CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761174Orig1s000

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 Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	April 1, 2021
To:	Amy Tilley Regulatory Project Manager **Division of Oncology 1 (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	JEMPERLI (dostarlimab-gxly)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761174
Applicant:	GlaxoSmithKline LLC

1 INTRODUCTION

On December 19, 2019, GlaxoSmithKline LLC submitted for the Agency's review the final part of their Rolling Submission of an Original Giologics License Application (BLA) 761174 JEMPERLI (dostarlimab-gxly) injection. The proposed indication for JEMPERLI (dostarlimab-gxly) injection is for the treatment of adult patients with recurrent or mimatch repair deficient endometrial cancer that has progressed following prior treatment with a platinum-containing regimen.

On February 13, 2020, the Division of Oncology 1 (DO1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for JEMPERLI (dostarlimab-gxly) injection. On July 14, 2020, DMPP and the Office of Prescription Drug Promotion (OPDP) completed a collaborative review of the JEMPERLI (dostarlimab-gxly) injection MG. On March 30, 2021 DO1 requested via email, that DMPP review the Applicant's revised proposed MG submitted on March 26, 2021, in response to labeling that DO1 sent to the Applicant on March 22, 2021 to align the language in the proposed labeling with the approved harmonized PD-1/L1 labeling across the class of products.

This memorandum documents the DMPP review and concurrence with the Applicant's revised proposed MG for JEMPERLI (dostarlimab-gxly) injection submitted on March 26, 2021, and subsequent revisions to the MG made by DO1 on March 31, 2021.

2 MATERIAL REVIEWED

- Draft JEMPERLI (dostarlimab-gxly) injection MG received on March 26, 2021, revised by the Review Division and received by DMPP on April 1, 2021.
- Draft JEMPERLI (dostarlimab-gxly) injection Prescribing Information (PI) received on March 26, 2021, revised by the Review Division and received by DMPP on April 1, 2021.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as revised by DO1.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.
- Harmonization of the JEMPERLI (dostarlimab-gxly) injection MG with the other PD-1/PL1 class product MGs should be addressed with the review of the in-house BLA 761223, as agreed upon between DO1 and DMPP on March 31, 2021.

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/

SHARON R MILLS
04/01/2021 02:29:40 PM

LASHAWN M GRIFFITHS
04/01/2021 03:14:02 PM

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:	August 27, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761174
Product Name and Strength:	Jemperli (dostarlimab-gxly)[a] Injection, 500 mg/10 mL
Applicant/Sponsor Name:	GlaxoSmithKline LLC
OSE RCM #:	2019-2380-2
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label received on April 3, 2020 and the revised carton labeling on July 22, 2020 for Jemperli. Division of Oncology 1 (DO1) requested that we review the revised container label and carton labeling for Jemperli (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to Office of Pharmaceutical Quality (OPQ) recommendations[b].

2 CONCLUSION

The revised container label and carton labeling for Jemperli are acceptable from a medication error perspective. We have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] The proposed nonproprietary name (dostarlimab-gxly) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 17. OSE RCM No.: 2019-2384.
[b] Tilley, A. TIME SENSITIVE re BLA 761174 dostarlimab - Addtl OBP Labeling IR. Silver Spring (MD): FDA, CDER, OND, DO1 (US); 2020 Mar 30. BLA 761174.

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/

TINGTING N GAO
08/27/2020 03:02:29 PM

CHI-MING TU
08/27/2020 03:13:15 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 14, 2020
To:	Amy Tilley Regulatory Project Manager **Division of Oncology 1 (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Maritsa Serlemitsos-Day, PharmD, BPCS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	JEMPERLI (dostarlimab-gxly)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761174
Applicant:	GlaxoSmithKline LLC

1 INTRODUCTION

On December 19, 2019, GlaxoSmithKline LLC submitted for the Agency's review the final part or their Rolling Submission of an Original Biologics License Application (BLA) 761174 for JEMPERLI (dostarlimab-gxly) injection.The proposed indication for JEMPERLI (dostarlimab-gxly) injection is for the treatment of adult patients with recurrent or advanced mimatch repair deficient endometrial cancer that has progressed following prior treatment with a platinum-containing regimen.

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 1 (DO1) on February 13, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for JEMPERLI (dostalimab-gxly) injection.

2 MATERIAL REVIEWED

- Draft JEMPERLI (dostarlimab-gxly) injection MG received on February 14, 2017, revised on June 18, 2020, and received by DMPP on June 29, 2020.
- Draft JEMPERLI (dostarlimab-gxly) injection Prescribing Information (PI) received on December 17, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on June 29, 2020.
- Approved KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection comparator labeling dated June 29, 2020.
- Approved LIBTAYO (cemipilimab-rwlc) injection comparator labeling dated June 25, 2020.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

SHARON R MILLS
07/14/2020 10:11:12 AM

MARITSA SERLEMITSOS-DAY
07/14/2020 10:22:56 AM

LASHAWN M GRIFFITHS
07/14/2020 10:53:11 AM

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

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

Memorandum

Date: August 28, 2020

To: Sakar Wahby, PharmD, Clinical Reviewer
Division of Oncologic Diseases I (DO-1)

Amy Tilley, Regulatory Project Manager, DO-1

William Pierce, PharmD, Associate Director for Labeling, DO-1

From: Maritsa Serlemitsos-Day, PharmD, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for JEMPERLI (dostarlimab-gxly) injection, for intravenous use

BLA: 761174

In response to DO-1's consult request dated February 13, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for JEMPERLI (dostarlimab-gxly) injection, for intravenous use (Jemperli). TESARO, Inc. has submitted a Biologics License Application (BLA) to support registration of Jemperli for the treatment of adult patients with recurrent or advanced mismatch repair deficient endometrial cancer that has progressed following prior treatment with a platinum-containing regimen.

OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DO-1 (Tilley) on June 29, 2020, and are provided below.

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.

OPDP has reviewed the attached revised container label received on April 3, 2020 and the revised carton labeling on July 22, 2020, submitted by the Sponsor to the electronic document room and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Maritsa Serlemitsos-Day at (301) 796-1760 or maritsa.serlemitsos-day@fda.hhs.gov.

21 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

MARITSA SERLEMITSOS-DAY
07/13/2020 11:14:24 AM

Clinical Inspection Summary

Date	5/18/2020
From	Yang-Min (Max) Ning, M.D., Ph.D. Kassa Ayalew, M.D., M.P.H. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sakar Wahby, Pharm.D. Gwynn Ison, M.D. Laleh Amiri-Kordestani, M.D. Amy Tilley, RPM Division of Oncology 1 (DO1) Office of Oncologic Diseases (OOD)
BLA #	761174
Applicant	GlaxoSmithKine LLC (GSK)
Drug	Dostarlimab (TSR-042)
NME (Yes/No)	Yes
Therapeutic Classification	Monoclonal antibody directed against programmed cell death 1 (PD-1)
Proposed Indication	Treatment of adult patients with recurrent or advanced endometrial cancer (EC) who have progressed on or after treatment with a platinum-containing regimen. Patients whose tumors are mismatch repair-deficient (dMMR) with no satisfactory alternative treatments.
Consultation Date	December 23, 2019
Review Priority	Priority
Summary Goal Date	May 22, 2020
Action Goal Date	August 19, 2020
PDUFA Date	August 20, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Cohort A1 of an ongoing, open-label trial (Study 4010-01-001) were submitted to the Agency in support of this Biologics License Application (BLA 761174) for dostarlimab. The study sponsor Tesaro and three clinical investigators, Dr. Jubilee Brown (Site 840071), Dr. Cara Mathews (Site 840035), and Dr. Lucy Gilbert (Site 124017), were selected for clinical inspections.

The inspections of Dr. Brown, Dr. Mathews, and the study sponsor Tesaro were performed, and there were no objectionable regulatory violations identified at the three entities. The scheduled inspection of Dr. Gilbert in Canada was cancelled because of the COVID-19 pandemic related travel restrictions to this foreign investigator site (see additional information in Section III of this summary).

Based on the results of the three completed inspections, the sponsor's oversight and management of this ongoing study was found to be adequate, and the clinical data generated from the two inspected investigator sites appear to be reliable and acceptable in support of this BLA.

II. BACKGROUND

Dostarlimab is an anti-programmed cell death 1 (PD-1) IgG_4 humanized monoclonal antibody. For the current BLA, the Applicant, GlaxoSmithKine LLC (GSK), seeks accelerated approval of dostarlimab for use in adult patients with recurrent or advanced endometrial cancer (EC) that has progressed on or after prior treatment with a platinum-containing regimen and whose tumors are mismatch repair deficient (dMMR). The investigational name of dostarlimab, under IND 126472, was TSR-042.

To support the proposed indication for dostarlimab in this BLA, the Applicant submitted clinical data from Cohort A1 (Part 2B) of an ongoing, open-label trial, Study 4010-01-001, titled "A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors". This cohort enrolled subjects with advanced EC whose tumors were positive for dMMR. The clinical data of this cohort represent the primary basis for the current application and the respective indication. The study sponsor for this trial is Tesaro, a subsidiary of the Applicant GSK.

Study 4010-01-001 (NCT02715284) is an ongoing, open-label Phase 1 trial in subjects with advanced solid tumors. It has two parts: Dose Escalation (Part 1) and Expansion Cohorts (Part 2A and Part 2B). Following the completion of Part 1 and Part 2A, the study sponsor determined the recommended Phase 2 dose (RP2D) to be 500 mg dostarlimab, administered intravenously every 3 weeks for the first 4 cycles followed by 1,000 mg dostarlimab administered every 6 weeks for all subsequent cycles. For Part 2B, subjects were enrolled into four expansion cohorts (Cohorts A1, A2, E, and F) according to their tumor type and/or dMMR status.

Cohort A1 was planned to enroll subjects with dMMR-positive advanced EC who had disease progression on or following prior treatment with a platinum-containing regimen. The tumor status of dMMR was determined based on local laboratory testing using an immunohistochemistry (IHC) assay. Subjects were also required to have evidence of disease progression and at least one measurable lesion at baseline. Subjects with endometrial sarcoma were excluded. Eligible subjects were scheduled to receive dostarlimab at the above dose schedules. Study treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria as specified in the protocol. Tumor assessments were to be performed with CT/MRI scans at baseline, 12 weeks after the first dostarlimab dose (84 ± 10 days), and then every 6 weeks (42 ± 10 days) thereafter until confirmation of disease progression. All scans were also submitted to a central imaging vendor and archived for blinded independent central review (BICR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

The primary efficacy measures were Overall Response Rate (ORR) and Duration of Response (DOR) as assessed by BICR per RECIST 1.1. The ORR was defined as the percentage of subjects with a RECIST v1.1-confirmed complete response (CR) or partial response (PR).

From 04/10/2017 through 07/08/2019 (data cutoff date for the interim analysis submitted to this BLA), Cohort A1 enrolled 104 subjects with advanced EC whose tumors were reported to be positive for dMMR. Of them, 30% were from 20 study sites in the U.S., and 70% from 27 study sites in Canada, France, Spain, Italy, U.K., and Denmark. As of the data cutoff date of 7/8/2019, all the subjects received at least one dose of dostarlimab and 70 subjects in Cohort A1 had at least 24 weeks of tumor assessment (or a follow-up time of ≥6 months). The study sponsor stated that the 70 subjects met the criteria for inclusion in the efficacy analysis set for this BLA.

For clinical inspections, the review division DO1 and OSI selected three clinical investigators (CI), Dr. Jubilee Brown (Site 840071), Dr. Cara Mathews (Site 840035), and Dr. Lucy Gilbert (Site 124017). The three CI sites had a high number of subjects enrolled when compared with other study sites for Cohort A1. Sites 840035 and 124017 were associated with a higher response rate (of 50% and 100%, respectively) than the reported overall response rate (of 43%) in the efficacy analysis set of this cohort. Given that dostarlimab represents an additional new molecular entity in the class of anti-PD1 immunotherapy, the study sponsor inspection was also requested to evaluate its oversight and management of this study, with a primary focus on Cohort A1.

III. RESULTS

1. **Jubilee Brown, M.D., (Site 840071)**
   1021 Morehead Medical Drive
   Charlotte, NC 28204

   Dr. Brown was inspected on February 25-27, 2020, as a data audit for Study 4010-01-001. This was the first FDA inspection of the investigator. The investigator site enrolled 8 subjects into the study, with 5 subjects to Cohort A1. Of the 5 subjects in Cohort A1, four were included, as of the data cutoff date, in the current submission. Three subjects (Subjects (b) (6)) met the criteria for inclusion in the efficacy analysis set and one subject (Subject (b) (6)) did not. At the time of the inspection, Subject (b) (6) was discontinued from study treatment due to disease progression, and the rest of subjects remained study treatment.

   Source records for all enrolled subjects were reviewed and compared with the Applicant's submitted Cohort A1 data listings for the site during the inspection. The reviewed records included the informed consent, eligibility criteria, CT/MRI scans performed and their submissions to the BICR, laboratory reports, efficacy endpoints' documentation, adverse events, concomitant medications, and electronic case report forms (eCRFs). Regulatory documents related to the conduct and oversight of the study at the site were also reviewed, including the Institutional Review Board (IRB) approvals of the protocol/amendments and

informed consent, financial disclosures, monitoring visits and site's responses to inquiries, reporting to the sponsor, protocol deviations, study drug accountability, and retention of study records.

The inspection found no significant regulatory violation in the investigator's conduct of this study at the site. The submitted data listings for this site were verifiable and supported by source documents. There was no evidence of under reporting of adverse events. At the conclusion of this inspection, no Form FDA 483 was issued to the investigator. One discussion item was that for three instances, dispensation of study treatment was not recorded contemporaneously on the drug accountability log. The investigator acknowledged the finding and understood the importance of record keeping per the procedures.

2. Cara Mathews, M.D., (Site 840035)
101 Dudley Street
Providence, RI 02905

Dr. Mathews was inspected from January 9 through January 17, 2020, as a data audit for Study 4010-01-001. This was the second FDA inspection of the investigator. The previous inspection was conducted between October 30 and November 2, 2018, and the compliance classification was No Action Indicated.

This investigator site enrolled 8 subjects into the study, with 4 subjects in Cohort A1. As of the data cutoff date, two subjects (Subjects (b) (6)) in Cohort A1 were discontinued from study treatment due to disease progression and the other two (Subjects (b) (6) (b) (6)) remained on study treatment. Of the 4 subjects in Cohort A1, Subjects met the criteria for the interim efficacy analysis in the current submission.

Source records for all subjects in Cohort A1 were reviewed and compared with the data listings for this site. Records reviewed during this inspection included, but were not limited to, the informed consent forms, source documentation, subject data, eCRFs, IRB's correspondence and approvals, study protocol and amendment, sponsor/monitor correspondence, and drug accountability records.

The inspection revealed no objectionable observations at the site, with no Form FDA 483 issued to the investigator at the end of this inspection. The Applicant's submitted data listings were verifiable with source records. All the scans performed before the data cutoff date were submitted to the sponsor's designated central laboratory for BICR. The inspection found no evidence of unreported adverse events.

A discrepancy was identified and reported for Subject (b) (6). This was related to an adverse event (Grade 1 fatigue). The reported start date was (b) (6) in the subject data listings. This date was found not to be consistent with the documented ongoing fatigue in the progress notes dated (b) (6). In review of these source documents, Dr. Mathews agreed that the onset date for the reported

fatigue for this subject should be earlier than the originally reported date. The investigator assured to communicate with the study sponsor and submit the correct onset date for this adverse event.

Reviewer's Comments: *The above-described discrepancy regarding the start date of Grade 1 fatigue does not appear to impact the safety profile of study treatment. Fatigue has been reported as one of the common treatment-emergent adverse events (≥15%) in the clinical study report.*

3. Tesaro (Study Sponsor)
1000 Winter Street
Waltham, MA 02451

The study sponsor was inspected from May 6 through May 12, 2020, to evaluate its oversight and management of Study 4010-01-001, with a primary focus on Cohort A1. This was the second inspection of the sponsor. The first inspection was conducted in Janauary 2017 and the compliance classification was No Action Indicated.

Currently, the established inspection report is not available. Based on the inspector's preliminary summary, the inspection included a review of the sponsor's organizational charts, work orders and agreements with contract research organizations (CRO) involved in the study, Standard Operating Procedures (SOPs), investigators' FDA 1572s and financial disclosures, monitoring plan, monitor qualifications, monitoring reports, test article accountability records, clinical management plan, safety management plan, adverse event reporting, electronic case report forms. Regarding the use of BICR for Cohort A1, the inspector also reviewed the CRO Parexel's Review Charter and related data transfer documents, including the data that was transferred from Parexel to the sponsor.

The inspection reported no objectionable observations, with no Form FDA 483 issued to the sponsor at the conclusion of the inspection. For Cohort A1, the BICR data for all 70 subjects that were included in the analysis set were verifiable at the sponsor's site. For the above three investigator sites, subjects' tumor response results in the submitted data listings were consistent with those conveyed to the sponsor from the BICR. There were no issues identified regarding the adverse event reporting.

Overall, this inspection showed that the study sponsor has had proper management and adequate oversight of the ongoing Study 4010-01-001.

Reviewer's Comments: *An amendment to this clinical inspection summary will be introduced if the EIR for the study sponsor Tesaro contains substantial differences that can alter the current GCP assessments.*

4. Lucy Gilbert, M.D., (Site 124017)
1001 Decarie Boulevard
Montréal, Quebec H4A 3J1
Canada

The inspection of this clinical investigator in Canada was scheduled in early April but was cancelled on March 16, 2020, by the Office of Regulatory Affairs (ORA) due to the COVID-19 related travel restrictions, which knowingly limited the ORA to conduct an onsite inspection. In addition, there was no possibility of access to records from a remote location. The review division DO1 was notified of the cancellation and status. To protect the health, safety, and welfare of FDA employees and study site's staff during the COVID-19 pandemic, the inspection need for this clinical investigator was reevaluated. Following discussions between the review division DO1 and OSI, a decision was made by DO1 not to proceed with this planned inspection for the current application. As a result, OSI is unable to assess the study conduct related to data reliability and study subject protection at Dr. Gilbert's site.

{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}*

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

cc:

Central Doc. Rm. BLA 761174
Review Division /Division Director/ L Amiri-Kordestani
Review Division /Medical Team Leader/G Ison
Review Division /Medical Officer/S Wahby
Review Division/Project Manager/A Tilley
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Khin
OSI/DCCE/GCPAB Branch Chief/K Ayalew
OSI/DCCE/GCPAB Officer/YM Ning
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/

YANGMIN NING
05/18/2020 06:22:24 PM

KASSA AYALEW
05/18/2020 06:24:16 PM

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:	March 9, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761174
Product Name and Strength:	Jemperli (dostarlimab-gxly)[a] Injection, 500 mg/10 mL
Applicant/Sponsor Name:	GlaxoSmithKline LLC
OSE RCM #:	2019-2380-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 3, 2020 for Jemperli. Division of Oncology 1 (DO1) requested that we review the revised container label and carton labeling for Jemperli (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

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

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] The proposed nonproprietary name (dostarlimab-gxly) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 17. OSE RCM No.: 2019-2384.

[b] Gao, T. Label and Labeling Review for Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Feb 19. RCM No.: 2019-2380.

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/

TINGTING N GAO
03/09/2020 09:47:28 AM

CHI-MING TU
03/09/2020 05:49:24 PM

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: February 24, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Amy Tilley, RPM
DO1

Subject: QT Consult to BLA 761174 (SDN 004)

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 1/10/2020 regarding the sponsor's QT assessment report. We reviewed the following materials:

- Cardiac Safety Report for Study: 4020-01-001 (Submission 0004);
- Summary of clinical pharmacology and safety (Submission 0004);
- Proposed Labeling (Submission 0004); and
- Highlights of clinical pharmacology and cardiac safety (Submission 0006).

1 IRT Responses for the Division

Request from the Division: Please evaluate the results of the concentration-QT interval relationship using Fridericia's formula (QTcF) and central tendency analysis submitted in Study 4010-01-001 (GARNET) for BLA 761174 (SDN 4) which has a Priority Review, is an NME with Breakthrough Therapy, and is being reviewed as an RTOR + AA.

IRT's response:

1) We agree with the sponsor's conclusion that the summary statistics of ECG data and the incidence of clinical noteworthy ECG interval values and rhythm abnormalities in Part 2B of study 4010-01-001 do not suggest a significant QTcF prolongation effect at the proposed therapeutic dose level.
2) The sponsor did not propose any QT-related language in section 12.2 of the proposed label in Submission 0004. This is consistent with the labeling practice for other monoclonal antibodies. We do not have additional comments related to the proposed label.

2 BACKGROUND

2.1 Product Information

Dostarlimab (also referred to as TSR-042) is a humanized monoclonal antibody (mAb) of the IgG4 subclass that binds with high affinity to PD-1 and blocks the interaction between PD-1 and its ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2). The sponsor is seeking accelerated approval for the treatment of adult patients with recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen whose tumors are mismatch repair deficient, as determined by an FDA-approved test. The proposed dosing regimen is 500 mg every 3 weeks for the first 4 cycles followed by 1,000 mg every 6 weeks thereafter starting with cycle 5. The drug should be administered as an intravenous infusion over 30 minutes.

2.2 Sponsor's position related to the question

The sponsor conducted QT assessment using data from study 4010-01-001. Refer to section 2.5 of this review for a detailed description of the sponsor's findings.

2.3 Nonclinical Cardiac Safety

In vitro: An in vitro human hERG assay was not conducted with dostarlimab.

In vivo: No stand-alone in vivo safety pharmacology studies were conducted with dostarlimab. Safety pharmacology endpoints assessing major organ system function, covering the cardiovascular (CV) system (electrocardiography and blood pressure), respiratory system, and central nervous system (CNS), were evaluated as part of the 4-week cynomolgus monkey repeat-dose toxicity study (see Module 2.6.6, Section 3.1.1). The administration of dostarlimab by a weekly IV dose for 4 weeks (5 total doses) to cynomolgus monkeys at dose levels of 0, 10, 30, or 100 mg/kg did not result in any dostarlimab-related effects on function of the CV system, respiratory system, or CNS (Study 273-0022-TX). [M 2.6.2, Section 4.2]

2.4 Clinical Cardiac Safety

Refer to section 2.5 of this review for a summary of the sponsor's QT assessment based on study 4010-01-001.

2.5 Summary results of prior QTc assessments

Study 4010-01-001 (GARNET) is a Phase 1 dose escalation and cohort expansion study of dostarlimab. In Part 2B, dostarlimab was administered as 500 mg Q3W IV for first 4 cycles and 1,000 mg Q6W IV for all subsequent cycles, in all study cohorts:

- Cohort A1 - Patients with dMMR/ MSI-H endometrial cancer (n=107)
- Cohort A2 - Patients with MMRp/ MSS endometrial cancer (n=161)
- Cohort E - Patients with NSCLC (n=67)
- Cohort F - Patients with dMMR/ MSI-H or POLE-mut solid tumors (n=109)

Clinical cardiac safety evaluation was based on the data from Part 2B patient populations of the study 4010-01-001. A total of 377 patients (76 male and 301 females) were included into the analysis. A standard 12-lead triplicate ECGs were recorded at screening, predose and at 0.5 h (End of Infusion) on Day 1 of Cycles 1, 4, 5, 8, and 12, at the End of treatment visit. Cycle 1 Day

1 0 h (predose) was considered as baseline. For the concentration-ΔQTcF analysis, time-matched PK samples (Predose and End of Infusion) were collected at the ECG timepoints.

Concentration-ΔQTcF modelling showed a slope that was close to zero and with no significant increase in QTcF at the geometric mean concentrations achieved in this study. The upper bounds of the 2-sided 90% CI of the model estimated ΔQTcF over the range of concentrations studied including the highest geomean concentration of 414.1 ug/mL was below the 10 msec threshold of regulatory concern specified in the ICH E14 guidance document and well below the limit for clinical relevance of 20 msec in an oncology setting suggested by some experts.

Central tendency analysis of ΔQTcF during the treatment process showed maximum mean ΔQTcF increase of 5.741 msec with the upper bound of 2-sided 90% CI of 8.043 msec at Cycle 5 Day 1, 0.5 h timepoint. At all other postdose timepoints the mean ΔQTcF was less than 5 msec and the upper 90% 2-sided CI ranged from 1.885 to 8.043 msec.

Incidence of clinically noteworthy QTcF interval values as specified by the ICH E14 showed 13.6% of patients had ECGs with QTcF values in ≥450 msec to <480 msec range, 2.4% patients had ECGs with QTcF values in ≥480 msec to <500 msec range and 1.3% patients with QTcF≥500 msec. Also, 13.6% patients had change from baseline values ≥30 msec range and 2.4% of patients had change from baseline ≥60 msec.

No clinically relevant changes were observed in heart rate, PR interval and QRS durations.

Ten (2.7%) patients were reported with clinically significant rhythm abnormalities. Of these 10 patients, one patient (Patient ID: (b) (6)) was reported with atrial fibrillation at Cycle 5 Day 1 predose, one patient (Patient ID: (b) (6)) with tachycardia and arrhythmia at Cycle 4 Day 1 predose, one patient (Patient ID: (b) (6)) with partial right bundle branch block at End of treatment visit and one patient (Patient ID: (b) (6)) with sinus bradycardia at Cycle 4 Day 1 end of infusion timepoint. Other 6 patients had a normal sinus rhythm. No patients had arrhythmias like torsades de pointes, ventricular tachycardia or ventricular fibrillation or any treatment-emergent morphological abnormality, which would suggest a potential pro-arrhythmic effect.

Reviewer's comments:

- *Monoclonal antibodies are expected to have a low likelihood for direct interaction with cardiac ion channels and a dedicated QT study is generally not recommended unless mechanistic considerations or data from clinical or non-clinical studies show a proarrhythmic risk (ICH E14 Q&A 6.3).*
- *PK/ECG sampling schedule in Part 2B of study 4010-01-001 is sparse and the exposure range is narrow. Therefore, concentration-QTc analysis is not appropriate for the QT assessment based on study 4010-01-001.*
- *Central tendency analysis and categorical analysis of the predose and end-of-infusion ECGs do not suggest any QT prolongation concerns.*
- *Cardiac AEs identified in this study do not suggest a risk of torsade per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death).*

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

---

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/

NAN ZHENG
02/24/2020 02:15:12 PM

CHRISTINE E GARNETT
02/24/2020 02:30:43 PM

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:	February 19, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761174
Product Name, Dosage Form, and Strength:	Jemperli (dostarlimab-gxly)[a] Injection, 500 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GlaxoSmithKline LLC
FDA Received Date:	December 17, 2019
OSE RCM #:	2019-2380
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

[a] The proposed nonproprietary name (dostarlimab-gxly) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, M. Suffix Review for Nonproprietary Name for Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 17. OSE RCM No.: 2019-2384.

1 REASON FOR REVIEW

As part of the review process for Jemperli (dostarlimab-gxly) Injection, the Division of Oncology 1 (DO1) requested that we review the proposed Jemperli 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
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS 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 Jemperli PI, container label, and carton labeling and determined that they may be improved for clarity.

4 CONCLUSION & RECOMMENDATIONS

The proposed Jemperli PI, container label, and carton labeling may be improved for clarity. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. General

   a. Revise the nonproprietary name on all labels and labeling to incorporate the suffix, -gxly, appended to the core name, dostarlimab so that it appears as dostarlimab-gxly throughout the labels and labeling.

2. Dosage and Administration Section

   a. In Table 1 in Section 2.2 Recommended Dosage, consider revising the abbreviation "Q6W" to "every 6 weeks" for clarity.

   b. In Section 2.4 Preparation and Administration, delete the abbreviation "(IV)" and spell out "IV" as "intravenous" to minimize misinterpretation.

   c. (b) (4)

4.2 RECOMMENDATIONS FOR GLAXOSMITHKLINE LLC

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

A. General Comments (Container labels & Carton Labeling)

1. As communicated to you in the February 4, 2020 General Advice Letter, we find the nonproprietary name, dostarlimab-gxly, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, dostarlimab-gxly will be the proper name designated in the license. Revise your proposed labels and labeling accordingly.

2. Revise (b) (4) to "Dosage: See prescribing information". to be consistent with the terminology in the Prescribing Information.

3. Consider revising the expiration date to the format YYYY-MMM. FDA's current thinking has been published in the *Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers*. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in

YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

4. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jemperli received on December 17, 2019 from GlaxoSmithKline LLC.

Table 2. Relevant Product Information for Jemperli	
Initial Approval Date	N/A
Nonproprietary Name	dostarlimab-gxly
Indication	treatment of adult patients with recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen whose tumors are mismatch repair deficient (dMMR), as determined by an FDA-approved test.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	500 mg/10 mL
Dose and Frequency	500 mg every 3 weeks for the first 4 cycles followed by 1,000 mg every 6 weeks thereafter starting with cycle 5
How Supplied	Carton of one single-dose vial
Storage	Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake.
Container Closure	10 mL (b) (4) [redacted]

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 Jemperli labels and labeling submitted by GlaxoSmithKline LLC.

- Container label received on December 17, 2019
- Carton labeling received on December 17, 2019
- Prescribing Information (Image not shown) received on December 17, 2019, available from \\cdsesub1\evsprod\bla761174\0004\m1\us\clean-draft-text.docx

G.2 Label and Labeling Images

Container label

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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/

TINGTING N GAO
02/19/2020 08:47:01 AM

CHI-MING TU
02/19/2020 09:37:06 AM