Consult Memorandum

Date: May 4, 2018
To: Quyen Tran RPM and Bindu Kanapuru MD CDER/OCE/OHOP/DOP2
From: Janaki Veeraraghavan CDRH/OIR/DMGP/MGB
Through: Donna Roscoe Branch Chief CDRH/OIR/DMGP/MGB; Reena Philip Division Director CDRH/OIR/DMGP
Subject: BLA781104

Drug Name: Moxetumomab pasudotox
Drug Sponsor: Astra Zeneca
Biomarker(s): CD20, DBA.44, Annexin A1, PAX5 and CD79a
Device Name: Various IHC test
Device Sponsor: None
CDRH Tracking Number: ICC 1800912.

Related Submissions:

I. BACKGROUND and PURPOSE
DHP is in receipt of an original BLA for a NME Moxetumomab pasudotox for treatment of adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analog. The application includes Minimal Residual Disease (MRD) assessment based on blinded independent central review (BICR) by immunohistochemistry (IHC) for 5 biomarkers – CD20, Annexin A1, DBA.44, PAX5 and CD79a - primarily in the bone marrow. DHP would like to consult CDRH regarding the MRD data.

II. MRD BIOMARKERS/ANALYTES
Primary Marker: CD20: All Bone marrow biopsy specimens in the study were stained for CD20 to assess MRD
Ancillary Markers: Annexin A1, CD20, Pax-5, DAB.44 and CD79a. These 4 markers were used variably on samples across the study.

MRD assessment:
Minimal residual disease (MRD) burden in study subjects was determined by blinded independent central review (BICR) with pathologist evaluation of H&E and IHC stained slides of Bone marrow biopsy or aspirate specimens from study subjects. Patient samples for MRD assessment were collected at baseline (4 weeks prior to treatment enrollment) and end of 6 cycles of therapy if subjects blood count was consistent with CR for at least 4 weeks. A post end of treatment assessment was also performed between days 181 and day 195. Additional interim analysis was performed at investigators discretion. Pathologist assessment of MRD was based on both H&E and IHC stains for the analytes noted above.
MRD assessment was performed by 3 pathologists, two were primary reviewers and one confirmatory reviewer and all were blinded to
- Subject demographics per GCP and HIPAA requirements
- Site assessments

www.fda.gov

Reference ID: 4319518
Study Treatment Assignment
Clinical history
Results of the Radiology Reviewer’s and Oncology Reviewer’s assessments
Results of the other Pathology Reviewers
The Confirmatory Reviewer will not know the reason for the discordance

The overall assessment was performed per the protocol in the flow chart below:

Pathology Review Flow Chart

[Diagram]
Reviewer Note: Bone marrow specimens appear to have been assessed at baseline,

II. DEVICE USE IN THE TRIAL
Sponsor used a mix of central lab testing and multiple lab developed test (LDT) for the following 5 biomarkers:

- CD20,
- Annexin A1,
- PAX5,
- DBA.44
- CD79a

These markers were assessed by immunohistochemistry tests on bone marrow biopsies or aspirates obtained at baseline and at end of treatment. The sponsor utilized local IHC test for staining patient bone marrow biopsy where tests were available and a central lab provided H&E, CD20 and CD79a stains for specimen’s from select sites where local testing was unavailable.

In response to an IR the sponsor clarified that all patient samples were tested for CD20 and that additional 4 biomarker testing was based on availability at local and central testing sites. And sponsor indicated that 56 patients from 20 sites had all slides stained locally and 24 patients from 12 sites had some or all slides stained by central Lab.

Clinical Cut off:
Bone Marrow biopsy samples were assessed for hairy cell percentage and classified as MRD positive or negative on the following criteria

Morphologically negative: <5% scattered staining with no clusters and sheeting

MRD Positive: IHC was <5% staining but clear clusters and sheets were present, If IHC staining was >5% with or without clustering or sheeting

Reviewer Note: It appears that the 5 biomarkers were not uniformly used to assess MRD status for the study subjects. While sponsor claims that CD20 was used universally they have not provided the criteria used to trigger staining for additional biomarkers or how these biomarker staining statuses contributed to the final MRD score.

In response to an information request on the criteria applied to assess MRD and if any pathologist scoring guide was provided for assessment of MRD status for study subjects the sponsor provided the following:

“No written pathologist interpretation guide was used by the blinded independent central review (BICR) pathologists in the pivotal Phase 3 and supportive Phase 1 HCL studies. According to the BICR pathologist who reviewed the IHC slides (i.e., the minimal residual disease [MRD] pathologist), Hematoxylin and Eosin (H&E) slides were reviewed before IHC slides, and high-level or low-level involvement (descriptive, not quantitative) was determined before counting the percentage of involvement. CD20 was used primarily to determine the presence and percentage of hairy cell involvement. CD20-positive HCL cells were distinguished from normal CD20-positive B cells based on typical hairy cell bone marrow infiltration patterns (interstitial infiltrative and/or in clusters) and IHC staining with other markers. Annexin A1 and DBA.44 were only used to confirm hairy cells in CD20-positive clusters; they were not used in isolation to confirm hairy cells in case of low-level involvement because both Annexin and DBA.44 stain other hematopoietic cells in the marrow. CD79a and PAX-5, which not only stain B cells but also plasma cells, were also supplementary to CD20 to confirm hairy cell infiltrates.
There was not a requirement for cells to be dual or multiple marker positive to qualify as MRD positive. Samples with no (0%) involvement were reported as MRD negative and any involvement was considered MRD positive.

Based on the response of the pathologist the evaluation of MRD status was based on a pathologist expertise and subjective criteria does not appear to have been standardized for the trial. Given the unknown variability in IHC methodology for various markers and the use of the 5 markers in uneven fashion though out the trial the reliability of the MRD measurement remains unclear.

MRD IHC protocol and analytical validation:
Sponsor did not provide the specific protocols for the 5 IHC tests used to assess IHC MRD in the study. In response to an information request sponsor clarified that protocols used at local sites may have differed and that details on the variation were not available. Sponsor states that CD20 and CD79a are considered standard and performed routinely in pathology labs. The following information was provided on the testing methodology:

- IHC staining was performed using commercially available antibodies and automated staining machines. Some sites noted that internal validation for lab developed test was performed. However, no specifics on the
- IHC staining was performed at laboratories that are credentialed (e.g. CLIA certified) and by technicians who are specifically trained.
- The quality of the stain was readily assessed by the pathologists when they interpret the IHC.

In addition, the sponsor notes that pathologist at local sites considered that commercially available antibodies for staining CD20 and CD79 a were reliable and robust. However, sponsor has not provided any analytical validation data to support this conclusion.

Reviewer Note: Absent protocols and analytical validation data it is not feasible to determine the adequacy of the MRD test performance for its intended use to assess minimal residual disease in the clinical study population. The reliability of the MRD results is unknown because of the study’s use of many local tests without an understanding of the variation in performance characteristic for the local tests and therefore the comparability of test results across study sites, raises an

III. MRD results

Specimen Adjudication for IHC testing:
For the Phase 3 study CD-ON-CAT-8015-1053, all 80 patients in the Intent-to-Treat (ITT) population were tested for IHC MRD and read by BICR. Seventy-nine patients (98.8%) had valid IHC MRD results including 33 patients (41.3%) as MRD negative and 46 patients (57.5%) as MRD positive. There was one patient without valid results due to non-evaluable biopsy specimens. Sixty-six patients (82.5%) had the best MRD result concordant with the best H&E assessment and the remaining 14 patients (17.5%) were different. Seven of the 14 patients had positive IHC MRD result while H&E assessment was negative, possibly because IHC MRD is a more sensitive method than H&E assessment. There were 5 patients whose best H&E assessment was positive but best MRD result was negative. One of the remaining two patients had un evaluable IHC MRD and another one had un evaluable H&E assessment.
Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>40 ug/kg N=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients Tested for MRD</td>
<td>80 (100%)</td>
</tr>
<tr>
<td>Number of Patients with Valid MRD Results</td>
<td>79 (98.8%)</td>
</tr>
<tr>
<td>MRD Negative</td>
<td>33 (41.3%)</td>
</tr>
<tr>
<td>MRD Positive</td>
<td>46 (57.5%)</td>
</tr>
<tr>
<td>Number of Patients without Valid MRD Results</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Number of Patients with Concordant H&amp;E Assessment</td>
<td>66 (82.5%)</td>
</tr>
<tr>
<td>Number of Patients with Discordant H&amp;E Assessment</td>
<td>14 (17.5%)</td>
</tr>
<tr>
<td>H&amp;E Positive and MRD Negative</td>
<td>5 (6.3%)</td>
</tr>
<tr>
<td>H&amp;E Negative and MRD Positive</td>
<td>7 (8.8%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>H&amp;E Not Evaluable</td>
<td></td>
</tr>
<tr>
<td>MRD Not Evaluable</td>
<td>1</td>
</tr>
</tbody>
</table>

Reviewer Note: The time point of MRD assessment (baseline, post treatment or 180 day assessment) is not specified for the data presented above.

Concordance between the MRD assessment by H&E and IHC methodology for MRD assessment is summarized in the table below

Table 2

<table>
<thead>
<tr>
<th>Best IHC MRD Results/Best H&amp;E Results</th>
<th>H&amp;E Negative</th>
<th>H&amp;E Positive</th>
<th>H&amp;E Not evaluable/Not done</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC MRD Negative</td>
<td>28 (35.0%)</td>
<td>5 (6.3%)</td>
<td>0</td>
<td>33 (41.3%)</td>
</tr>
<tr>
<td>IHC MRD Positive</td>
<td>7 (8.8%)</td>
<td>38 (47.5%)</td>
<td>1 (1.3%)</td>
<td>46 (57.5%)</td>
</tr>
<tr>
<td>IHC MRD Not evaluable / Not done</td>
<td>1 (1.3%)</td>
<td>0</td>
<td>0</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (45.0%)</td>
<td>43 (53.8%)</td>
<td>1 (1.3%)</td>
<td>80 (100.0)</td>
</tr>
</tbody>
</table>

Sponsor was requested to clarify the direction in which the discordance was resolved for the 5 IHC negative H&E positive cases and in response the following data was provided by the sponsor.
In response to a request to clarify the number of study subjects tested with the 5 markers for IHC MRD, the sponsor stated that Post-baseline immunohistochemistry (IHC) staining was performed for 68 patients and provided the following data:

<table>
<thead>
<tr>
<th>IHC marker</th>
<th>CD20</th>
<th>CD79a</th>
<th>PAX5</th>
<th>Annexin A1</th>
<th>DBA.44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>68</td>
<td>58</td>
<td>47</td>
<td>20</td>
<td>23</td>
</tr>
</tbody>
</table>

IHC = immunohistochemistry

Reviewer Note: Based on the tables above it appears that the MRD data for all patients was at baseline and that post baseline assessment is available for 68 of the 80 patients. The sponsor has not provided an explanation for missing data on 12 patients.

The following data was provided as an update to baseline and post baseline IHC MRD measurements in the trial population.
Table 3  Summary of IHC MRD Results per BICR – ITT population
(Study CD-ON-CAT-8015-1053)

<table>
<thead>
<tr>
<th>Category</th>
<th>40 µg/kg N=80</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline and Post-Baseline</td>
</tr>
<tr>
<td>Number of Patients with IHC pathology report by BICR</td>
<td>80 (100%)</td>
</tr>
<tr>
<td>Number of Patients with Valid MRD Results</td>
<td></td>
</tr>
<tr>
<td>MRD Negative</td>
<td>79 (98.8%)</td>
</tr>
<tr>
<td>MRD Positive</td>
<td>33 (41.3%)</td>
</tr>
<tr>
<td>Number of Patients with MRD results by</td>
<td></td>
</tr>
<tr>
<td>BICR, but without Valid MRD Results</td>
<td>46 (57.5%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Not Done</td>
<td>0</td>
</tr>
<tr>
<td>Number of Patients with Concordant H&amp;E Assessment</td>
<td>66 (82.5%)</td>
</tr>
<tr>
<td>Number of Patients with Discordant H&amp;E and MRD</td>
<td></td>
</tr>
<tr>
<td>Assessments</td>
<td>14 (17.5%)</td>
</tr>
<tr>
<td>H&amp;E Positive and MRD Negative</td>
<td>5 (6.3%)</td>
</tr>
<tr>
<td>H&amp;E Negative and MRD Positive</td>
<td>7 (8.8%)</td>
</tr>
<tr>
<td>Not Evaluable/Not Done</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>H&amp;E Not Evaluable/Not Done</td>
<td></td>
</tr>
<tr>
<td>MRD Not Evaluable/Not Done</td>
<td>1</td>
</tr>
</tbody>
</table>

H&E = Hematoxylin and Eosin; IHC = immunohistochemistry; MRD = minimal residual disease

As reported in Table 1 of AstraZeneca’s response to FDA’s clinical information request received on 23Mar2018 (response submitted in Serial No. 0009 on 02Apr2018).

CDRH RESPONSE TO [SPONSOR/CDER] QUESTIONS

Question from DHP Clinical to CDRH: DHP is in receipt of an original BLA for a NME. The application includes MRD assessment based on blinded independent central review (BICR) by immunohistochemistry (IHC) and primarily in the bone marrow. DHP would like to consult CDRH regarding the MRD data.

CDRH Comment: The MRD data included in the submission was generated with a subject bone marrow aspirate or biopsy specimens being tested with variety of local tests for five biomarkers: CD20, Annexin A1, DBA44 and CD79a. Sponsor has indicated that all specimens form the study were assessed with CD20 with the ancillary biomarkers being used variably. No scoring algorithm was provided for the use of ancillary biomarkers and sponsor did not clearly describe the criteria used apply these in MRD assessment. Staining protocols and performance characteristics of the local lab tests as well as the central lab was not provided for review and the sponsor asserted that pathologist considered these tests to be robust and reliable. Furthermore, it appears that while baseline MRD status was available for the entire study population post baseline assessment was available for only 68 patients.

The MRD data included in the submission is uninterpretable for the following reasons
1) The use of multiple local tests with unknown protocols and performance characteristics, and therefore the reliability of the MRD measure is unknown.
2) The comparability of testing metrics between the various local tests was not demonstrated.
3) The use of non-uniform use of the 4 markers across the study subjects making the interpretation of the data harder.
4) Lack of detail on the scoring criteria/algorithm for using the four additional biomarkers suggests a level of subjectivity for assessing MRD and therefore variable.

V. DISEASE BACKGROUND

Waiting on CDER review to incorporate for our records.

CLOSEOUT CHECKLIST

1. After Branch and Division review, remove Part II from the memo and upload your final CDRH consult pdf to DARRTS.
2. In CTS, upload the full consult memo (with Part II), the meeting package and meeting minutes (if available), and add comments, as needed. Then make recommendation to close the ICC.
3. Close ICCR form in SharePoint.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WANDA D NGUYEN
09/12/2018
Review completed by Janaki on 5/4/18
1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Lumoxiti (moxetumomab pasudotox-tdfk) for injection (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.\(^a\) In addition, the Agency requested revisions to the IV Solution Stabilizer carton label and container labeling in an email dated August 20, 2018\(^b\).

2 CONCLUSION

The revised container label, and carton labeling for Lumoxiti (moxetumomab pasudotox-tdfk) for injection are acceptable from a medication error perspective. We have no further recommendations at this time.

\(^a\) Ogbonna, C. Label and Labeling Review for Lumoxiti (moxetumomab pasudotox) BLA 761104. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 03. RCM No.: 2017-2435.

\(^b\) Nguyen, W. Email to Jessica Allmond. Silver Spring (MD): FDA, OMPT/CDER/OND/OHOP/DHP(US); 2018 AUG 20.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CASIMIR I OGBONNA
08/27/2018

HINA S MEHTA
08/30/2018
Date of This Review: August 1, 2018
Responsible OND Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761104
Product Name and Strength: Lumoxiti (moxetumomab pasudotox-tdfk) injection, 1 mg/vial
Product Type: Single Ingredient Product
Applicant/Sponsor Name: AstraZeneca
FDA Received Date: January 29, 2018
OSE RCM #: 2018-887
DMEPA Primary Reviewer: Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Deputy Director: Danielle Harris, PharmD, BCPS
1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffix for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761104.

1.1 Regulatory History

AstraZeneca was notified of the Agency’s intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Lettera.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

moxetumomab pasudotox-tdfk

FDA generated a four-letter suffix, -tdfk. This suffix was evaluated using the principles described in the applicable guidanceb.

We determined that the FDA-generated suffix -tdfk, is not too similar to any other products’ suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 COMMUNICATION OF DMEPA’S ANALYSIS

These findings were shared with OPDP. In email correspondence dated August 1, 2018, OPDP did not identify any concerns that would render this suffix unacceptable. DMEPA also communicated our findings to the Division of Hematology Products (DHP) via e-mail on August 1, 2018.

4 CONCLUSION

We find the suffix -tdfk acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to moxetumomab pasudotox-tdfk.

4.1 Recommendation for AstraZeneca

We find the nonproprietary name, moxetumomab pasudotox-tdfk, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, moxetumomab pasudotox-tdfk will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of this suffix will be re-evaluated.


b See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from:


Reference ID: 4300758
when you respond to the deficiencies. If we find the suffix unacceptable upon our re-evaluation, we would inform you of our finding.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CASMIR I OGBONNA  
08/01/2018

DANIELLE M HARRIS  
08/02/2018
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date: August 1, 2018

To: Ann Farrell, MD
   Director
   Division of Hematology Products (DHP)

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)

   Nisha Patel, PharmD
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): LUMOXITI (moxetumomab pasudotox)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761104

Applicant: AstraZeneca

Reference ID: 4300422
1 INTRODUCTION

On November 30, 2017, AstraZeneca submitted for the Agency’s review a Biologics License Application (BLA) 761104 for TRADENAME (moxetumomab pasudotox) for injection. The proposed indication is for the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog (PNA).

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 Hematology Products (DHP) on January 10, 2018 for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) for TRADENAME (moxetumomab pasudotox) for injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (moxetumomab pasudotox) for injection MG received on November 30, 2017, and received by DMPP and OPDP on July 17, 2018.
- Draft TRADENAME (moxetumomab pasudotox) for injection Prescribing Information (PI) received on November 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 17, 2018.

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 PHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

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

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

------------------------------------------------------------
MORGAN A WALKER
08/01/2018

NISHA PATEL
08/01/2018

LASHAWN M GRIFFITHS
08/01/2018
In response to DHP’s consult request dated January 10, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and Instructions for Use (IFU) for the original BLA submission for LUMOXITI™ (moxetumomab pasudotox) for injection, for intravenous use (Lumoxiti).

**PI, Medication Guide, and IFU:** OPDP’s comments on the proposed labeling are based on the draft PI and IFU emailed to OPDP on July 17, 2018. We have no comments on the draft PI and IFU at this time.

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

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NISHA PATEL
07/31/2018
**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***

<table>
<thead>
<tr>
<th>Date of This Review:</th>
<th>July 03, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Hematology Products (DHP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>BLA 761104</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td>Lumoxiti (moxetumomab pasudotox) injection</td>
</tr>
<tr>
<td>(a) mg/vial</td>
<td></td>
</tr>
<tr>
<td>Product Type:</td>
<td>Single ingredient</td>
</tr>
<tr>
<td>Rx or OTC:</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant/Sponsor Name:</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>FDA Received Date:</td>
<td>November 30, 2017</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2017-2435</td>
</tr>
<tr>
<td>DMEPA Safety Evaluator:</td>
<td>Casmir Ogbonna, PharmD, MBA, BCPS, BCGP</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Hina Mehta, PharmD</td>
</tr>
</tbody>
</table>

---

\(^a\) The product strength is being evaluated by Office of Pharmaceutical Quality (OPQ). For purposes of label and labeling review we evaluated the strength as \((b) (4)\) mg per vial.
1 REASON FOR REVIEW
This review responds to a request from the Division of Hematology Products (DHP) to review the Prescribing Information (PI), carton labeling, and container labels for Lumoxiti (moxetumomab pasudotox) injection for areas of vulnerability that may lead to medication errors. On November 30, 2017, AstraZeneca submitted an original BLA 761104 for Lumoxiti (moxetumomab pasudotox) injection, a CD22-directed immunotoxin indicated for the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog (PNA).

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>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C – N/A</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D – N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E – N/A</td>
</tr>
<tr>
<td>Other**</td>
<td>F</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A = not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance
** May 16, 2018 Information Request and May 22, 2018 Applicant Response

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED
DMEPA evaluated the proposed Prescribing Information (PI), carton labeling, and container labels for areas of vulnerability in regards to medication error. We note that Section 3 of the PI states the following:
For Injection: *(b)(4) mg lyophilized powder in a single-dose vial for reconstitution and further dilution.*

We defer to the Office of Pharmaceutical Quality (OPQ) to determine the acceptability of the strength statement in Section 3 of the PI. However, per the Applicant, we note that the actual strength will be listed on the carton labeling and container label.
Additionally, we note that the product is to be used with an Intravenous Solution Stabilizer (IVSS), which is not co-packaged with the drug product, Lumoxiti. Given our concerns that health care providers may only administer the IVSS or forget to use the IVSS during preparation of the drug product, we sent an Information Request (IR) on May 16, 2018 requesting that the Applicant submit their plans to mitigate the risk of this error. On May 22, 2018, the Applicant responded to the IR, stating that multiple drug product vials may be needed to prepare the dose which is dependent on the patient weight (dose is 0.04 mg/kg administered as a 30-minute intravenous infusion) but only one vial of IVSS is needed per infusion bag preparation. The Applicant stated that separate packaging reduces risk of the IVSS being used as a diluent to reconstitute the drug as well reduces risk using multiple IVSS vials for infusion bag preparation. Furthermore, the Applicant states that the

Therefore, given the product distribution and labels and labeling, we find the Applicant’s proposal acceptable in this instance.

We identified areas of concern in the PI, carton labeling and container labels that should be revised to improve the clarity of the information presented. We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the PI and 4.2 for the carton and container labels to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. HIGHLIGHTS OF PRESCRIBING INFORMATION
   1. Dosage and Administration
      a. Combine the first two bullets for clarity. Revise to “0.04 mg/kg as an intravenous infusion over 30 minutes on days 1, 3, and 5 of each 28-day cycle. (2.1)”

B. FULL PRESCRIBING INFORMATION
   1. Section 2.4 Instructions for Reconstitution, Dilution, and Administration
a. Consider revising the title of step 2 from “(b)(4)” to “Reconstitution”, and step 3 from “(b)(4)”, to “Dilution”.

4.2 RECOMMENDATIONS FOR ASTRAZENECA

We recommend the following be implemented prior to approval of this BLA 761104:

A. Lumoxiti Carton Labeling


B. Intravenous Solution Stabilizer Carton Labeling

C. Container Label for Lumoxiti and IV Solution Stabilizer:

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:
   DDMMMYYYY (e.g., 31JAN2013)
   MMMYYYY (e.g., JAN2013)
   YYYY-MMM-DD (e.g., 2013-JAN-31)
   YYYY-MM-DD (e.g., 2013-01-31)
Table 2. Relevant Product Information for Lumoxiti

<table>
<thead>
<tr>
<th>Initial Approval Date</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>moxetumomab pasudotox</td>
</tr>
<tr>
<td>Indication</td>
<td>For the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog (PNA).</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Lyophilized powder</td>
</tr>
<tr>
<td>Strength</td>
<td>(b) (4) mg</td>
</tr>
<tr>
<td>Dose and Frequency</td>
<td>0.04 mg/kg administered as a 30-minute intravenous infusion on Days 1, 3, and 5 of each 28-day cycle. Patients should continue treatment until a maximum of 6 cycles, disease progression, or unacceptable toxicity.</td>
</tr>
<tr>
<td>How Supplied</td>
<td>LUMOXITI (moxetumomab pasudotox) for Injection:</td>
</tr>
<tr>
<td></td>
<td>- Sterile, preservative-free, white to off-white lyophilized powder supplied in individually boxed single-dose vials.</td>
</tr>
<tr>
<td></td>
<td>- Each vial delivers (b) (4) mg moxetumomab pasudotox.</td>
</tr>
<tr>
<td></td>
<td>IV Solution Stabilizer:</td>
</tr>
<tr>
<td></td>
<td>- Sterile, preservative-free, colorless to slightly yellow, clear solution free from visible particles supplied in individually boxed single-dose vials.</td>
</tr>
<tr>
<td></td>
<td>- Each vial contains 1 mL solution. Do not use the IV Solution Stabilizer to reconstitute LUMOXITI.</td>
</tr>
<tr>
<td>Storage</td>
<td>Refrigerate LUMOXITI and IV Solution Stabilizer at 2°C to 8°C (36°F to 46°F), in original carton to protect from light. Do not freeze. Do not shake.</td>
</tr>
</tbody>
</table>
APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 14, 2018, we searched DMEPA’s previous reviews using the terms, Lumoxiti. Our
search identified no previous reviews.

APPENDIX F. INFORMATION REQUEST

\cdsesub1\evsprod\bla761104\0019\m1\us\multiple-module-information-amendment.pdf

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 Lumoxiti labels and labeling
submitted by AstraZeneca.

- Intravenous Solution Stabilizer Carton Label received on November 30, 2017
- Intravenous Solution Stabilizer Container Label received on November 30, 2017
- Carton label received on November 30, 2017
- Container label received on November 2017
- Prescribing Information received on November 30, 2017

\cdsesub1\evsprod\bla761104\0001\m1\us\draft-labeling-text-clean.pdf

---

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

/s/

CASIMIR I OGBONNA
07/03/2018

HINA S MEHTA
07/09/2018
Ophthalmology Consult Review of BLA 761104

BLA 761104

Submission Date: November 30, 2017
Consult Request Date: April 23, 2018
Review completed: June 6, 2018

Name: Moxetumomab pasudotox
Applicant: AstraZeneca AB
Class: CD22-directed immunotoxin

Background: Please access the safety data on ocular toxicity for moxetumomab pasudotox reported in the pivotal Hairy Cell leukemia trial CAT-1053 and in the safety database. Visual disorders AEs (EYE DISORDERS SOC) were reported in 24/80 subjects in the CAT-1053 study and 29/165 subjects in the overall safety population. Screening ophthalmological assessments were conducted in the pivotal CAT-1053 study. One patient had event of Grade 2 vision blurred and Grade 2 bilateral optic ischemic neuropathy on the 1002 NHL study (safety population) and treatment was permanently discontinued for this patient. The Sponsor has not proposed inclusion of ocular toxicity in the PI.

Please address specifically the following in your review:
1. Are screening and follow up ophthalmological assessments required for patients receiving moxetumomab?
2. Are any dose modifications (treatment interruption or discontinuation) needed to manage specific ocular toxicities?
3. Are there any other additional measures that should be taken to mitigate the risk of visual AEs and ensure that the risks to subjects are reasonable?

EDR link to BLA 761104: \CDSESUB1\evsprod\BLA761104\0001

Potential Errors and/or Misstatements in the Application:

The original application contained a number of errors in the principle study report: cd-on-cat-8015-1053-clinical-report.pdf

These errors included in Listing 16.2_7.11:

<table>
<thead>
<tr>
<th>Column Headings</th>
<th>Third Column should be Retinal Abnormalities, not Renal Abnormalities. Fourth Column should be Retinal- Specify, not Renal – Specify.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject:</td>
<td>Retinal degeneration is reported in the left eye, but not the right on June 25, 2013. Retinal degeneration is reported in the right eye, but not the left on January 22, 2014.</td>
</tr>
<tr>
<td>Subject:</td>
<td>Intraocular Pressure slightly high on left eye is listed as a corneal finding, but the cornea does not cause elevations in intraocular pressure.</td>
</tr>
<tr>
<td>Subject:</td>
<td>A cataract was incorrectly listed as a corneal abnormality.</td>
</tr>
</tbody>
</table>

Reference ID: 4274339 (b) (6)
Amblyopia and strabismus were incorrectly listed as lens abnormalities.

Glaucoma was incorrectly listed as a corneal abnormality.

Cataracts were listed as retinal abnormalities.

Epiretinal Gliosis is listed as a retinal degeneration adverse event, but not listed on the ophthalmic examination.

An unknown phrase is listed as a retinal abnormality (i.e., Dehiscence of the retina)

An epiretinal membrane was described as resolving without being surgically removed.

The study report focuses on the Ocular Adverse Events of Special Interest (Ocular AESIs) as though they were inclusive of all ocular events. The Ocular AESIs were defined as any clinically significant change in vision, retinal abnormalities, or choroidal disturbance that occurred during the course of the study. But it was not clear why this definition was used for Ocular AESI. Forty percent of the ocular adverse events were not reported as Ocular AESIs because they did not have Preferred Terms (PT) included on a particular list. The events which were not listed as Ocular AESI, but were reported in the trial included: Conjunctivitis, Conjunctival hyperaemia, Conjunctival haemorrhage, Cataract, Dry eye, Lacrimation increased (likely to be Dry eye), Eye discharge, Eye contusion, Eye pain, Eye swelling, Abnormal sensation in the eye, Ocular discomfort, Eyelid oedema, Ocular hyperaemia, and Periorbital oedema.

Response to Consult Questions:

Question 1. Are screening and follow up ophthalmological assessments required for patients receiving moxetumomab?

Response: The monitoring and reporting of ophthalmic adverse events in Study Cat-8015-1053 was not sufficient to adequately characterize the effect of moxetumomab pasudotox on the eye. It is therefore not possible to determine whether ophthalmological assessments should be required for patients receiving moxetumomab.

Question 2. Are any dose modifications (treatment interruption or discontinuation) needed to manage specific ocular toxicities?

Response: The submitted clinical trials did not evaluate the effect that dose modifications of moxetumomab would have on ocular toxicities.
3. Are there any other additional measures that should be taken to mitigate the risk of visual AEs and ensure that the risks to subjects are reasonable?

Response: The monitoring and reporting of ophthalmic adverse events in Study Cat-8015-1053 was not sufficient to adequately characterize the effect of moxetumomab pasudotox on the eye. It is therefore not possible to determine whether ophthalmological assessments should be required for patients receiving moxetumomab.

Summary Review Comments: The monitoring and reporting of ophthalmic adverse events in Study Cat-8015-1053 was not sufficient to adequately characterize the effect of moxetumomab pasudotox on the eye. In a number of cases, the applicant has inaccurately characterized or classified the adverse events. The relative seriousness of each ocular event and the potential relationship of the ocular event to the drug product cannot be ascertained based on the reports from the investigator or applicant. The most serious ocular event reported was an ischemic optic neuropathy, but there is only a single report and the relationship to the drug product is unclear. It is therefore recommended that the following ocular adverse events be added to the labeling:

Labeling: Adverse Reactions: Clinical Trials Experience

Ocular adverse reactions occurred at a frequency of 1 to 10% including: blurred vision, conjunctivitis, conjunctival hemorrhage, cataracts, ocular discomfort and/or pain, dry eye, ocular discharge, and ocular swelling/peri-orbital edema.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
06/07/2018
This memo responds to your consult to us dated 2/27/2018 regarding the potential for QT prolongation for moxetumomab pasudotox. The QT-IRT reviewed the following materials:

- CD-ON-CAT-8015-1053 CSR submitted to Sequence #0001 dated 11/29/2017;
- CD-ON-CAT-8015-1053 Protocol submitted to Sequence #0001 dated 11/30/2017;
- Introduction included in module 2.2 submitted to Sequence #0001 dated 11/29/2017;
- Summary of Clinical Safety submitted to Sequence #0001 dated 11/30/2017; and

1. **QT-IRT Responses to the Division**

**Question:** DHP would like to consult QT/IRT regarding the EKG assessments that were conducted in the pivotal and supportive studies in BLA 761104. DHP would like to know if there are any potential risks, including QT prolongation, with moxetumomab pasudotox.

**QT-IRT’s response:** The clinical data do not suggest a significant risk for QT prolongation.
2. BACKGROUND

**Product Information**

Moxetumomab pasudotox is an approximately 63 kDa recombinant immunotoxin targeting the B cell-specific surface antigen cluster of differentiation 22 (CD22). Moxetumomab pasudotox is composed of an immunoglobulin light chain variable domain (VL) and a heavy chain variable domain (VH) genetically fused to a truncated form of Pseudomonas exotoxin (PE38).

Following specific binding of CD22 on the surface of B cells via the anti-CD22 moiety, the complex is rapidly endocytosed and then processed to release the exotoxin. The truncated PE38 protein lacks the cell binding domain (Domain Ia) to reduce nonspecific cellular toxicity, but retains the sequences to allow for translocation to the cytosol and catalysis of ADP ribosylation of elongation factor 2. The primary pharmacologic effect of moxetumomab pasudotox is inhibition of protein synthesis of cells expressing the target protein, CD22, resulting in apoptotic cell death.

The recommended dose of moxetumomab pasudotox is 0.04 mg/kg administered as a 30-minute intravenous infusion on Days 1, 3, and 5 of each 28-day cycle. Patients should continue treatment until a maximum of 6 cycles, disease progression, or unacceptable toxicity.

**Preclinical cardiac safety**

Cardiovascular/respiratory evaluations following single and repeated dosing with moxetumomab pasudotox at doses up to 1.35 mg/kg were conducted on 56 monkeys.

Potential effects on the cardiovascular system were evaluated following single and repeated dosing with moxetumomab pasudotox by performing electrocardiograms and measuring blood pressure, and heart rate. PR-interval, QRS duration, QT-interval and QTc were determined and the data was interpreted by a board-certified veterinary cardiologist.

There were no ECG findings in the 2-cycle toxicity study.

**Clinical cardiac safety**

No formal QT evaluation has been done for moxetumomab pasudotox as it is a large targeted molecule and therefore has a low likelihood of direct ion channel interactions.

In the pivotal study, centrally-read ECGs were collected between 30 to 60 min after end of infusion on days 1 and 5 in the first cycle in the pivotal study (CD-ON-CAT-8015-1053; n=80). In total the study included 3 planned ECGs (cycle 1 days 1 and 5) and end of treatment. The results of planned ECGs are shown in Table 1.

Two patients (2.7%) had a QTcF value exceeding 500 ms.

- PID (b) had an ongoing medical history of ECG QT prolonged. The QTcF at screening was 482 ms and the QTcF value exceed 500 ms on Cycle 1 Day 5 (507 ms), Pre-Cycle 2 (509 ms) and Pre-Cycle 3 (511 ms). At other times the QTcF ranged from 480 ms to 500 ms.
- PID (b) had a maximal increase in the QTcF compared to baseline exceeding 90 ms. The QTcF at screening was 414 ms and the QTcF value was 509 ms on Cycle 1 Day 5. At other times, the QTcF ranged from 398 to 418 ms.
Table 1: Categorical ECG analysis of pivotal study (CD-ON-CAT-8015-1053)

<table>
<thead>
<tr>
<th>Parameters/Criteria</th>
<th>Moxetumomab Pasudotox P3 40 μg/kg (N = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF value (n = 74)</td>
<td></td>
</tr>
<tr>
<td>&gt; 450 ms</td>
<td>3 (4.1%)</td>
</tr>
<tr>
<td>&gt; 480 ms</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>&gt; 500 ms</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>QTcF change from baseline (n = 74)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30 ms</td>
<td>12 (16.2%)</td>
</tr>
<tr>
<td>&gt; 90 ms</td>
<td>1 (1.4%)</td>
</tr>
</tbody>
</table>

Source: Summary of Clinical Safety, Table 2.7.4.4.2.1-1, Page 200

An evaluation of AEs of interest, as defined by the “Torsade de Pointes/QT prolongation” MedDRA v19.0 SMQ was performed using the ISS dataset and MAED. The adverse events are summarized in Table 2, where the severity of the adverse event was graded using CTCAE v4.0.

Two subjects reported ventricular arrhythmias in Study CD-ON-CAT-8015-1053. Subject reported the arrhythmia during screening prior to receiving treatment. Subject experienced both Grade 1 ventricular arrhythmia and QT prolongation as described in the patient narrative below. The patient appeared to be taking the QT-prolonging medication pentamidine for pneumonia and reported Grade 1 hypokalemia which is another risk factor for QT prolongation and arrhythmia. Therefore, a causal relationship between the arrhythmia and QT prolongation AEs and moxetumomab treatment cannot be made since these AEs are confounded by the comorbid conditions of the patient who was experiencing concurrent SAEs of lung infection, pyrexia, cough and dyspnea.

Table 2: Listing of AEs from the SMQ Torsade de Pointes/QT prolongation applied to pooled adult clinical studies (N=165)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dose</th>
<th>Adverse event</th>
<th>Analysis Start Relative day</th>
<th>Days since last dose</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAT-8015-1001/1</td>
<td>5 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>215</td>
<td>2</td>
<td>1*</td>
</tr>
<tr>
<td>CAT-8015-1001/1</td>
<td>30 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>61</td>
<td>25</td>
<td>1*</td>
</tr>
<tr>
<td>CAT-8015-1001/1</td>
<td>30 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>66</td>
<td>5</td>
<td>1*</td>
</tr>
<tr>
<td>CAT-8015-1001/1</td>
<td>50 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>202</td>
<td>3</td>
<td>1*</td>
</tr>
<tr>
<td>CAT-8015-1001/1</td>
<td>50 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>63</td>
<td>3</td>
<td>1*</td>
</tr>
<tr>
<td>CAT-8015-1001/1</td>
<td>50 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>175</td>
<td>3</td>
<td>1*</td>
</tr>
<tr>
<td>Subject</td>
<td>Dose</td>
<td>Adverse event</td>
<td>Analysis Start Relative day</td>
<td>Days since last dose</td>
<td>Grade</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>------------------------</td>
<td>----------------------------</td>
<td>----------------------</td>
<td>-------</td>
</tr>
<tr>
<td>CAT-8015-CP-218</td>
<td>20 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>1</td>
<td>1</td>
<td>2*</td>
</tr>
<tr>
<td>CD-ON-CAT-8015-1053</td>
<td>40 μg/kg</td>
<td>Ventricular arrhythmia</td>
<td>-9</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>CD-ON-CAT-8015-1053</td>
<td>40 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>56</td>
<td>24</td>
<td>2*</td>
</tr>
<tr>
<td>CD-ON-CAT-8015-1053</td>
<td>40 μg/kg</td>
<td>Ventricular arrhythmia</td>
<td>6</td>
<td>1</td>
<td>1**</td>
</tr>
<tr>
<td>CD-ON-CAT-8015-1053</td>
<td>40 μg/kg</td>
<td>Electrocardiogram QT prolonged</td>
<td>9</td>
<td>4</td>
<td>1*</td>
</tr>
</tbody>
</table>

*Grade 1: QTc 450 to 480 ms; Grade 2: QTc 481 to 500 ms; Grade 3: QTc ≥ 501 ms on at least two separate ECGs; Grade 4: QTc ≥ 501 ms or ΔQTc > 60 ms and torsade de pointes/polymorphic ventricular tachycardia/signs or symptoms of serious arrhythmia

** Grade 1: Asymptomatic, intervention not indicated; Grade 2: Non-urgent medical intervention indicated; Grade 3: Medical intervention indicated; Grade 4: Life-threatening consequences; hemodynamic compromise; urgent intervention indicated; Grade 5: Death

Narrative for “Ventricular Arrhythmia”:

Subject [ ... ] is a 64-year-old White, non-Hispanic male from the United States who participated in study CD-ON-CAT-8015-1053, a pivotal multicenter trial of moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. The subject was enrolled on [ ... ].

The subject’s prior medical history included basal cell carcinoma of the right shin ( ... ) and multiple squamous cell carcinomas ( ... ). His surgical and medical procedure history included squamous cell carcinoma excision (right hand, ... ), skin cancer excision ( ... ), 2 hernia repairs, and appendectomy. Ongoing medical history conditions included Grade 1 platelet count decreased, Grade 3 neutrophil count decreased, Grade 4 lymphocyte count decreased, Grade 3 white blood cell count decreased, Grade 1 anemia, sinus bradycardia, hepatic calcification of uncertain etiology, osteoarthritis of the cervical spine, plasma cell myeloma (smoldering multiple myeloma), carotid arteriosclerosis, and Grade 1 skin erythema. In addition, the subject had events of Grade 1 chills ( ... ) and Grade 4 white blood cell count decreased ( ... ) reported at Screening. Throughout the study, the subject was receiving concomitant medications including ergocalciferol, tocopherol, unspecified vitamins, and ascorbic acid as supplements.

The subject had a history of hairy cell leukemia that was first diagnosed on [ ... ]. He received 4 prior lines of anticancer therapy including first-, second-, and third-line treatment with cladribine ( ... , respectively) and...
fourth-line treatment with bendamustine and rituximab (0). The best response to the last line of therapy was partial response. At baseline, the subject had leukemic cells present in the peripheral blood smear, leukemic cells present in the bone marrow biopsy (60%-70%), and decreased neutrophil count (0.99 x 10^3/µL).

No additional concomitant medications were reported at the time of the events of lung infection, pyrexia, cough, and dyspnea.

The subject received moxetumomab pasudotox starting on [redacted]. Moxetumomab pasudotox was administered by IV infusion at 40 µg/kg on Day 1, Day 3, and Day 5 of each 28-day treatment cycle. Dose administration on Cycle 1 Day 3 was delayed by 1 day due to the AEs of lung infection, cough, fatigue, and dyspnea. Dose administration on Cycle 1 Day 5 was interrupted (reason not specified); the subject received the entire dose of study medication. The subject received a total of 18 doses of moxetumomab pasudotox and completed all 6 planned treatment cycles. The last dose of study medication was received on [redacted].

Per protocol, during moxetumomab treatment, the subject received concomitant medications to mitigate the risk of renal insufficiency (acetylsalicylic acid and IV fluids), allergic reaction (hydroxyzine and ranitidine), fever (paracetamol), tumor lysis syndrome (none reported), and opportunistic infections (valacyclovir).

On [redacted] (Cycle 1 Day 2), the subject experienced SAEs of Grade 3 lung infection and Grade 1 pyrexia; on [redacted], the subject experienced an SAE of Grade 1 cough; and on [redacted], the subject experienced an SAE of Grade 2 dyspnea. The event of pneumonia was considered an AE by the sponsor. The subject was admitted to the hospital on [redacted]. The subject was treated with oral azithromycin (0), IV vancomycin (0), and IV piperacillin (0) for infection, and inhaled salbutamol (0) for prophylaxis and relief of bronchospasm. The subject began treatment with inhaled pentamidine for pneumonia prophylaxis on [redacted], which continued until [redacted].

At the time the subject experienced the SAEs of lung infection, pyrexia, cough, and dyspnea, the subject also experienced nonserious AEs of Grade 1/2 hypoalbuminemia (treated with human albumin), Grade 1 chills, Grade 4 white blood cell count decreased, Grade 1 pleural effusion, Grade 1 headache (treated with oral paracetamol), Grade 1 hyponatremia (treated with IV sodium chloride), Grade 1 fatigue, Grade 1 decreased appetite, Grade 1 hypokalemia (treated with oral potassium chloride), Grade 1 pain in extremity, Grade 1 ventricular arrhythmia, Grade 2 hypophosphatemia, Grade 2 anemia, and Grade 1 electrocardiogram QT prolonged. The subject also received treatment with filgrastim (0) for neutropenia, enoxaparin (0) for thromboembolism prophylaxis, and docusate for constipation prophylaxis. Around the same time the subject also received fentanyl and midazolam (0) during bronchoscopy.

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 cdercrpqt@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARS JOHANNESEN
04/04/2018

CHRISTINE E GARNETT
04/04/2018

Reference ID: 4244068
Clinical Inspection Summary
BLA 761104

CLINICAL INSPECTION SUMMARY

<table>
<thead>
<tr>
<th>Date</th>
<th>March 22, 2018</th>
</tr>
</thead>
</table>
| From       | Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer  
             Janice Pohlman M.D., M.P.H., GCPAB Team Leader  
             Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief  
             Division of Clinical Compliance Evaluation  
             Office of Scientific Investigations |
| To         | Bindu Kanapuru, M.D., Medical Officer  
             Nicole Gormley, M.D., Clinical Team Leader  
             Quyen Tran, Regulatory Project Manager  
             Division of Hematology Products |
| BLA        | 761104         |
| Applicant  | AstraZeneca AB (subsidiary, Medimmune) |
| Drug       | moxetumomab pasudotox [CAT-8015] |
| NME        | Yes, Priority Review |
| Therapeutic Classification | Recombinant immunotoxin, containing an anti-CD22 monoclonal antibody and truncated Pseudomonas exotoxin |
| Proposed Indication | Treatment of adult patients with relapsed or refractory hairy cell leukemia |
| Consultation Request Date | December 5, 2017 |
| Summary Goal Date | June 1, 2018 |
| Action Goal Date | June 30, 2018 |
| PDUFA Date | July 20, 2018 |

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

A clinical site (Dr. Wyndham Wilson) was selected by the Division of Hematology Products (DHP) for inspection of study conduct for Study CD-ON-CAT-8015-1053, submitted in support of BLA 761104. The sponsor was also inspected for this application. The study data, from this clinical site, as reported by the sponsor to the BLA are considered to be reliable in support of the requested indication.

The regulatory classification for Dr. Wyndham is Voluntary Action Indicated (VAI). The regulatory classification for the sponsor is No Action Indicated (NAI).

2. BACKGROUND

Purine analogs such as cladribine and pentostatin remain the current standard for first line or second line treatment for hairy cell leukemia (HCL). Moxetumomab pasudotox is a recombinant
immunotoxin containing an anti-CD22 monoclonal antibody and truncated Pseudomonas exotoxin proposed for the treatment of adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analog (PNA)

**Study CD-ON-CAT-8015-1053**

CD-ON-CAT-8015-1053 was a multicenter, open-label, single-arm study of moxetumomab pasudotox in subjects with relapsed or refractory HCL. The primary study objective was to determine the rate of durable complete response in multiply relapsed hairy cell leukemia (HCL) with moxetumomab pasudotox. Patients with histologically confirmed hairy cell leukemia with symptomatic splenomegaly, platelets < 100,000 per cubic millimeter, neutrophils < 1,000 per cubic millimeter, and hemoglobin < 10 g/dL were study eligible.

Approximately 80 subjects received treatment with moxetumomab pasudotox (40 µg/kg) by intravenous (IV) infusion over 30 ± 10 minutes on Days 1, 3, and 5 of each 28-day cycle for up to 6 cycles, until documentation of complete response (CR), progressive disease, initiation of alternate therapy, or unacceptable toxicity. Of these 80 enrolled subjects, 50 completed 6 cycles of treatment.

The primary efficacy endpoint is durable complete response based on blinded independent central review (BICR). Durable CR was defined as CR in which hematologic remission was maintained for greater than 180 days. Clinical response assessment was conducted by the investigator based on hematologic parameters with or without physical examinations prior to initiation of each treatment cycle and during post end of treatment (EOT) visit when full disease assessment is not required. Full disease assessments were conducted during treatment (if applicable for subjects with CR based on clinical response assessment), at EOT, and 181 days post EOT (for subjects with CR or PR).

This multicenter study was conducted internationally, with the largest contribution of patients from the U.S. (about a third of the total enrolled subjects), and the rest of the enrolled subjects from Western Europe (Belgium, Poland, Great Britain, Germany, Spain, France, Norway and Italy). The first subject was treated in 2013 and the data cutoff date was May 24, 2017 for this interim clinical study report. A total of 80 subjects were enrolled in the study and treated with at least 1 dose of moxetumomab pasudotox (40 µg/ kg). The study is ongoing.
3. RESULTS (by site):

<table>
<thead>
<tr>
<th>Name of Clinical Investigator/Sponsor Address</th>
<th>Protocol # 761104/ Site #/# Subjects</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
</thead>
</table>
| Wyndham Wilson, M.D.  
9000 Rockville Pike, Building 37, Room 5124  
Bethesda, MD 20892 | Site # 1010  
26 total | January 23 to 25, 2018 | VAI |
| AstraZeneca AB (subsidiary, MedImmune)  
1 MedImmune Way  
Gaithersburg, MD 20878 | Sponsor for Study Protocol 761104 | January 31 to February 5, 2018 | NAI |

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are 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.

Clinical Investigator

1. Windham Wilson, M.D./ Site #1010

Dr. Wyndham Wilson was the principal investigator (PI) for this study during the time covered by the clinical study report in the NDA. Dr. Kreitman, took over as PI after the treatment phase (BLA study report cutoff date) was available to discuss the study and procedures during the inspection.

The inspection was conducted from January 23 to 25, 2018. A total of 28 subjects were screened and 26 subjects were enrolled. For three subjects who discontinued, two subjects developed hemolytic-uremic syndrome and one study patient was unresponsive to therapy. Twenty-three study subjects completed the treatment phase of the study. A comprehensive review of study subjects’ records enrolled at this site was conducted. Specifically, 26 subject SAE records and 11 subjects’ records for primary efficacy (durable treatment response) were evaluated.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.
Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be compliant with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was issued and shared with DHP.

Specifically, a severe adverse event (Grade 3 pneumonia with prolongation of hospitalization) that required expedited reporting was reported three days late to the sponsor. This isolated finding was eventually reported to the sponsor and included in the study report. Dr. Kreitman’s written response dated February 1, 2018, appeared adequate.

**Sponsor**

2. **AstraZeneca AB (subsidiary, Medimmune)**

This inspection was conducted from January 31 to February 5, 2018.

The sponsor inspection included review of the following: regulatory site set up, financial disclosures, site management and monitoring, and the Clinical Trial Management System. Clinical sites monitoring files were reviewed during the inspection. Monitoring reports indicated that the clinical study sites received adequate periodic monitoring to determine that they had obtained appropriate IRB approvals, and reported protocol deviations and serious adverse events. The five highest enrollment clinical study site document files were assessed. With eventually reporting of adverse events to the Agency, there was no under-reporting of serious adverse events.

Oversight by the sponsor appeared to be adequate in general. A Form FDA 483 was not issued to the sponsor at the end of the inspection.

{See appended electronic signature page}

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

CONCURRENCE:
CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC: Central Doc. Rm.
DHP/Division Director/ Ann Farrell
DHP /Medical Team Leader/ Nicole Gormley
DHP/Medical Officer/ Bindu KanapuruDHP/Project Manager/Quyen Tran
OSI/Office Director/David Burrow (Acting)
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman
OSI/DCCE/GCP MO/Anthony Orencia
OSI/ GCP Program Analyst/Yolanda Patague
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------------
ANTHONY J ORENCIA
03/22/2018

JANICE K POHLMAN
03/22/2018

KASSA AYALEW
03/22/2018

Reference ID: 4238291