CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761137Orig1s000

OTHER REVIEW(S)

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:	November 21, 2019
To:	Julia Beaver, MD Director **Division of Oncology Products 1 (DOP 1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Dvorsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PADCEV (enfortumab vedotin-ejfv)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761137
Applicant:	Astellas Pharma US, Inc.

1 INTRODUCTION

On July 15, 2019, Astellas Pharma US, Inc. submitted for the Agency's review an Original Biologics License Application (BLA) 761137 for TRADENAME (enfortumab vedotin) injection for the proposed indication: (b) (4)

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 (DOP 1) on July 29, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME enfortumab vedotin injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (enfortumab vedotin) injection PPI received on July 15, 2019, and received by DMPP and OPDP on November 14, 2019.
- Draft TRADENAME (enfortumab vedotin) injection Prescribing Information (PI) received on July 15, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 14, 2019.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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MORGAN A WALKER
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LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: November 20, 2019

To: Elaine Chang, M.D.
Division of Oncology Disease (DO 1)

Rajesh Venugopal, MPH, MBA, Regulatory Project Manager, (DO 1)

William Pierce, PharmD, Associate Director for Labeling, (DO 1)

From: Emily Dvorsky, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for PADCEV™ (enfortumab vedotin-ejfv) for injection, for intravenous use

BLA: 761137

In response to DO 1's consult request dated July 29, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA/BLA submission for PADCEV™ (enfortumab vedotin-ejfv) for injection, for intravenous use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DO 1 (Fatima Rizvi) on November 14, 2019 and are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 6, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or emily.dvorsky@fda.hhs.gov.

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EMILY M DVORSKY
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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:	November 15, 2019
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761137
Product Name and Strength:	Padcev (enfortumab vedotin-ejfv) for Injection, 20 mg/vial and 30 mg/vial
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
OSE RCM #:	2019-1569-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Astrellas submitted revised container labels and carton labeling received on November 6, 2019 for Padcev. Division of Oncology 1 (DO1) requested that we review the revised container labels and carton labeling for Padcev (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Astrellas implemented all of our recommendations[b] and we have no additional recommendations at this time.

[a] Gao, T. Label and Labeling Review for Padcev (BLA 761137). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Oct 29. RCM No.: 2019-1569.
[b] 1.11.3 Clinical Information Amendment. Northbrook (IL): Astellas Pharma US, Inc. 2019 Nov 6. Available from: \\cdsesub1\evsprod\bla761137\0027\m1\us\1-11-3--clinical-information-amendment.pdf.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 6, 2019

Container labels

(b) (4)

Carton labeling

(b) (4)

(b) (4)

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Clinical Inspection Summary

Date	November 6, 2019
From	Yang-min (Max) Ning, M.D., Ph.D. Aisha Johnson, M.D., M.P.H., M.B.A. Kassa Ayalew, M.D., M.P.H. OSI/DCCE/GCPAB
To	Elaine Chang, M.D. Chana Weinstock, M.D. Rajesh Venugopal, Pharm.D. OCE/OHOP/DOP1
BLA #	761137
Applicant	Astellas Pharma Global Development, Inc.
Drug	Enfortumab vedotin
NME	Yes
Therapeutic Classification	Antibody drug conjugate
Proposed Indication(s)	For the treatment of patients with locally advanced or metastatic urothelial cancer (mUC) who have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and who have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting
Consultation Request Date	July 26, 2019
Summary Goal Date	November 22, 2019
Action Goal Date	December 2019
PDUFA Date	March 15, 2020

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Clinical data from an ongoing, single-arm study (SGN22E-001) were submitted to the Agency in support of a new Biologics License Application (BLA) for enfortumab vedotin for the above proposed indication. Three clinical investigator sites (10030, 10008, and 10003) and the contract research organization (CRO) Seattle Genetics, Inc., were selected for clinical inspections.

The inspections verified the Applicant's submitted clinical data with source documents at the three clinical investigator sites and evaluated the CRO's practices and procedures. There were no significant Good Clinical Practice (GCP) compliance deficiencies in the conduct of this study at these sites.

Based on the results of these inspections, the data reported by these three investigator sites and the CRO appear to be acceptable and supportive of this BLA and the respective indication.

II. BACKGROUND

Enfortumab vedotin is an antibody drug conjugate that targets Nectin-4, an adhesion protein located on the surface of cancer cells. It is comprised of a fully human IgG1-kappa antibody conjugated to monomethyl auristatin E (MMAE), a microtubule disrupting agent. Its safety and efficacy have been investigated in patients with advanced urothelial carcinoma.

To support the proposed indication in this BLA, the Applicant submitted clinical data from Cohort 1 of an ongoing study [SGN22E-001 (NCT03219333)]. This study is an open-label, single-arm, Phase 2 trial of enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer who have received prior immune checkpoint inhibitor. The study has two cohorts: Cohort 1 enrolled patients who also received prior treatment with platinum-containing chemotherapy and Cohort 2 is for those who have not received prior platinum-containing or other chemotherapy and who are deemed ineligible for treatment with cisplatin at time of enrollment. (Note that data from Cohort 2 were not submitted in this BLA). The primary efficacy measure was the confirmed objective response rate (ORR) as assessed by independent central review (ICR).

Study subjects received enfortumab vedotin at a dose of 1.25 mg/kg, administered as an intravenous infusion over approximately 30 minutes on Day 1, 8, and 15 of each 28-day cycle. Study treatment continued until disease progression as assessed by the Investigator, unacceptable toxicity, or other discontinuation criteria as specified in the protocol. Tumor assessments were performed at baseline, every 8 weeks (±1 week), and then every 12 weeks (±1 week) after completion of one year of treatment. Scans were submitted to the ICR facility for determination of tumor responses.

From 10/9/2017 through 3/1/2019 (the data cutoff date for the submitted analysis), the study enrolled 152 subjects with 128 subjects in Cohort 1. The majority (93%) of subjects were from 37 study sites in the U.S. The Applicant reported that for Cohort 1, ICR-assessed ORR was 44% (95% CI: 35.1%, 53.2%) in 125 subjects who received study treatment, with a median duration of response of 7.6 months (range: 0.95, 11.3+).

Three clinical investigator sites were selected for clinical inspections. These sites had a relatively high number of subjects among all study sites. Two of the three sites were associated with a higher ORR than the reported overall ORR of 44% for Cohort 1. For two investigator sites (10030 and 10003), there was no history of FDA clinical inspections of the investigators prior to this application. Inspection of the CRO Seattle Genetics, Inc., which holds the Trial Master Documentation for this application, was also requested and conducted. Seattle Genetics, Inc. was inspected twice in 2011 and 2017, with Voluntary Action Indicated (VAI) as the final compliance classification for each inspection. The reported observations in the 2011 inspection included “failure to follow investigational plan” and “inadequate and inaccurate records”. In the 2017 inspection, the reported observations were “failure to submit 15-day initial and follow-up reports in a timely manner” and “inadequate written procedures for the receipt, evaluation and reporting of post-marketing adverse experiences to FDA”.

III. RESULTS

1. Dr. Bradley McGregor: Study Site #10030

This Study Site 10030 was inspected on August 27-30, 2019 as a data audit for the Study SGN22E-001. For Dr. McGregor, this was the initial FDA inspection. The site screened 17 subjects and enrolled 15 of them into this single-arm study before the data cutoff date, with 14 subjects in Cohort 1 and one in Cohort 2. At the time of inspection, two subjects in Cohort 1 remained on study treatment, eleven discontinued, and one withdrew. According to the site data listings that were verified in this inspection, 8 of the 14 subjects in Cohort 1 discontinued due to radiographic disease progression and 3 discontinued due to adverse events [Subjects (b) (6) (acute kidney injury), (b) (6) (peripheral sensory neuropathy) and (b) (6) (peripheral sensory neuropathy)].

All the subjects' source records were reviewed and compared with the Applicant's submitted data listings for this site. The source records included subjects' enrollment log, study charts (paper and electronic), informed consent forms (ICF), electronic case report forms (eCRF), and records for subjects' eligibility, laboratory tests, adverse events, and test article. The study-related documents were also reviewed at the site. These documents included the copy of study protocol and amendments, the approvals of the protocol/amendments and ICFs by the Institutional Review Board (IRB) for the study, Form FDA 1572s, Financial Disclosure forms, training records, the Group Delegation of Authority and Signature Log, study monitoring records, and documented protocol deviations.

The inspection revealed no significant deficiencies in GCP compliance. No Form FDA 483 was issued at the end of the inspection. The reported data were verifiable, with no discrepancies found between the source data and the submitted site-level data listings. One reported finding was that source documents were not well organized between paper and electronic charts. This was discussed at the close-out meeting. The investigator acknowledged the finding and agreed that "source documentation could have been more organized".

2. Dr. Daniel Petrylak: Study Site #10008

This Site 10008 was inspected on September 16-20, 2019 as a data audit for the study SGN22E-001. For the investigator, this was the second FDA inspection. The first FDA inspection was conducted in May 2007 and the final GCP compliance classification for this inspection was No Action Indicated.

The current inspection reviewed source records for all the enrolled subjects at the site. As of the data cutoff date, the site enrolled 9 subjects into Cohort 1 and one into Cohort 2. Four subjects in Cohort 1 remained on study treatment, five were discontinued due to disease progression. No subjects were discontinued for adverse events. The source records reviewed during the inspection were the protocol, Finance Disclosure Form, Form FDA

1572, IRB approvals, Informed Consent Forms, primary efficacy endpoint, inclusion and exclusion criteria, training record, delegation log, drug accountability and other source documents". These records were examined and compared with the documents and data listings submitted to the NDA. The inspection also reviewed the IRB's oversight of the study conduct, sponsor's monitoring, reports of the site to Sponsor, and study record retention.

The inspection found no significant GCP compliance deficiencies in the study conduct at the site. No Form 483 was issued to the investigator. Source data for each subject were verifiable with the data in the eCRF system and the submitted data listings for the site. No discrepancies were identified. All adverse events and protocol deviations were reported to the Sponsor. At the end of this inspection, two documentation-related inspectional findings were discussed. The first one was "some subjects did not complete their health questionnaires forms and left them blank" (e.g., EORTC QLQ-C30). There was no documentation of the reason that these questions were not answered. In the eCRF, these unanswered questions were marked as "not answered". The second finding was that the investigator did not sign the Study-Initiation-Visit training log after he participated in the training. The investigator acknowledged the findings and responded that he would implement appropriate preventive and corrective actions.

3. Dr. Evan Yu: Study Site #10003

The study site was inspected on September 16-19, 2019 as a data audit for the Study SGN22E-001. This was the first FDA inspection for this principle investigator. At the time of the inspection, the site enrolled 9 of the 12 screened subjects, with 6 subjects in Cohort 1. Of the 6 subjects, one subject remained on study treatment, five discontinued due to disease progression (Subjects (b) (6)), withdrawal (Subject (b) (6)), and death (Subject (b) (6), secondary to aspiration pneumonia).

The inspection reviewed all subjects' source records, including the signed informed consent forms, eligibility documentation, prior cancer treatments, scans performed, laboratory reports, infusion visits, adverse events, concomitant medications, clinic and nursing notes. These records were compared with the Applicant's submitted data listings to examine for consistency and accuracy. The inspection also audited documents that were associated with the conduct and monitoring of this study at the site. The reviewed documents included the IRB's approvals of the original protocol, protocol amendments and related informed consents, delegation of authority, signed financial disclosures and From FDA 1572s, test article control logs, sponsor's protocol training and monitoring records, reporting to the sponsor and submissions of scans to the ICR facility for independent review.

The inspection verified the submitted data listings with source data at the site, with no discrepancies or objectionable observations reported. No Form FDA 483 was issued. Note that the inspection found that central laboratory and independent review results were not provided to the site. At the close-out meeting, documentation of adverse events was discussed as an inspectional finding. This related to lack of documentation of a few

adverse events (e.g., lightheadedness, fatigue, anemia, and nausea) which were found in the infusion nurse notes on infusion days. The investigator acknowledged the finding and proposed his corrective and preventive action plans.

4. CRO: Seattle Genetics, Inc.

Seattle Genetics, Inc., was inspected on October 1-4, 2019 for its conduct of the study SGN22E-001. The inspection included a comprehensive review of the Trial Master File, monitoring of clinical study sites, evaluation of written procedures relevant to the study conduct, drug safety reporting, and overall records maintenance for adequacy, accuracy, and retention. Additional inspectional coverage included review of the following areas: the agreement between the CRO and the current Sponsor (Astellas Inc., the holder for IND 116360) for the development of enfortumab vedotin, organization and personnel, outsourced services and contractors, selection and training of clinical site monitors and clinical investigators, financial disclosures and related updates, electronic systems used for the study and relevant instructions and training to clinical investigator sites, monitoring activities (visits and reports), test article control, quality assurance, data collection and handling.

The inspection revealed no significant compliance violations or deficiencies, with no Form FDA 483 issued. For this study SGN22E-001, the CRO was reported as the "Study Sponsor" and was responsible for monitoring study sites in the U.S., including reporting safety information to the IND Sponsor and participating investigators. At the close-out meeting, there were two CRO-related items discussed with the management of Seattle Genetics, Inc.: 1) the timing/frequency of site monitoring visits at some sites in the U.S. did not occur as outlined in the Clinical Monitoring Plan; 2) IND safety report information was submitted late by Seattle Genetics to the IND holder (Astellas) on two occasions, leading to subsequent delays in reporting to the FDA outside of the required 15-day timeframe. The CRO's management acknowledged the discussion items and proposed to evaluate the items and make improvements to its processes.

<u>Reviewer's Comments:</u> The above discussion items were verified with examination of the corresponding Exhibits collected from the CRO inspection. Regarding Item 1: Six of 37 study sites in the U.S. were found to have the first interim monitoring visits (IMV) completed 5-10 weeks after the first subject received the first dose of enfortumab vedotin. This is not consistent with the Clinical Monitoring Plan, which states "Conduct the first IMV for each site within approximately 2 weeks after the first subject receives the first dose of enfortumab vedotin". Regarding Item 2, the late submissions occurred in 2 of the 153 reports submitted from the CRO to the IND Sponsor. Overall, the discussed items represent findings of non-compliance, which were considered minor for this inspection. In general, the CRO appears to adequately conduct and monitor the study and maintain the required records and data for this study.

PRIMARY REVIEW: {See appended electronic signature page}

Yang-min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Aisha Johnson, M.D., M.P.H., M.B.A.
Acting Team Lead
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Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

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

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Review Division /Division Director/J Beaver
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Review Division/Medical Officers/E Chang
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Khin
OSI/DCCE/Branch Chief/K Ayalew
OSI/DCCE/Team Leader/A Johnson
OSI/DCCE/GCP Reviewer/YM Ning
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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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:	October 29, 2019
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761137
Product Name and Strength:	Padcev (enfortumab vedotin-ejfv)[a] for Injection, 20 mg/vial and 30 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
FDA Received Date:	September 3, 2019
OSE RCM #:	2019-1569
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

[a] The proposed nonproprietary name (enfortumab vedotin-ejfv) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Padcev (IND 116360 and BLA 761137). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 7. OSE RCM No.: 2018-2494 and 2019-1571.

1 REASON FOR REVIEW

As part of the review process for Padcev (enfortumab vedotin-ejfv) for Injection, the Division of Oncology Products 1 (DOP1) requested that we review the proposed Padcev Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed PI, container labels, and carton labeling for Padcev and determined that they may be improved to ensure safe product use.

4 CONCLUSION & RECOMMENDATIONS

The proposed PI, container labels, and carton labeling for Padcev may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section 2.3 Instructions for Preparation and Administration, Dosage and Administration Section
    a. Consider un-bold and relocate these negative statements “Do NOT administer PADCEV as an IV push or bolus.” and “DO NOT mix PADCEV

with, or administer as an infusion with, other medicinal products." to the end of Section 2.3 to minimize the risk of these statements being read as affirmative actions.

b. Spell out the route of administration so that the statement reads as "Do NOT administer PADCEV as an intravenous push or bolus."

2. How Supplied/Storage and Handling Section

a. Revise (b) (4) to "Carton of one XX mg single-dose vial" to clarify that each carton contains one single-dose vial.

4.2 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

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

A. General Comments (Container labels & Carton Labeling)

1. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., -020- for the 20 mg/vial, and -030- for the 30 mg/vial). Revise the product code in the NDC numbers to ensure that the middle 4 digits are different between the strengths. If for some reason that middle digits cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-**XXXX**-XX.

B. Container Labels

1. Consider re-organize the statements in the order of importance so that it reads as followings:

   For intravenous infusion only
   Must reconstitute and dilute before use

   Single-dose vial. Discard unused portion

   If space permits, ensure there is sufficient white space between the statements "Must reconstitute…" and "Single-dose…" to improve readability.

2. Include the statement in bold red font on the side panel, "CAUTION: Cytotoxic Agent". Cytotoxic products require special handling procedures.

3. Consider revising the statement of dosage from (b) (4) to read as follows "Dosage: See Prescribing Information"

C. Carton Labeling

1. Consider re-organize the statements in the order of importance so that it reads as followings:

   For intravenous infusion only
   Must reconstitute and dilute before use

   Single-dose vial. Discard unused portion

   Ensure there is sufficient white space between the statements "Must reconstitute…" and "Single-dose…" to improve readability.

2. Include the statement in bold red font on the principal display panel, "CAUTION: Cytotoxic Agent". Cytotoxic products require special handling procedures.

3. On the side panel of the carton, bold the volume required for Sterile Water for Injection and add a space between the "10" and "mg/mL" so that the sentence reads "After reconstitution with X.3 mL of Sterile Water for Injection, USP, the concentration of PADCEV (enfortumab vedotin-ejfv) is 10 mg/mL." This will ensure the healthcare providers note the specific amount of Sterile Water for Injection required for each vial strength.

4. As currently presented, the font size of the text on the two side panels are small and appears difficult to read. Consider removing the statement (b) (4) from the top of the two side panels of the carton, and increase the font size of the remaining text to improve readability.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Padcev received on September 3, 2019 from Astellas Pharma US, Inc..

Table 2. Relevant Product Information for Padcev	
Initial Approval Date	N/A
Active Ingredient	enfortumab vedotin-ejfv
Indication	treatment of patients with locally advanced or metastatic urothelial cancer who have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and who have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.
Route of Administration	Intravenous
Dosage Form	for Injection
Strength	20 mg/vial and 30 mg/vial
Dose and Frequency	1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.
How Supplied	Carton of one single-dose vial
Storage	Store PADCEV vials at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Do not shake.
Container Closure	The container closure system for both strengths consists of a 10 mL-clear (b) (4) glass vial with (b) (4) a 20 mm gray (b) (4) rubber stopper (b) (4) and an aluminum seal with flip-off top (green for 20 mg/vial and yellow for 30 mg/vial).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Container labels received on September 3, 2019
- Carton labeling received on September 3, 2019
- Prescribing Information (Image not shown) received on September 3, 2019 available from \\cdsesub1\evsprod\bla761137\0011\m1\us\ev-uspi-28aug2019-clean.doc

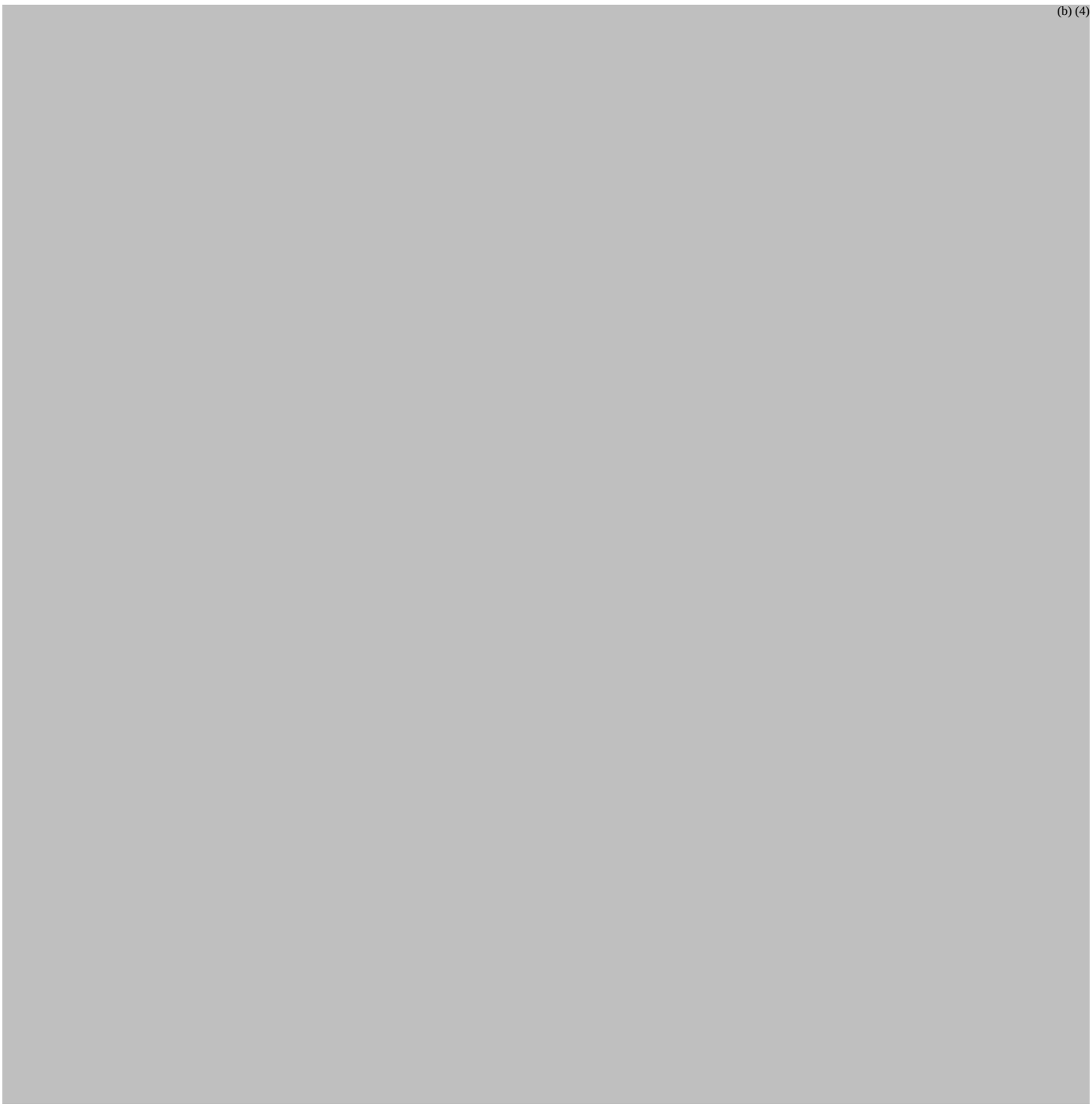
G.2 Label and Labeling Images

Container labels

(b) (4)

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

Carton labeling


(b) (4)

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 15, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Rajesh Venugopal, RPM
DOP1

Subject: QT-IRT Consult to BLA 761137 (SDN 001)

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

This memo responds to your consult to us dated 7/30/2019 regarding the sponsor's concentration-QTc report. The QT-IRT reviewed the following materials:

- Study 7465-CL-0101 study report and concentration-QTc report (Submission 0001);
- Proposed label (Submission 0011); and
- Highlights of clinical pharmacology and cardiac safety (Submission 0001).

1 QT-IRT Review of the Sponsor's Concentration-QTc Analysis

We agree with the sponsor's conclusion that enfortumab vedotin does not cause a large mean increase on QTc interval at the proposed therapeutic dose (i.e., 1.25 mg/kg on Days 1, 8, and 15 of each 28-day cycle). We agree with the proposed label language in section 12.2:

Cardiac Electrophysiology
At the recommended dose (b) (4) PADCEV had no large QTc prolongation (>20 msec).

2 BACKGROUND

2.1 Product Information

Enfortumab vedotin, also referred to as ASG-22CE, is a Nectin-4 targeted antibody-drug conjugate (ADC) comprised of a fully human IgG1 kappa antibody (AGS-22C3) conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable

maleimidocaproyl valine-citrulline (vc) linker. The target indication for enfortumab vedotin is for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have received a PD-1 or PD-L1 inhibitor and who have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

The proposed therapeutic dose for enfortumab vedotin is 1.25 mg/kg administered on days 1, 8, and 15 of a 28-day cycle.

Reviewer's comments: *The molecular size of enfortumab vedotin and AGS-22C3 suggest a low likelihood of direct interaction with cardiac ion channels. The systemic exposure of the small molecule payload, unconjugated MMAE, at the proposed therapeutic dose is not significantly higher than the exposure of two FDA-approved ADC products containing MMAE (i.e. polatuzumab vedotin and brentuximab vedotin). Overall, enfortumab vedotin is expected to have a low QT prolongation risk due to direct cardiac ion channel interaction.*

2.2 Sponsor's position related to the question

Not applicable.

2.3 Nonclinical Cardiac Safety

The in vitro binding potency for MMAE to the hERG channel was examined in up to 100 µM concentrations using a conventional whole cell voltage clamp method. From these studies, the MMAE IC50 of the hERG channel was determined to be greater than 100 µM. An IC50 estimate of 100 µM is approximately 19405-fold greater than the human Cmax of MMAE observed in subjects who received enfortumab vedotin at 1.25 mg/kg.

In nonhuman primates, there were no drug-related changes in ECGs (qualitative examination of each tracing for abnormalities as well as a quantitative measurement of the QT- and RR-interval from a QRS complex and derived QTc) when performed following the first and final (4th) dose of AGS-22M6E (b) (4) at dose levels up to 3 mg/kg given once a week for 4 weeks or 6 mg/kg given once a week for 2 weeks. In addition, an approximate molar equivalent of free MMAE in a 3 mg/kg per week dose, 0.0545 mg/kg or greater (0.1093 mg/kg or approximately the molar equivalent of 6 mg/kg dose given once a week for 2 weeks), was also administered once a week for 4 weeks with no drug-related changes observed in ECGs.

2.4 Clinical Cardiac Safety

Overall, the incidence of changes in 12-lead ECGs was low and similar across the safety analysis groups. Abnormal/clinically significant ECG interpretations by the investigator were reported in the enfortumab vedotin 1.25 mg/kg group at baseline in 2 subjects (0.6%). Postbaseline abnormal/clinically significant ECG interpretations by the investigator were reported at the end of treatment/safety follow-up in 1 subject (0.7%).

In the enfortumab vedotin 1.25 mg/kg group, TEAEs of QT prolongation were experienced by 2 subjects (0.6%) with 1 each of Grade 1 and Grade 2 in severity. Only the Grade 2 event of QT prolongation was considered related and neither event was considered serious. Two subjects experienced TEAEs of cardiac arrest with 1 event of Grade 4 in severity and 1 event leading to death. Neither event of cardiac arrest was considered related and both were considered serious. Two subjects experienced TEAEs of syncope with both TEAEs Grade 3 in severity. Neither event of syncope was considered related or serious. One event of syncope led to dose interruption, but the subject continued to receive enfortumab vedotin. No other cardiac adverse events of QT prolongation, torsade de pointes, sudden death, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation and/or flutter, syncope or seizure were observed in these studies at the time of data cutoff.

2.5 Summary results of prior QTc assessments

The sponsor conducted concentration-QTc analysis using data from Japanese subjects in Study EC-102. Study EV-102 is an ongoing Phase 1, open-label, randomized study. In this study, enfortumab vedotin was administered on days 1, 8 and 15 of a 28-day cycle. Subjects were randomized to receive either a 1.0 (n = 9) or 1.25 mg/kg (n = 8) dose of enfortumab vedotin. After the first cycle, subjects assigned to the 1 mg/kg dose were able to escalate to 1.25 mg/kg if no toxicities precluding escalation occurred. PK/ECG data collected at predose, end of infusion (EOI), 0.5, 2, 4, and 48 hrs post EOI of the Cycle 1 Day 1 and Day 15 doses were used for the concentration-QTc analysis.

12-lead ECGs were measured in triplicate at approximately 2-minute intervals. ECG charts were sent to the central laboratory, (b) (4) and analyzed to calculate the QT, PR, RR and QRS intervals.

Mean estimates of HR and QTcF did not show a time-dependent trend across dosing periods, including QTcF interval at the approximate times of maximum MMAE concentrations. Hysteresis plots did not show significant delayed effect. Scatter plots of ADC or MMAE concentrations versus ΔQTcF intervals did not show a clear trend in linear concentration-QTcF intervals relationship. The data were analyzed with a linear mixed effects model without effect compartment (ΔQTcF ~ 1 + CONC (ADC or MMAE)). Neither model suggested a positive exposure-response relationship. The model predicted mean effect were less than 10 msec and the upper bound of the two-sided 90% confidence interval were less than 20 msec at the geometric mean Cmax of ADC or MMAE.

Of the 19 patients randomized, one patient had a QTcF change from baseline > 30 msec at 2 hrs and 48 hrs post EOI during Cycle 1, Day 15 and the safety follow-up visit, respectively. No patients had a QTcF interval > 450 msec or a change from baseline > 60 msec. Generally, no clinically meaningful mean changes from baseline in ECG parameters were observed.

Reviewer's comments: *ECG monitoring schedule appears adequate to capture drug effect around Tmax of the ADC and MMAE, and to capture potential delayed effect due to protein trafficking. The sample size may not be adequate to exclude large mean effect with by-timepoint analysis. The sponsor did not provide by-timepoint summary of the ECG findings. The reviewer did not conduct independent analysis on the dataset.*

2.6 Relevant details of planned Phase 3 study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

3 Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose	1.25 mg/kg (up to a maximum of 125 mg for subjects ≥ 100 kg) administered as an intravenous (IV) infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.	
MTD	Maximum tolerated dose has not been identified for enfortumab vedotin.	
Principal Adverse events	The data described in this section reflects subject exposure to enfortumab vedotin in 125 subjects with locally advanced or metastatic urothelial cancer who received at least one dose of enfortumab vedotin 1.25 mg/kg and had prior treatment with a PD-1 or PD-L1 inhibitor and a platinum- based chemotherapy. Serious adverse events occurred in 46% of patients. The most common serious adverse reactions (≥ 2%) were rash (3%), nausea (2%), vomiting (2%) and fatigue (2%). The most common any grade adverse reactions (≥ 20%) were rash, fatigue, decreased appetite, alopecia, dysgeusia, peripheral neuropathy, nausea, diarrhea and dry skin. In Cohort 1, adverse events leading to discontinuation occurred in 16% of subjects; the most common adverse reaction leading to discontinuation was peripheral neuropathy (6%). Adverse events leading to dose interruption occurred in 64% of subjects; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%) and fatigue (6%). Adverse events leading to dose reduction occurred in 34% of subjects; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%) and fatigue (4%).	
Maximum dose tested	Single Dose	Not applicable
	Multiple Dose	1.25 mg/kg as an IV infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.
Exposure Achieved at Maximum Tested Dose	First Cycle (popPK)	Enfortumab vedotin: Cmax: 26.9 (23.8) µg/mL; Ctrough: 0.172 (148) µg/mL; AUC_{d0-28}: 104 (41.6) day*µg/mL Free MMAE: Cmax : 4.25 (50.8) ng/mL; Ctrough: 0.372 (127) ng/mL; AUC_{d0-28}: 59.1 (58.5) day*ng/mL
Linear PK	0.5 – 1.25 mg/kg	
Accumulation at steady state	Based on population PK analysis, minimal to no accumulation of enfortumab vedotin and free MMAE was observed. The accumulation ratio of Ctrough after Cycle 3 to Ctrough after Cycle 1 was 1.14 and 1.05 for enfortumab vedotin and free MMAE, respectively.	
Metabolites	Clearance of the IgG1 antibody is believed to be similar to endogenous IgG1, i.e., degradation to small peptides and individual amino acids. A small fraction of MMAE is metabolized. In vitro data indicate that the metabolism of MMAE occurs primarily via oxidation by CYP3A4. The metabolism of MMAE was evaluated clinically and in human hepatocytes. These studies indicated the metabolic pathways of hydroxylation, demethylation, dehydrogenation and hydrolysis were involved in the biotransformation of MMAE.	
Absorption	Bioavailability	Not applicable.
	Tmax (median at 1.25 mg/kg)	Enfortumab vedotin: At end of infusion, approximately 1 hour post start of infusion; Free MMAE: 2.00 days (48 hours) post start of infusion
Distribution	Vss (L) mean	(based on popPK) Enfortumab vedotin: 10.9 L; Free MMAE: 217.6 L
	% bound	Enfortumab vedotin: Not applicable; Free MMAE: 67.9% at 1 nM; 77.5% at 10 nM; 82.2% at 100 nM
Elimination	Route	Enfortumab vedotin: Antibody degradation to small peptides and individual amino acids; Free MMAE: The excretion of MMAE occurs mainly in feces with a smaller proportion in urine.
	Half-life (popPK)	Enfortumab vedotin elimination exhibited a multi-exponential decline with a mean elimination half-life of 3.35 days (80.5 hours). Elimination of MMAE appeared to be limited by its rate of release from enfortumab vedotin. MMAE elimination exhibited a multi-exponential decline with a mean terminal half-life of 2.44 days (58.5 hours).

	CL (L/hour)	(popPK, mean) Enfortumab vedotin: 0.104 L/hour; Free MMAE: 2.72 L/hour
Intrinsic factors	Age, Sex, Race	PopPK analysis indicates that age [range: 24 to 87 years; 54% (200/369) > 65 years, 20% (72/369) > 75 years], sex [68% (250/369) Male], or race [83% (305/369) Caucasian, 11% (42/369) Asian, 2% (8/369) Black and 4% (14/369) others or unknown] does not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin or free MMAE.
	Hepatic & Renal Impairment	The pharmacokinetics of enfortumab vedotin and free MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab vedotin to subjects with mild (creatinine clearance; CrCL > 60–90 mL/min; n=135), moderate (CrCL 30–60 mL/min; n=147) or severe (CrCL < 30 mL/min; n=8) renal impairment. Based on popPK analysis, no significant differences in AUC exposure of enfortumab vedotin and free MMAE were observed in subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. Based on popPK analysis using data from clinical trials in subjects with metastatic urothelial cancer, no significant difference in clearance of enfortumab vedotin and free MMAE was observed in subjects with mild hepatic impairment (bilirubin of 1 to 1.5 × ULN and AST < ULN, or bilirubin ≤ ULN and AST > ULN, n=31) compared to subjects with normal hepatic function. Enfortumab vedotin has not been studied in subjects with moderate or severe hepatic impairment.
Extrinsic factors	Drug interactions	Effects of Other Drugs on Enfortumab Vedotin Drug interaction assessments have not been conducted with enfortumab vedotin. Co-administration of another MMAE-containing ADC with ketoconazole, a potent CYP3A4 inhibitor, increased MMAE exposure by approximately 34%. Co-administration of another MMAE-containing ADC with rifampin, a potent CYP3A4 inducer, reduced MMAE exposure by approximately 46%. Effects of Enfortumab Vedotin on Other Drugs Coadministration of another MMAE-containing ADC did not affect exposure to midazolam, a CYP3A4 substrate. Enfortumab vedotin is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes. In vitro studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other CYP450 isoforms. MMAE did not induce major CYP450 enzymes in human hepatocytes. In vitro studies indicate that MMAE is a substrate and not an inhibitor of the efflux transporter P-glyco-protein (P-gp). In vitro studies determined that MMAE was not a substrate of breast cancer resistance protein (BCRP), multidrug resistance- associated protein 2 (MRP2), organic anion transporting polypeptide 1B1 or 1B3 (OATP1B1 or OATP1B3), organic cation transporter 2 (OCT2), or organic anion transporter 1 or 3 (OAT1 or OAT3). MMAE was not an inhibitor of the bile salt export pump (BSEP), P-gp, BCRP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations.
	Food Effects	Not applicable
Expected High Clinical Exposure: Concomitant administration of a strong inhibitor of CYP3A4 could increase free MMAE exposure by approximately 34%.		

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CHRISTINE E GARNETT
10/15/2019 10:53:32 AM

Ophthalmology Consult Review of BLA 761137

Consult Request Date: August 8, 2019
Review completed: December 1, 2019

Product name: Enfortumab vedotin

Applicant: Astellas Pharma US, Inc

Division Request: A new NME BLA 761137 application has come in for DOP1 on July 15, 2019. This will be a priority review under The Program (so, 8 month review clock) with a PDUFA due date of March 15, 2020. But targeting an earlier action date of December 10, 2019. The link to the submission is as follows: \\CDSESUB1\evsprod\BLA761137\0001
Reason for consult is to review ocular toxicities with the new BLA and to evaluate if the sponsor did the appropriate evaluation, and assist with labeling. Please provide DOP1 with a reviewer.

Eye Examination
A complete eye examination was performed at baseline by a qualified ophthalmologist or optometrist. All clinical studies included visual acuity. In Studies EV-201 and EV-102, the examination also was to include slit lamp, tonometry examination and dilated fundus examination.

In Study EV-201, baseline exams were required for everyone and end of treatment exams were required for anyone with a corneal AE observed during the study. In addition, slit lamp examinations were to be conducted on at least the first 60 enrolled subjects (from Cohorts 1 and/or 2) on cycle 2 day 22 and cycle 6 day 22. The Independent Data Monitoring Committee (IDMC) evaluated data from the cycle 2 day 22 and cycle 6 day 22 slit lamp examinations to determine the necessity for continued monitoring. On 11 July 2018, the IDMC reviewed cycle 2 day 22 slit lamp data for 43 evaluable subjects and recommended that slit lamp exams at cycle 2 day 22 could be discontinued for the remaining subjects. As of the preparation of this submission, there was insufficient data to determine the necessity of continuing with cycle 6 exams; therefore, they were continued.

In Study EV-101, eye exams were conducted at baseline and cycle 2 day 22 for all subjects and as needed for subjects with ocular findings or symptoms. In Study EV-102, ophthalmic examinations, including visual acuity testing, funduscopy, slit lamp microscopy and ophthalmotonometry, were performed at Screening, cycle 1 day 22, cycle 3 day 1 and day 1 of all odd cycles thereafter. If 3 consecutive eye exams (not including the exam at Screening) revealed no significant findings consistent with a drug related ocular change, then ophthalmic exams were only conducted at the onset of any eye symptoms going forward.

Reported Results:
Eye Disorders from Table 13 From Section 2.7.4 Summary-Clin-Safety: Treatment-emergent Adverse Events (≥ 10% of Total Subjects†) by System Organ Class and Preferred Term (Jul 2019: Page 29 of 98.

MedDRA (v20.0) **System Organ Class** Preferred term, n (%)	**EV-201 Cohort 1 1.25 mg/kg (n = 125)**	**EV-201 Cohort 2 1.25 mg/kg (n = 27)**	**EV-201 All Cohorts 1.25 mg/kg (n = 152)**	**Enfortumab Vedotin 1.25 mg/kg (n = 310)**	**All Enfortumab Vedotin (n = 379)**
Overall	**125 (100)**	**27 (100)**	**152 (100)**	**309 (99.7)**	**376 (99.2)**
Eye Disorders	**63 (50.4)**	**12 (44.4)**	**75 (49.3)**	**144 (46.5)**	**161 (42.5)**
Dry eye	29 (23.2)	10 (37.0)	39 (25.7)	59 (19.0)	61 (16.1)
Lacrimation increased	18 (14.4)	3 (11.1)	21 (13.8)	45 (14.5)	48 (12.7)
Vision blurred	19 (15.2)	3 (11.1)	22 (14.5)	38 (12.3)	46 (12.1)

Reviewer's Comments: *Dry eye and lacrimation increased are terms usually representing the same clinical entity. Dry eye may also be listed as keratitis or superficial punctate keratitis. Dry eye/lacrimation increased/keratitis often leads to blurred vision. It is not possible from the table or other summaries to identify the total number of individual patients with dry eye signs and symptoms. Therefore, using Listing 13.2.7.1 Treatment-Emergent Adverse Events Safety Analysis Set, a listing was created by this reviewer of all reported ocular adverse events in Study EV-201. See below.*

Site-Num	ID	Cohort	Onset Day	Dry or Watery	Dry, Watery or Keratitis	Dry Eyes	Watery eyes	Keratitis	Blurred Vision	Discomfort	Blepharitis	Cataract	Incidental or Redundant Findings
10004-0003	(b) (6)	1	43										Infective conjunctivitis, Subconj hem, eye infection
10004-0004		1	64										Senile furrow corneal degeneration
10066-006		1	120	Yes	Yes	Dry Eyes		Punctate keratitis	Blurred vision				
10004-0007		1	57		Yes			Punctate keratitis					
10004-0011		1	43	Yes	Yes	Dry Eyes							
10004-0012		1	57	Yes	Yes	Dry Eyes							
10004-0014		1	85	Yes	Yes	Limbal stem cell deficiency		Punctate keratitis					
10069-0016		1	127						Blurred vision				
10007-0019		1	36						Blurred vision				
10003-0020		1	323	Yes	Yes	Dry Eyes		Keratoconjunctivitis		Ocular discomfort			
10007-0021		1	64						Blurred vision				
10007-0025		1	29										Viral keratitis
10003-0030		1	80										
10004-0034		1	55		Yes			Punctate epithelial erosions	Blurred vision				Retinopathy
10004-0035		1	96										Herpes zoster v1
10068-0037		1	15					Conjunctivitis					
10030-0038		1	36	Yes	Yes		Watery eyes						
10063-0040		1	15		Yes			Keratitis	Blurred vision	Eye pain			Double vision
10008-0043		1	78	Yes	Yes	Dry Eyes	Watery eyes				Blepharitis		
10011-0045		1	99						Blurred vision				

	(b) (6)												
10019-0048		1	36	Yes	Yes		Watery eyes		Blurred vision				
10008-0049		1	50	Yes	Yes	Dry Eyes		Superficial punctate keratitis					
10003-0050		1	140										Respiratory Infection with orbital discharge
10065-0051		1	150									Cataract	Foreign body right eye
10005-0052		1	8		Yes			Keratitis		Eye pain			
10008-0054		1	15	Yes	Yes	Meibomian gland dysfunction	Watery eyes	Superficial punctate keratitis	Blurred vision				Posterior vitreous detachment, Pigment lesion on eyelid
10011-0059		1	43	Yes	Yes	Dry eyes	Watery eyes	Superficial punctate keratitis	Blurred vision				
10003-0060		1	30	Yes	Yes		Eye tearing						
10019-0063		1	50	Yes	Yes	Dry eyes		Keratopathy			Blepharitis	Cataract	Pinguecula
10008-0064		1	43	Yes	Yes	Dry Eyes	Watery eyes						
10001-0065		1	29						Blurred vision				
10008-0066		1	44										Posterior vitreous detachment
10030-0070		1	86	Yes	Yes		Eye tearing	Conjunctivitis					
10062-0071		1	8	Yes	Yes		Tearing		Blurred vision				
10004-0072		1	33									Cataract	
10008-0073		1	44								Blepharitis		Pinguecula; Peripapillary atrophy
10017-0075		1	45	Yes	Yes	Dry Eyes			Blurred vision				
10017-0077		1	56	Yes	Yes	Dry Eyes	Watery eyes	Keratitis					Punctal stenosis
10009-0079		1	226	Yes	Yes		Watery eyes						
10008-0080		1	37	Yes	Yes	Dry Eyes					Blepharitis		
10005-0081		1	155	Yes	Yes	Dry Eyes							Epiretinal membrane
10060-0082		1	8	Yes	Yes	Dry Eyes							

	(b) (6)												
10007-0083		1	153	Yes	Yes	Dry Eyes							
10015-0087		1	1	Yes	Yes	Dry Eyes							
10009-0092		1	99	Yes	Yes	Meibomian gland disfunction			Blurred vision				
10001-0093		1	85	Yes	Yes	Dry Eyes				Eye irritation			
10066-0097		1	16	Yes	Yes	Dry Eyes							
10020-0102		1	57	Yes	Yes	Dry Eyes							
10030-0104		1	155		Yes			Keratopathy			Blepharitis		
10020-0106		1	8	Yes	Yes	Dry Eyes	Watery eyes		Blurred vision			Cataract	Itchy eyes
10030-0108		1	183									Cataract	
10009-0109		1	42	Yes	Yes	Dry Eyes		Superficial punctate keratitis	Blurred vision		Blepharitis		Visual acuity decreased; Age related macular degeneration; Madarosis
10011-0110		1	85	Yes	Yes		Watery eyes						
10003-0111		1	167	Yes	Yes	Dry Eyes							Lattice retinal degeneration
10006-0112		1	114										Upper respiratory infection, Eye discharge
81010-0113		1	43										Corneal opacity
10010-0114		1	43	Yes	Yes	Dry Eyes							Whorl keratopathy
10017-0116		1	29	Yes	Yes		Watery eyes						Blood spot left eye
10011-0117		1	15					Punctate keratitis					
10009-0122		1	15	Yes	Yes		Watery eyes		Blurred vision		Blepharitis		Episcleritis
10052-0125		1	15	Yes	Yes	Dry Eyes			Blurred vision				
10008-0126		1	28	Yes	Yes	Dry Eyes		Superficial keratitis					Tear breakup time decreased
10001-0127		1	77	Yes	Yes	Dry Eyes	Lacrimation increased	Conjunctivitis			Madarosis		Cotton-wool spots; Eye purritis

	(b) (6)												
10019-0128		1	85	Yes	Yes	Dry eyes	Watery eyes	Conjunctivitis	Blurred Vision		Blepharitis		
81005-0132		1	29	Yes	Yes		Watery eyes						
81003-0136		1	15	Yes	Yes		Eye discharge						
Cohort 1 Summary			66	41	46	30	19	20	19	4	9	5	
10007-0001		2	141	Yes	Yes	Dry Eyes							
10008-0044		2	43	Yes	Yes	Dry eyes	Watery eyes	Superficial punctate keratitis	Blurred vision		Blepharitis		Posterior vitreous detachment, macular pigment, allergic conjunctivitis
10016-0074		2	190	Yes	Yes	Dry Eyes					Madarosis		Erythema of eyelid
10061-0115		2	78	Yes	Yes		Watery eyes						
81009-0133		2	8	Yes	Yes	Dry Eyes							
10002-0141		2	1	Yes	Yes	Dry Eyes							
10062-0142		2	1										Flashing lights, subepithelial corneal scar
10014-0143		2	71	Yes	Yes	Dry Eyes			Blurred vision				
10010-0144		2	49	Yes	Yes	Dry Eyes							
10014-0146		2	94	Yes	Yes	Dry Eyes							
10005-0149		2	45	Yes	Yes	Dry eyes	Tearing		Blurred vision	Ocular burning			Photophobia
10069-0151		2	45	Yes	Yes	Dry Eyes							
Cohort 2 Summary	27		12	11	11	10	3	1	3	1	2	0	
Total	152		78	52	57	40	22	21	22	5	11	5	

Reviewer's Comments:

1. *Regarding Study 201: of the 152 patients in the study, 78 reported an ocular adverse event. Of the 78 reported ocular adverse events, 5 had bacterial and/or viral infections affecting the ocular structures and 2 had a posterior vitreous detachment highly likely to be associated with advancing age without any dry eye findings.*
2. *The blurred vision reported in this study is almost always likely to be related to dry eye disease in the patient. Although there are other potential causes of decreased vision such as cataracts or macular degeneration, of the 5 patients reported to have cataracts, only one reported decreased vision.*
3. *Of the 152 patients in the study, 63 (41%) had signs or symptoms of dry eye disease (reported as either dry eyes/tearing/keratitis (58) or blurring without another cause of blurring (5)).*
4. *Reporting of ocular adverse events in this trial was inconsistent. There are only a couple of reports of posterior vitreous detachments and cataracts; however, based on the ages of the patients, it is highly likely that there were additional patients with these findings, but not reported.*
5. *A Warning/Precaution concerning dry eye signs and symptoms is recommended such as:*

   "Ocular disorders occurred in 46% of the 310 patients treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, increased tearing, limbal stem cell deficiency and other events associated with dry eyes.

   Dry eye symptoms were reported in approximately 40% of patients. The median time to onset to symptomatic dry eye disorder was 6 weeks.

   Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after a slit lamp exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders."

Wiley A. Chambers, M.D.,
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
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