24, 2015, a Type B Clinical Pre-BLA Meeting was held to discuss the clinical trial results to support the mUC BLA

Genentech, Inc. submitted an original Biologics License Application (BLA) on January 12, 2016 for the use of atezolizumab (MPDL3280A) as treatment for adult patients with locally advanced or metastatic urothelial carcinoma (mUC) (b) (4)

This submission was submitted as a Rolling Review.

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.

In addition, the following labeling issues were identified:

1. Superscript the Registered Sign (®) following the product name.
2. The Medication Guide needs to start on a new page to avoid the information starting halfway the page.

All SRPI format deficiencies of the PI and other labeling issues identified above 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 March 16, 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 the 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

Reference ID: 3900828

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 present 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:

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**.

Reference ID: 3900828

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 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:

Reference ID: 3900828

Selected Requirements of Prescribing Information

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 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

YES 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:

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:

Reference ID: 3900828

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:

Reference ID: 3900828

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:

Reference ID: 3900828

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:

Reference ID: 3900828

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:

Reference ID: 3900828

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.

Reference ID: 3900828

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

/s/

KIM J ROBERTSON
03/11/2016

CHRISTY L COTTRELL
03/11/2016