CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761223Orig1s000

OTHER REVIEW(S)

351(a) BLA IMMUNOGENICITY ASSESSMENT

Application Type	BLA
Application Number	761223
Submit Date	12/18/2020
PDUFA Goal Date	08/18/2021
Review Date	04/26/2021
Division/Office	DOP1/OND
Product Code Name	TSR-042
Non-proprietary Name	Dostarlimab
Proposed Proprietary Name[Error! Bookmark not defined.]	Jemperli
Pharmacologic Class	Monoclonal antibody
Applicant	GSK
Applicant Proposed Indication(s)	Treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
Recommended Regulatory Action	Approval

Immunogenicity Reviewers

Primary Reviewer	Zhenzhen Liu, Ph.D., OBP/DBRRIII
Secondary Reviewer	Susan Kirshner, Ph.D., OBP/DBRRIII

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1. Summary Basis of Recommendation/Executive Summary

1.1 Immunogenicity Executive Summary and Recommendation

Dostarlimab (TSR-042, Jemperli) is a humanized IgG4-kappa monoclonal antibody that binds to PD-1 resulting in inhibition of the binding to PD-L1 and PD-L2. The binding of PD-1 to PD-L1 and PD-L2 suppresses T cell activation and cytokine production in the tumor microenvironment. Thus, dostarlimab has been developed as one of the antitumor therapeutic agents. In this BLA, dostarlimab is being developed by GSK, Inc. as a monotherapy for patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. Prior to this BLA submission, BLA 761174 for dostarlimab for dMMR endometrial cancer was submitted dated 12/19/2019 and approved on 04/22/2021. Due to inability to inspect the drug substance manufacturing site during the COVID19 pandemic, the approval of BLA 761174 was delayed, which resulted in this BLA was submitted as a separate BLA instead of being submitted as a supplemental BLA.

Dostarlimab immunogenicity was studied in 549 advanced solid tumor patients enrolled in Study 4010-01-001 (Garnet). The study was conducted in 2 parts. Part 1 (n=21) evaluated safety, PK, and PD of weight-based escalating doses of 1, 3, and 10 mg/kg dostarlimab administered every 2 weeks, and Part 2 further evaluated the safety and clinical activity of dostarlimab in patients with various types of advanced solid tumors. Part 2 was conducted in 2 subparts. Part 2A (n=13) evaluated safety, tolerability, and PK of dostarlimab at 2 fixed doses regimens (500 mg Q3W or 1000 mg Q6W), and Part 2B (expansion cohort, n=515) explored clinical activity in patients with prespecified tumor types at the recommended therapeutic dose regimen of 500 mg dostarlimab Q3W for the first four 3-week cycles followed by 1000 mg Q6W for all subsequent cycles. Samples for immunogenicity assessment were collected at the following timepoints: pre-dose on Day 1, concurrent with PK trough samples at pre-dose, at or after 96 hours postdose for all cycles, and at a safety follow-up visit (approximately 90 days after the last dose of dostarlimab). The immunogenicity results presented in this BLA are from the 01 March 2020 data cut as opposed to the 08 July 2019 data cut in BLA 761174.

For immunogenicity assessment, GSK used a multi-tiered testing paradigm including screening, confirmatory, and titering assays to detect anti-drug antibodies (ADA) in the patient serum samples from all cohorts of the clinical study comprising patients with multiple tumor types. GSK contracted (b) (4) to develop and validate the MesoScale Discovery (MSD) platform electrochemiluminescence (ECL) bridging ELISA used for ADA testing. The assay was validated for use with cancer patient sera and is suitable for its intended purpose. Using this assay, 16.8% of the patients tested ADA positive at baseline, 3.1% of the patients developed ADA during the entire study, and for patients receiving the recommended therapeutic dose, the overall incidence of treatment-emergent ADA was only 2.1%. An indirect competition ligand binding assay was developed and validated by (b) (4) The assay was validated using healthy volunteer sera and is suitable for identifying ADAs with neutralization activity. Using this NAb assay, 1.7% of patients developed neutralizing ADAs, and for patients receiving the recommended therapeutic dose, the overall incidence of treatment-emergent neutralizing ADA was only 1.0%.

There are no approvability issues arising from our immunogenicity assay assessment because the assays used were adequately validated and the available clinical immunogenicity data suggest that the ADA rate is low and the presence of ADA does not seem to impact PK, PD, safety and efficacy of dostarlimab. Therefore, we recommend approval of the BLA.

1.2 Deficiencies and Other Recommended Comments to Applicant

No deficiencies.

2. Review

2.1 Background Immunogenicity Information

For dostarlimab immunogenicity assessment, a binding ADA assay and a neutralization assay were developed and validated:

- A MesoScale Discovery (MSD) platform electrochemiluminescence (ECL) bridging ELISA was developed and validated (b) (4) for detection, confirmation, and titer determination of ADAs in human serum. This assay was first developed and validated (b) (4) (b) (4) (b) (4) GSK submitted two validation reports in Module 5.3.1.4:
  - KB-0083-RI-AV-RPT-02: Validation of an ECL Method for the Analysis of Antibodies to TSR-042 in Human Serum. This full method validation report is an amended version of the final report KB-0083-RI-AV-RPT-01 that submitted under BLA 761174. Refer to BLA 761174 Immunogenicity Review Memo for the overall ECL assay validation assessment. The differences between these two versions are summarized and assessed in this memo.
  - KB-0240-RI-AV-RPT-04: Validation of an ECL Method for the Analysis of Abs to TSR-042 in Human Serum. This is a partial and cross validation of the ECL method (b) (4) (b) (4) This review focuses on evaluating this partial/cross validation of the ADA assay.
- An indirect competition ligand binding assay was developed and validated (b) (4) (b) (4) to detect neutralizing ADAs. GSK provided a letter to cross-reference BLA 761174 Module 5.3.14 NAb Assay Method Validation Report: TES-R6445.

2.2 Validation of the Binding Anti-Drug Antibody Assay

2.2.1 Method Principle

The ECL method used by the Applicant is a standard bridging immunoassay. In brief, serum samples mixed with biotinylated TSR-042 and sulfo-tagged TSR-042 are added to a streptavidin plate. After washing, the plate is stopped with read buffer and the ECL response is read. The resulting ECL signal is proportional to the amount of ADA present in the human serum. Analyses are conducted in three tiers: an initial screening analysis for ADA positive samples is followed by a confirmatory analysis and then a titer analysis.

2.2.2 KB-0083-RI-AV-RPT-02: Validation of an ECL Method for the Analysis of Antibodies to TSR-042 in Human Serum

Report No.	**KB-0083-RI-AV-RPT-01**	**KB-0083-RI-AV-RPT-02**	**Assessor Notes and Comments**
BLA	761174	761223	*N/A*
Issue date	09/27/2018	10/05/2020	*N/A*
Validation/Test Site(s)	(b) (4)		*N/A*

	[redacted] (b) (4)		
Changes from report 01 to 02	Cover page	Corrected Sponsor address and updated Test Site address	*These changes have no impact on method validation status.*
	Section 1.0 Signature Page	Added statements regarding (b) (4) acquisition and (b) (4) Merger, Project Scientist updated	
	Section 2.0 Compliance Statement	Project Scientist updated	
	Section 13.6 Data Collection and Analysis	Removed the reference to (b) (4) as it was not used in this study.	
	Section 14.0 Validation Results	Two additional analytical runs (Batch 38 and 39) were executed after the initial validation. Intra-batch precision %CV of %inhibition was added to the confirmatory assay as below: 4.1% LPC (40.0 ng/mL) 0.1% MPC 0.0% HPC Short-term stability of LPC in serum when stored refrigerated for 24 hours was repeated in Batch 39 after original validation was completed. The results met the acceptance criteria	*The additional data further support that the method is precise and PC is stable when stored refrigerated for 24 hours.*
	Section 16.0 Conclusion	Updated to include additional statements	*The additional statement was regarding the additional analytical runs (batch 38 and 39) which contained validation parameters for confirmation assay intra-assay precision and the screen assay short term stability in matrix. The method validation status was not impacted.*
	Section 19.0 Tables	Tables 7 and 8 added for Batches 38 and 39	*The additional tables are the results for precision of ECL for PCs tested in batches 38 and 39. The results show that the method is still precise as all %CV were within the AC of ≤20%.*
	Section 20.0 Appendices	Additional Certificates of Analysis for reagents used added. Laboratory Methods and Assay Histories updated to current,	*These changes have no impact on method validation status.*

		effective versions. Throughout Report: Formatting updated Pages and table numbers updated Principal Investigator changed to Project Scientist	

2.2.3 KB-0240-RI-AV-RPT-04: Partial and Cross Validation of an ECL Method for the Analysis of Abs to TSR-042 in Human Serum

In this partial and cross validation study, the new cut points for the screen, confirm, and titer assays were determined in response to the newly manufactured biotin and Sulfo tag TSR-042 at (b) (4) In addition, precision was evaluated at the (b) (4) test site. Cross validation was performed to demonstrate comparability of results from blinded samples run at (b) (4)

2.2.3.1 Partial and Cross Validation Acceptance Criteria

Summary of Screening Assay Partial Validation	
Validation Parameter	**Acceptance Criteria**
Screening Cut Point	Derived to target the prescribed 5% false positive rate
Inter-Batch Precision (% CV)	Precision ≤20% for HPC, MPC and LPC
Summary of Confirmatory Assay Partial Validation	
Validation Parameter	**Acceptance Criteria**
Inter-Batch Precision (% CV)	Precision ≤20% for HPC and LPC
Confirmatory Cut Point	Based on % inhibition, calculated to represent a 1.0% false positive rate
Summary of Titer Assay Partial Validation	
Validation Parameter	**Acceptance Criteria**
Precision of Titer Determination	Endpoint titers determined between analysts and runs should be within one dilution step
Titer Cut Point	Calculated to represent a 0.1% false positive rate, which will be used to determine the end point titer of a sample titered in the method
Summary of Cross Validation	
Validation Parameter	**Acceptance Criteria**
Screen (n=30)	80% of samples should match categorically (positive/negative)
Confirmation	80% of samples should match categorically (positive/negative)
Titer	80% of samples should match within one dilution step

2.2.3.2 Partial and Cross Validation Exercises

Partial and Cross Validation Results and Reviewer Assessment for the ECL ADA Assay

Validation	Report: KB-0240-RI-AV-RPT-04 (Signed and approved on 11/24/2020)	Reviewer Comment
Contract Research Org	(b) (4)	*CRO Addresses:* (b) (4) *The Applicant stated that study documents from this validation report may contain both locations.*
Positive control (PC)	Purified rabbit anti-TSR-042 polyclonal antibody Lot No.: APE07102.01 Concentration: 0.49 mg/mL Storage: -80 ºC Retest date: 07/03/2019	*The assay used in-house controls. Use of in-house controls for 351(a) products is a standard industry practice. The rabbit pAb was used throughout the cross-validation process.*
LPC	3.45 ng/mL (LPC1) 40 ng/mL (LPC2)	*It is unclear how the LPC2 concentration of 40 ng/mL was determined. However, they are below 100 ng/mL, which is acceptable to be used as LPC for an ADA assay.* *The LPC1 concentration of 3.45 ng/mL was determined later using 1% assay failure rate, which is acceptable.*
MPC	500 ng/mL	*Acceptable.*
HPC	20,000 ng/mL	*This is acceptable because the ELC value for the HPC are proportionally higher than those for the LPC and MPC.*
Matrix and Negative Control (NC)	Human serum	*The use of human serum as the matrix is common industry practice and is acceptable. Pooled sera were used in the initial cut point assessment only, this is common practice as well.*
MRD	1/4	*Acceptable.*
Screening cut-point (SCP)	Individual serum lots from 48 cancer subjects were divided into 3 groups with 16 subjects per group. Each group was tested on a single plate by 2 analysts, 3 times each, for a total of 18 independent plates. The SCP was determined as 1.09 (parametric) using the log-transformed S/N ratio values after outlier removal and 5% false positive rate (FPR).	*The approach used to determine the SCP is acceptable because the relevant sources of variability such as inter-analyst, inter-run, intra-run, and inter-subject variability are pooled and incorporated into the SCP calculations. Using cancer*

<table>
<tr><td></td><td>The new SCP was determined in response to the newly manufactured biotin and Sulfo tag TSR-042 at (b) (4) (b) (4)</td><td>patient sera to determine SCP is appropriate. Use of 5% FPR for SCP determination is acceptable and consistent with the FDA 2019 assay guidance.

The new SCP is lower than the original SCP of 1.24, thus more samples could be detected positive at the screening layer which is more conservative.</td></tr>
<tr><td>Confirmatory cut-point (CCP) Floating</td><td>The same 48 cancer samples used in the screening assay were tested without added drug (unspiked), and with excess of TSR-042 (spiked). For assessment of the CCP, the percent signal inhibition (%INH) by TSR-042 for each sample was calculated as 100 × [1-(spiked/unspiked)]. The CCP of 21% was determined as statistically using 1% FPR after outlier removal.

The new CCP was determined in response to the newly manufactured biotin and Sulfo tag TSR-042 at (b) (4) (b) (4)</td><td>The approach used to determine the CCP is acceptable because the relevant sources of variability such as inter-analyst, inter-run, intra-run, and inter-subject variability are pooled and incorporated into the CCP calculations. Use of 1% FPR for CCP determination is acceptable and consistent with the FDA 2019 assay guidance.

The new CCP is lower than the original CCP of 40.7%, thus more samples could be detected positive at the confirmatory layer which is more conservative.</td></tr>
<tr><td>Titer Cut Point (TCP)</td><td>A parametric TCR of 1.26 was estimated using the same data and statistical methods for establishing the SCP but with a more extreme probability level (0.1% FRR)

The new TCP was determined in response to the newly manufactured biotin and Sulfo tag TSR-042 at (b) (4) (b) (4)</td><td>The approach used to determine the TCP is acceptable because this is a common industry practice and consistent with that USP <1106> recommendation.

The new TCP is comparable to the original TCP of 1.19.</td></tr>
<tr><td>Intermediate Precision (IP)/inter-assay variability</td><td>Inter-assay precision (%CV) was assessed in the (b) (4) laboratory. The estimates of assay precision for the negative and positive control samples were calculated using the mean ECL value of duplicate wells of the HPC and LPC generated by two analysts in each of 2 independent assay runs (4 plates total).

<table>
<tr><th></th><th>Screening</th><th>Confirmatory (% Inhibition)</th><th>Titer (endpoint titer difference)</th></tr>
<tr><td>NC %CV</td><td>11.3%</td><td>not provided</td><td>not applicable</td></tr>
<tr><td>LPC %CV</td><td>1.8%</td><td>0.7%</td><td>not provided</td></tr>
<tr><td>MPC %CV</td><td>2.2%</td><td>0.1%</td><td>3</td></tr>
<tr><td>HPC %CV</td><td>1.7%</td><td>0%</td><td>not provided</td></tr>
</table>
</td><td>The inter-assay precision was evaluated in duplicates by at least 2 analysts in 4 runs in the screening and confirmatory assays, respectively. They all met the pre-defined acceptance criteria of CV%≤20%.

The titer inter-assay precision was evaluated using MPC by 2 analysts in 4 independent runs. The results show that the inter-assay precision is overall adequate for a titration assay

Overall, the provided data support that the ECL assay is precise when performed at the new site (b) (4) (b) (4)</td></tr>
</table>

Cross Validation of Sample Testing	Thirty (30) blinded serum samples were tested in both the (b) (4) facilities. The new conjugates and associated cut points were used for the evaluation. In the screening assay, 29/30 (96.7%) of samples scored identically between the two sites. In the confirmatory assay, 4/4 (100%) samples scored identically between sites. Titration matched for the one sample that was tested at both locations.	*In addition to "positive/negative" results, precision (%CV) at both sites were provided and all within 10%.* *The provided data show that the ADA results generated at the two sites are overall comparable, therefore both (b) (4) are qualified to perform ADA testing for cancer patients who received dostarlimab.*
ADA Assay Assessment	**The method is generally suitable for the detection, confirmation, and titering of anti-TSR-042 antibodies in human serum from individuals with solid tumors at both (b) (4) (b) (4) This ADA testing method is a semi-quantitative method, therefore, only checking the intermediate precision at the receiving lab (b) (4) and comparing the testing results (positive or negative) between the sending lab (b) (4) and the receiving lab (b) (4) are adequate to support that the receiving lab (b) (4) is qualified for this ADA testing.**	

2.3 Facility Inspection Summary

No bioanalytical inspection was scheduled.

2.4 Assessment of Assay performance in Clinical Studies

The table below summarizes patient disposition from study 4010-01-001 for ADA evaluation.

Table 1: Patient Disposition for Anti-dostarlimab Antibodies Assay

	Part 1	Part 2A Q3W	Part 2A Q6W	Part 2B	Total
Number of patients enrolled	21	6	7	515	549
Number of patients without immunogenicity results	0	0	0	2	2
Number of patients without baseline results	0	0	0	4	4
Number of patients without post baseline results at a scheduled visit	0	0	0	127	127
Number of evaluable patients[a]	21	6	7	384	418

[a] Patients with a baseline result and at least one postdose result at a scheduled visit were considered evaluable for treatment-emergent antibodies to dostarlimab.

The ADA incidence at baseline is listed in Table 2.

Table 2: Prevalence of Anti-dostarlimab Antibodies at Baseline

	Baseline Prevalence of Patients who are ADA Positive	
	n/N	%
Part 1	0/21	0.0
Part 2A - Q3W	1/6	16.7
Part 2A - Q6W	1/7	14.3
Part 2B	89/509	17.5
Total	91/543	16.8

n=number of patients with positive results; N=Number of patients with sample at baseline

The number of evaluable patients with treatment-emergent ADAs at any time during the study is shown by Part in Table 4. As shown, 3.1% of the patients from all parts of the study developed ADAs, while 2.1% of the patients treated at the recommended dose developed ADAs.

Table 4: Incidence of Patients with Treatment-Emergent Anti-Dostarlimab Antibodies Post-Baseline, by Part

		Treatment-Induced ADA		Treatment-Boosted ADA		Treatment-Emergent ADA[a]		ADA Inconclusive	
	N	n	%	n	%	n	%	n	%
Part 1	21	2	9.5	0	0.0	2	9.5	4	19.0
Part 2A - Q3W	6	0	0.0	1	16.7	1	16.7	1	16.7
Part 2A - Q6W	7	1	14.3	1	14.3	2	28.6	0	0.0
Part 2B	384	6	1.6	2	0.5	8	2.1	1	0.3
Total	418	9	2.2	4	1.0	13	3.1	6	1.4

[a] Treatment-induced or -boosted
N=Number of evaluable patients; n=number of evaluable patients in the category

Samples confirmed ADA positive were further evaluated for dostarlimab NAb in the NAb assay. The number of patients with positive NAb results are shown in Table 7 by study part and ADA response category. As shown, 1.7 % of the patients from all parts of the study developed NAbs, while 1.0% of the patients treated at the recommended dose developed NAbs.

Table 7: Patients with Positive NAb Results

		Treatment-Unaffected ADA		Treatment-Induced ADA		Treatment-Boosted ADA		Total Treatment-Emergent[a]	
	N	n	%	n	%	n	%	n	%
Part 1	21	0	0.0	2	9.5	0	0.0	2	9.5
Part 2A - Q3W	6	0	0.0	0	0.0	0	0.0	0	0.0
Part 2A - Q6W	7	0	0.0	0	0.0	1	14.3	1	14.3
Part 2B	384	37	9.6	3	0.8	1	0.3	4	1.0
Total	418	37	8.9	5	1.2	2	0.5	7	1.7

[a] Treatment-induced and treatment-boosted
N=Number of evaluable patients; n=number of evaluable patients in the category

For detailed analysis on the impact of ADA on efficacy and safety, refer to the Clinical and Clinical pharmacology reviews.

Zhenzhen Liu

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Susan Kirshner

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

FROM: Lubna Merchant, M.S., PharmD.
Acting Director, DMEPA
Deputy Director, OMEPRM
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

THROUGH: Gerald Dal Pan M.D., M.H.S.,
Director, Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

SUBJECT: Evaluation of the nonproprietary name for BLA 761223.

GlaxoSmithKline LLC (GSK) submitted two new Biologics License Applications (BLA 761174 and BLA 761223) pursuant to Section 351(a) of the Public Health Service Act. BLA 761174, Jemperli (dostarlimab-gxly) was submitted on December 19, 2019 and approved on April 22, 2021. BLA 761223 was submitted on December 18, 2020. The BLA 761223 cross references BLA 761174. The drug substance in BLA 761223 is already covered by BLA 761174, and both BLAs proposed a liquid formulation[1] in a single-dose vial with strength presentation 500 mg/10 mL (50 mg/mL).

The proposed product is a programmed death receptor-1 (PD-1)–blocking antibody indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (BLA 761174) and solid tumors (BLA 761223). Both BLAs propose the same formulation, in the same dosage form, strength, dose, frequency of administration, and route of administration and differ only in indication. GSK is proposing a single U.S. prescribing information (USPI) and proposing the same proprietary name, Jemperli, for both indications (BLAs).

[1] The official USP recognized dosage form for the proposed formulation is *Injection*

Under FDA's prescription drug user fee bundling policy, after initial submission, a pending original or supplemental application should not be amended to add a new indication or claim.[2] If the original application is not yet approved, a request for approval of other new indications or claims should be submitted in a separate, original application. Thus, GSK submitted two separate BLAs. However, as noted above, the drug substance in BLA 761223 is already covered by BLA 761174, and the BLAs share the same formulation, dosage form, strength, dose, frequency of administer, and route of administration—*i.e.*, they differ only in indication.

GSK is proposing to have a single USPI that would include all approved indications. GSK is also proposing to have the same proprietary name, Jemperli, for both BLAs.

FDA issued a final guidance entitled Nonproprietary Naming of Biological Products on January 13, 2017 stating the Agency's intention to designate proper names that include four-letter distinguishing suffixes for biological products.[3] Both of these 351(a) applications are within the scope of this guidance.

As such, dostarlimab-gxly was the proper name designated in the license for BLA 761174. We carefully considered whether the nonproprietary name for BLA 761223 should include a different distinguishing suffix than that designated for BLA 761174 or whether the proper name considerations for this product warrant departing from the January 2017 final guidance and designating the same proper name (*i.e.*, dostarlimab-gxly) for BLA 761223. Among the factors we have considered are the following:

1. We note that the formulation, dosage form, strength, dose, frequency of administration, and route of administration are identical for BLA 761174 and BLA 761223. The two BLAs only differ in indication.
2. We note above that under FDA's prescription drug user fee bundling policy, after initial submission, a pending original or supplemental application should not be amended to add a new indication or claim[4]. If the original application is not yet approved, a request for approval of other new indications or claims should be submitted in a separate, original application. Thus, GSK submitted two separate BLAs. If one of the BLAs was approved prior to submission of the second indication, the additional indication could be managed under a supplement to the approved BLA, which would not have resulted in a change to the proper name under the approach to nonproprietary naming described in the final guidance.

[2] See the recommendations in section III.A.7 of Guidance for Industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (Dec. 2004), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf

[3] Available at https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf (hereafter "naming guidance").

[4] See the recommendations in section III.A.7 of Guidance for Industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (Dec. 2004), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf

3. GSK is proposing to have a single USPI that includes all indications and the same proprietary name. The naming convention of using the same proprietary name for different indications is generally found acceptable. We have not identified any safety or misbranding concerns that would render the proprietary name, Jemperli, unacceptable for BLA 761223.
4. As noted in the final Nonproprietary Naming of Biological Products guidance, distinguishing nonproprietary names will facilitate pharmacovigilance when other means to track a specific dispensed product are not readily accessible or available; facilitate accurate identification of these biological products by health care practitioners and patients; and help prevent inadvertent substitution that may lead to medication errors. As the guidance explains, a distinguishing suffix supports the tracking of product-specific events over time, our ability to track adverse events to a specific manufacturer (and as appropriate, to a manufacturing lot or manufacturing site for a particular biological product), and our ability to detect safety signals throughout the life cycle of a product so that the Agency and the manufacturer can act swiftly and in a targeted manner to identify and address a problem. As noted above, the formulation, dosage form, strength, dose, frequency of administration, and route of administration for both BLAs are same—*i.e.*, they differ only in indication. Also, as noted above, GSK is the applicant for BLA 761174 and BLA 761223.

Given the above factors, a different nonproprietary name for BLA 761223 would not be designated in this particular case. The addition of a different suffix to the nonproprietary name for BLA 761223, could create confusion and would not further the goals of the naming convention.

This memorandum documents the justification for and supervisory concurrence with the decision to depart from the recommendations in the January 2017 final Nonproprietary Naming of Biological Products guidance in approving the same nonproprietary name for BLA 761223.[5] We based this determination upon consideration of all the factors outlined above. If any of the factors enumerated above were to change, we may reconsider the appropriate proper name format for this BLA. The following comments will be communicated to GSK in an advice letter.

Comments for GSK for BLA 761223

We have determined that dostarlimab-gxly will be the proper name designated in the license should your 351(a) BLA be approved during this review cycle.

[5] See 21 C.F.R. § 10.115(d)(3) "Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence."

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/

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GERALD J DALPAN
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Clinical Inspection Summary

Date	May 12, 2021
From	Yang-min (Max) Ning, M.D., Ph.D. Min Lu, M.D., M.P.H. Kassa Ayalew, M.D., M.P.H. GCPAB/OSI/CDER/FDA
To	Sakar Wahby, Pharm.D. Gwynn Ison, M.D. Laleh Amiri-Kordestani, M.D. Amy Tilley, RPM DO1/OOD/CDER/FDA
BLA #	761223
Applicant	GlaxoSmithKine LLC (GSK)
Drug	Dostarlimab
New Molecular Entity	No
Therapeutic Classification	Monoclonal antibody directed against programmed cell death receptor-1
Proposed Indication	Treatment of patients who have recurrent or advanced solid tumors that are mismatch repair deficient (dMMR), and who have no satisfactory alternative treatments
Consultation Request Date	January 27, 2021
Inspection Summary Date	May 15, 2021
Action Goal Date	June 7, 2021
PDUFA Date	August 18, 2021

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Clinical data from Cohorts A1 and F of an ongoing, open-label trial (Study 4010-01-001-P2B) were submitted to the Agency in support of the Biologics License Application (BLA) 761223 for dostarlimab for use in patients with dMMR recurrent or advanced solid tumors who have no satisfactory alternative treatments. Three investigators, Dr. Charles Leath, III (Site 840047), Dr. Susan Ellard (Site 124019), and Dr. Thierry Andre (Site 250016), were selected for clinical inspection.

The inspection of Dr. Leath found no regulatory violations. The Applicant's submitted data were verifiable with source records at the investigator site. There was no evidence of underreporting of adverse events or protocol deviations.

For Dr. Ellard in Canada, a Remote Regulatory Assessments (RRA) was performed since

an onsite Good Clinical Practice (GCP) inspection was not possible due to the COVID-19 pandemic-related travel restrictions. The RRA revealed no GCP violations and the reviewed subject source records supported the Applicant's submitted data for the investigator site, with no discrepancies noted in subject cohort assignments and related efficacy and safety assessments.

For Dr. Andre in France, the inspection was planned for two months but later was canceled due to the COVID-19 pandemic related travel restrictions to the investigator site. RRA is unable to be performed due to the European Union General Data Protection Regulation (GDPR) which limits international transfers of personal data. This cancellation and the inability to conduct an RRA for Dr. Andre were communicated to the DO1 review team in March 2021 and a decision was made by the review division to forgo the intended inspection for the current submission.

Based on the results of the inspection and the RRA, Cohorts A1 and F of Study 4010-01-001-P2B appear to have been adequately conducted and the clinical data generated from Drs. Leath and Ellard appear to be acceptable in support of this BLA.

II. BACKGROUND

Dostarlimab is a programmed death receptor-1 (PD-1)-blocking antibody that received FDA accelerated approval on 4/22/2021 for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC) that has progressed on or following a prior platinum-containing regimen. For this BLA, the Applicant GSK submitted clinical data from Cohorts A1 and F of an ongoing trial (Study 4010-01-001-P2B) and proposed a new indication for dostarlimab.

Study 4010-01-001-P2B is Part 2B, Expansion Cohorts, of an open-label Phase 1 trial (NCT02715284) of TSR-042 (dostarlimab) in subjects with advanced solid tumors. Part 1 and Part 2A of this trial were designed to assess the safety and determine the recommended Phase 2 dose (RP2D). Part 2B was planned to have five cohorts (Cohorts A1, A2, E, F, and G) and subjects were to be assigned to one of the cohorts per their tumor type, dMMR status, and/or other biomarkers. Subjects in each cohort were scheduled to receive TSR-042 at the determined RP2D, which was 500 mg administered intravenously every three weeks for the first 4 cycles followed by 1,000 mg every six weeks for all subsequent cycles. Relevant to this BLA, key study information on Cohorts A1 and F is summarized below.

Cohort A1 was designed to enroll subjects with dMMR recurrent or advanced EC who had disease progression on or following prior treatment with a platinum-containing regimen. Cohort F was to enroll subjects with dMMR recurrent or advanced non-EC solid tumors that had progressed following up to 2 prior lines of systemic therapy and who had no alternative treatment options. The status of dMMR was determined using an immunohistochemistry (IHC) test. Subjects were also required to have evidence of disease progression and at least one measurable lesion at baseline. Subjects with endometrial

sarcoma were excluded. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. ORR was defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR).

Subjects in both cohorts received TSR-042 as a 30-minute intravenous infusion (-5 minutes to +15 minutes) at the above RP2D schedules. Study treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria as listed in Section 4.3 of the study protocol. If none of the criteria was met, study treatment could continue for up to 2 years. Continuation of study treatment beyond 2 years was allowed following discussion between the Investigator and Sponsor.

Tumor assessments were performed with CT/MRI scans (the chest, abdomen, and pelvis) at baseline, 12 weeks after the first dose (84 ± 10 days), and then every 6 weeks (42 ± 10 days) thereafter until confirmation of disease progression. All study scans were required to be submitted to a central imaging vendor and archived for central review per RECIST v 1.1.

From 04/10/2017 through 03/01/2020 (data cutoff date for the planned analysis of ORR in subjects with dMMR solid tumors), Cohort A1 enrolled 126 subjects with dMMR advanced EC and Cohort F enrolled 144 subjects with dMMR advanced non-EC tumors. Of them, 15% were from 22 study sites in the United States (U.S) and 85% from 44 study sites in Canada, Czech Republic, Denmark, France, Italy, Poland, Spain, and the U.K. Subjects who received at least one dose of study treatment were included in the safety analysis. Subjects with measurable disease at baseline [per the central review] who had at least 24 weeks of tumor assessment were included in the efficacy analysis for the current BLA.

The DO1 review team and OSI selected the above-described three investigators for clinical inspections. Relative to other domestic sites in the U.S., Dr. Leath site enrolled a high number of subjects and was associated with a tumor response rate of 100% in subjects with dMMR EC. The two foreign investigators were selected because of insufficient domestic data for Cohort F. These two foreign sites enrolled 34% of subjects allocated on Cohort F. Dr. Andre's site had the highest enrollments of subjects for this cohort and Dr. Ellard's site was associated with a response rate of 60% for subjects with dMMR advanced non-EC tumors, which is higher than the reported overall response rate of 45% for subjects in Cohort F.

III. RESULTS

1. **Dr. Charles Leath, III [Site 840047]**
   1700 6th Avenue South, Suite 10250
   Birmingham, AL 35233

Dr. Leath III was inspected on April 19-22, 2021, as a data audit for Study 4010-01-001-P2B. For the investigator, this was the first FDA inspection. The site enrolled four subjects into Cohort A1 of the study and had no subjects in Cohort F. As of the data cutoff date, two subjects (b) (6) remained on study treatment and two subjects (b) (6) were discontinued from study treatment due to adverse event (AE) or confirmed disease progression. Of note, Subject (b) (6) (b) (6) died from pneumonia following AE-related discontinuation of study treatment.

All subjects' source records were reviewed during the inspection and were compared with the Applicant's submitted data for the site. The reviewed source records included the informed consent forms, medical history, subject eligibility criteria, protocol-required assessments, submissions of scans to the central review vendor, AEs and serious AEs (SAE), laboratory reports, concomitant medications, and subject data in electronic case report forms (eCRF). Regulatory files and study procedures were also examined, including the documented site training for the study, Institutional Review Board (IRB) approvals of all the protocol/amendments and related informed consent versions and dates, signed FDA 1572s, Delegation of Authority, financial disclosures, data entry into the designated eCRF system [Medidata RAVE] and access management, study monitoring, reporting of SAEs to the sponsor, study drug control and accountability logs.

The inspection found that source records were complete and accurate, with no regulatory violations identified. All the treated subjects were found to have met the eligibility criteria, including documented evidence of their dMMR status and prior platinum therapy. The Applicant's submitted data were verifiable with source records. All the scans were performed according to the study protocol and were subsequently transmitted to the sponsor's designated central review laboratory (b) (4) There was no evidence of unreported AEs, SAEs, or protocol deviations. Of note, an additional subject (b) (6) (b) (6) in Cohort A1 was discontinued from study treatment due to an SAE of pneumonitis, which occurred after the data cutoff date of 3/1/2020. This SAE was also reported in a timely manner.

No Form FDA 483, Inspectional Observations, was issued to Dr. Leath III at the conclusion of this inspection.

2. **Dr. Susan Ellard [Site 124019]**
399 Royal Avenue
Kelowna, British Columbia
V1Y5L3
Canada

For Dr. Ellard, a Remote Regulatory Assessment (RRA) was performed from March 9 through March 30, 2021, to review the investigator's conduct of Study 4010-01-001-P2B. The RRA served as an alternative to the intended onsite inspection because the COVID-19 pandemic made travel to the investigator site impossible. For the investigator, this was no prior FDA inspection.

The investigator site screened 20 subjects and enrolled 14 into the study, with 3 allocated to Cohort A1, 6 to Cohort F, and 5 to other cohorts. As of the data cutoff date of 3/1/2020, four subjects (b) (6) (b) (6) in Cohort F continued receiving study treatment. The three subjects in Cohort A1 and the other two subjects in Cohort F were discontinued from study treatment due to confirmed disease progression or adverse event(s).

The RRA involved WebEx conference calls with the investigator and study staff, reviews of source documents uploaded by the site to an FDA-designated online account, and comparisons of source records with the Applicant's submitted data for the site. The reviewed subject records consisted of redacted electronic copies of the informed consent, eligibility criteria and related case medical history, histopathology reports for the dMMR status, CT scans performed and related central submission confirmations, adverse events and serious adverse event reporting forms. In addition, the RRA reviewed the administration of this study at the investigator site, including the signed Statement of Investigator, study protocol/amendments at the site and related approvals from the Research Ethics Board (REB) as well as the REB's approved informed consents and continuing oversight of this ongoing study.

This RRA identified no GCP compliance issues. All the subjects in Cohorts A1 and F were examined for their dMMR status and eligibility, with no issues noted. The Applicant's submitted data were verifiable with the source data reviewed. All scans were found to have been submitted to the independent central review vendor (b) (4) per the Image Acquisition Guideline and the site had no results from the central review. All serious adverse events were reported to the study sponsor in a timely manner.

Reviewer's Comments*: The RRA was associated with considerable logistical constraints of information exchange, which limited in-depth reviews of some compliance components (i.e., site training, monitoring activities, etc.) and/or prevented direct access to site's case report system and a detailed examination of site's control of investigational product (i.e., total amounts received and the storage condition upon receipt).*

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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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cc:

Review Division /Division Director
Review Division /Project Manager
Review Division /Clinical Team Lead
Review Division/Medical Officer
OSI/DCCE/GCPAB Reviewer
OSI/Office Director
OSI/DCCE/Division Director
OSI/DCCE/GCPAB Branch Chief
OSI/DCCE/GCPAB Team Lead
OSI/GCP Program Analyst
OSI/Database PM

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

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

Memorandum

Date: May 5, 2021

To: Amy Tilley, Regulatory Project Manager
Division of Oncology 1 (DO1)

William Pierce, PharmD, Associate Director for Labeling, DO1

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

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

BLA: 761223

In response to DO1's consult request dated February 16, 2021, OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for the original BLA submission for JEMPERLI (dostarlimab-gxly) injection, for intravenous use.

Labeling: OPDP's comments on the proposed PI are based on the draft PI available in Sharepoint on May 5, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the MG was completed, and comments on the proposed MG were sent under separate cover on May 3, 2021.

Carton and Container Labels: A review of carton and container labels was requested on the consult request form; however, no carton and container labels were submitted to this BLA. Therefore, OPDP will not be reviewing carton and container labels for this BLA.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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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:	May 3, 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)** Lynn Panholzer, PharmD 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 761223
Applicant:	GlaxoSmithKline LLC

1 INTRODUCTION

On December 18, 2020, GlaxoSmithKline LLC ,submitted for the Agency's review an original Biologics License Application (BLA) 761223 for JEMPERLI (dostarlimab-gxly) injection for the proposed indication for JEMPERLI (dostarlimab-gxly) is for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

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 16, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for JEMPERLI (dostarlimab-gxly) injection.

2 MATERIAL REVIEWED

- Draft JEMPERLI (dostarlimab-gxly) injection MG received on December 18, 2020, revised on April 21, 2020, and received by DMPP on April 21, 2021.
- Draft Prescribing Information (PI) received on December 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on April 22, 2021.
- Approved KEYTRUDA (pembrolizumab) injection comparator labeling dated November 10, 2020, and March 22, 2021.

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)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

Date of This Review:	March 2, 2021
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761223
Product Name, Dosage Form, and Strength:	Jemperli (dostarlimab-xxxx[a]) Injection, 500 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GlaxoSmithKine LLC (GSK)
FDA Received Date:	April 3, 2020[b], July 22, 2020[b], and December 18, 2020
OSE RCM #:	2020-2696
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

[a] The nonproprietary name suffix for this BLA has not been designated yet. Therefore, the suffix placeholder '-xxxx' is used throughout this review.

[b] Cross-referenced from BLA 761174.

1 REASON FOR REVIEW

Jemperli (dostarlimab-xxxx) Injection is currently pending FDA review under BLA 761174 for mismatch repair deficient (dMMR) endometrial cancer. On December 18, 2020, GlaxoSmithKine submitted BLA 761223 for Jemperli to propose an additional indication for the use of Jemperli for dMMR recurrent or advanced solid tumors. In BLA 761223, GlaxoSmithKine cross-referenced the container label and carton labeling submitted to BLA 761174.

As part of the review process for Jemperli (BLA 761223), 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 Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
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 and determined that it is acceptable from a medication error perspective.

We reviewed the proposed Jemperli container label and carton labeling cross-referenced in BLA 761174 and found the proposed container label and carton labeling acceptable from a medication error perspective in our previous label and labeling memo.[c]

[c] Gao, T. Label and Labeling Review Memo for Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 9. RCM No.: 2019-2380-2.

4 CONCLUSION & RECOMMENDATIONS

The proposed Jemperli PI, container label, and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jemperli received on December 18, 2020 from GlaxoSmithKine LLC (GSK).

Table 2. Relevant Product Information for Jemperli	
Initial Approval Date	N/A
Nonproprietary Name	dostarlimab-xxxx
Indication	Treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced: • endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen, or • solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	500 mg/10 mL
Dose and Frequency	Doses 1 to 4: 500 mg every 3 weeks Begin 3 weeks after Dose 4 (Dose 5 onwards): 1,000 mg every 6 weeks
How Supplied	Carton of one single-dose vial
Storage	Store vial refrigerated 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) clear glass vial with a 20 mm (b) (4) (b) (4) gray (b) (4) elastomeric stopper (b) (4) (b) (4) and a 20 mm aluminum overseal with a white matte flip-off top.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 31, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Jemperli. Our search identified 3 previous reviews[d,e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[d] 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.

[e] Gao, T. Label and Labeling Review Memo for Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 9. RCM No.: 2019-2380-1.

[f] Gao, T. Label and Labeling Review Memo for Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 9. RCM No.: 2019-2380-2.

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,[g] along with postmarket medication error data, we reviewed the following Jemperli labels and labeling submitted by GlaxoSmithKine LLC (GSK).

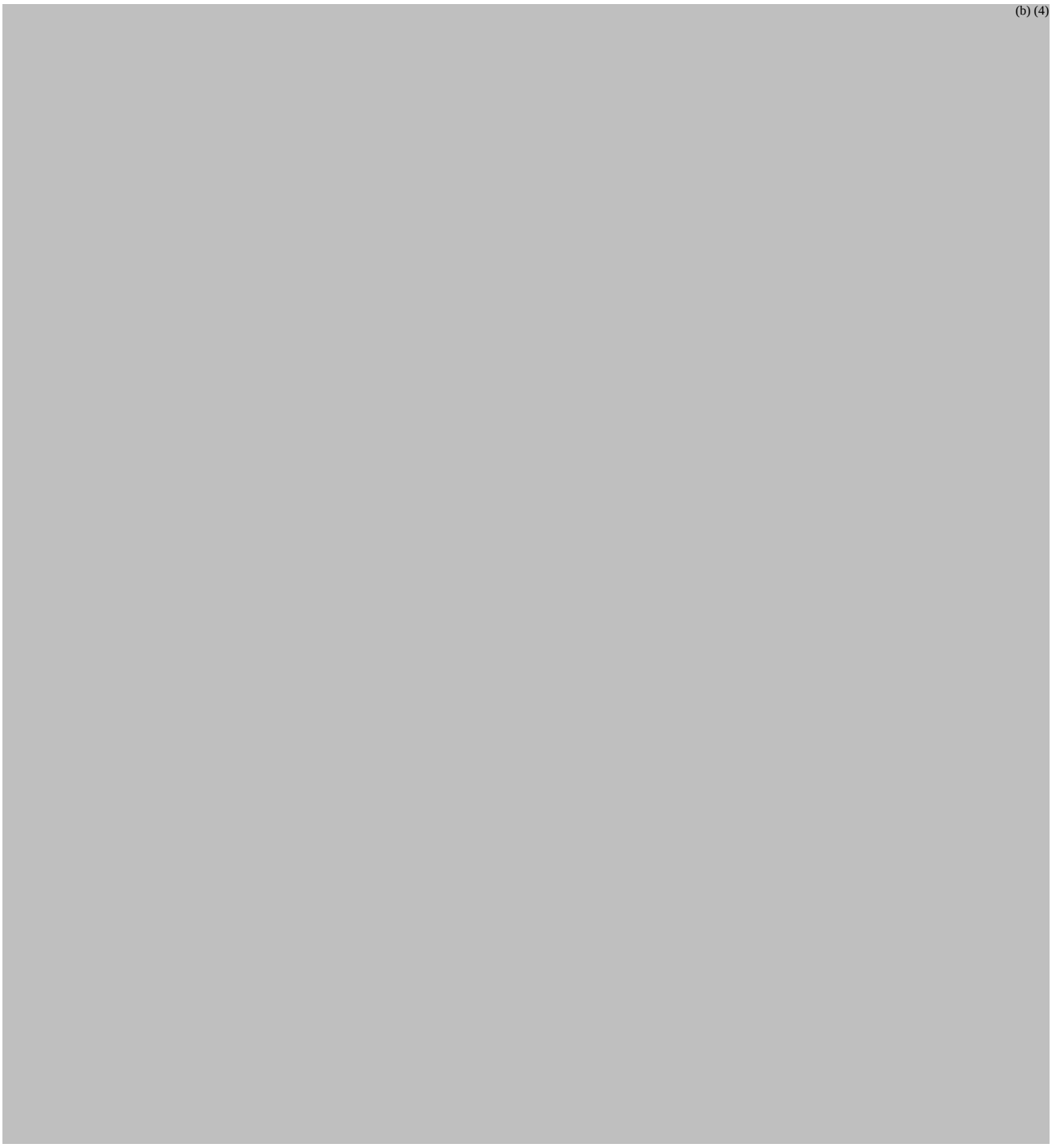
- Container label received on April 3, 2020 to BLA 761174 (Cross-referenced)
- Carton labeling received on July 22, 2020 to BLA 761174 (Cross-referenced)
- Prescribing Information and Medication Guide (Image not shown) received on December 18, 2020, available from \\CDSESUB1\evsprod\bla761223\0001\m1\us\114-labeling\1141-draft\draft-proposed.docx

G.2 Label and Labeling Images

Container label

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

Carton labeling



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