CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761223Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	August 12, 2021
Assessor:	Koung Lee, RPh, MSHS Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Tracy Denison, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research III
Application:	BLA 761223
Applicant:	GlaxoSmithKline LLC (GSK)
Submission Dates:	12/18/2020 and 6/29/2021
Product:	JEMPERLI (dostarlimab-gxly)
Dosage form(s):	Injection
Strength and Container-Closure:	500 mg/10 mL (50 mg/mL) single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for approval 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.
Recommendations:	The prescribing information and medication guide submitted on June 29, 2021 are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labeling for consistency with recommended labeling practices. (see Appendix B)

No container label and carton labeling were submitted for this application. The container label submitted April 3, 2020, and the carton labeling submitted July 22, 2020 were found acceptable

on August 12, 2020 by OBP for BLA 761174. BLA 761174 was the original BLA for dostarlimab for a different indication and was approved April 22, 2021. The Applicant for this application has crossed referenced these labeling pieces.

The prescribing information submitted August 4, 2020 was found acceptable on August 12, 2020 by OBP for BLA 761174.

BLA 761174 provides for 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.

BLA 761223 provides 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.

The quality sections (Title; Dosage and Administration; Dosage Forms and Strengths; Description; and How Supplied/Storage and Handling sections) of the prescribing information for BLA 761223 are identical to the quality sections in the approved prescribing information for BLA 761174 except that BLA 761223 includes the pH in the Description section.

CONCLUSION

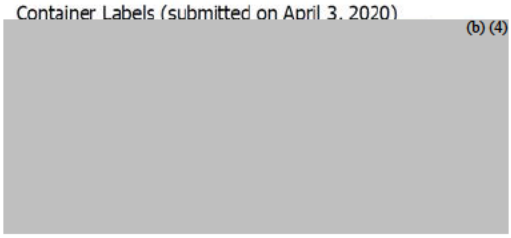
The container label and carton labeling were cross referenced to BLA 761174 which is already approved. The prescribing information and medication guide were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on December 18, 2020) \\CDSESUB1\evsprod\bla761223\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf
- Container Label was not submitted but cross referenced to BLA 761174

Container Labels (submitted on April 3, 2020)



- Carton Labeling was not submitted but cross referenced to BLA 761174

Carton Labeling (submitted on July 22, 2020)

Appendix B: Evaluation Tables

Container label and carton labeling evaluation: Please refer to Labels and Labeling Assessment for BLA 761174 dated August 5, 2020.

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No

	☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Patient Information Labeling Evaluation (N/A)
Instructions for Use Evaluation (N/A)

APPENDIX C. Acceptable Labeling

- Prescribing Information and Medication Guide (submitted on 6/29/2021)
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Koung Lee

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Tracy Denison

Digitally signed by Tracy Denison
Date: 8/12/2021 02:29:03PM
GUID: 53725fbb0005b7b3ff10aa8a0ade1295

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: March 13, 2017
To: Administrative File, STN 761223/0001
From: Reyes Candau-Chacon, Ph.D., Reviewer, CDER/OPQ/OPMD/DBM2
Madushini Dharmasena, Ph.D., Reviewer, CDER/OPQ/OPMD/DBM2
Michael Shanks, Reviewer, CDER/OPQ/OPMD/DBM2
Through: Candace Gomez-Broughton, Ph.D., Branch Chief, CDER/OPQ/OPMD/DBM2
Subject: New Biologic License Application (BLA)
US License: 1727
Applicant: GlaxoSmithKline LLC
Facilities: Drug Substance: (b) (4)
(FEI Number: (b) (4))
Drug Product : (b) (4)
(FEI: (b) (4))

Product: Dostarlimab (TSR-042)
Dosage: 500mg/10mL sterile liquid solution in vials for intravenous infusion
Indication: Treatment of adult patients with recurrent or advanced mismatch repair deficient endometrial cancer that has progressed following prior treatment with a platinum-containing regimen.
Due date: August 18, 2021

Recommendation for Approvability: BLA 761223 is recommended for approval from a microbial control, sterility assurance, and microbiology product quality perspective.

Drug Substance and Drug product Facility Assessment Recommendation:
(b) (4) - Approve
(b) (4) - Approve

Review Summary
GlaxoSmithKline LLC has submitted BLA 761223 to obtain approval for Dostarlimab. BLA 761223 was submitted in eCTD on December 18, 2020 and contained modules 1, 2, and 4; module 3 is

cross-referenced to BLA 761174. BLA 761174 was submitted as a rolling application on November 4, 2019 with Module 3 under sequence 0003 on November 26, 2019. BLA 761174 was recommended for approval from a microbial control, sterility assurance, and microbiology product quality perspective (refer to 761174 BLA DS microbiology review memo, uploaded in Panorama on April 30, 2020 and 761174 BLA DP microbiology review memo, uploaded in Panorama on May 28, 2020).

The drug substance manufacturing site (b) (4) was evaluated by multiple tools including 704 (a)(4) record review, remote assessment, and on-site inspection to support approval of BLA761174. The on-site pre-license inspection resulted in a VAI recommendation (b) (4) (b) (4) The drug product manufacturing site (b) (4) was inspected by CDER/OPQ/OPMA and ORA during the review cycle of BLA 761174 (b) (4) and it was concluded as VAI to support approval of BLA 761174. (b) (4) was recently inspected by ORA ((b) (4) post-approval of BLA 761174) and the outcome of that inspection was VAI.

Michael Shanks

Digitally signed by Michael Shanks
Date: 8/10/2021 02:42:39PM
GUID: 530ccee5000e6dd4f24ae71fb1d5aaa5

Madushini Dharmasena

Digitally signed by Madushini Dharmasena
Date: 8/10/2021 02:58:23PM
GUID: 5aecc01b00af3fb623ee1f6f17a576ea

Zhihao Peter Qiu

Digitally signed by Zhihao Peter Qiu
Date: 8/10/2021 05:09:52PM
GUID: 508da7480002bfb5825e149b2b4eb91d

Recommendation: Approval

OPQ EXECUTIVE SUMMARY

BLA Number: 761223
Assessment Number: 1
Assessment Date: August 6, 2021

Drug Name/Dosage Form	Jemperli (dostarlimab-gxly) Injection
Strength/Potency	500 mg dostarlimab-gxly solution in a 10 mL single dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment of adult patients with 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
Applicant/Sponsor	GlaxoSmithKline LLC (GSK)

Product Overview

Dostarlimab-gxly is a humanized IgG4 monoclonal antibody directed against programmed cell death receptor 1 (PD-1). It is produced by recombinant DNA technology in a mammalian expression system using a stably transfected Chinese Hamster Ovary (CHO) cell line. Dostarlimab-gxly is a glycosylated homodimer consisting of two identical heavy chains and two identical light chains, with 12 intra-chain disulfide bonds and 4 inter-chain disulfide bonds. The heavy chain includes a mutation of serine 228 to proline in the hinge region of the constant region, which stabilizes the IgG4 against the formation of half antibodies. Dostarlimab has a single N-linked glycosylation site on Asn 293 of each heavy chain. The predominant N-linked glycoforms are core fucosylated biantennary glycans with 0 (G0F), 1 (G1F), and 2 (G2F) terminal galactose residues. The level of afucosylated species is very low at around (b) (4) %, which is consistent with the Fc-related bioactivity results that dostarlimab does not exhibit effector functions. The calculated molecular mass of deglycosylated dostarlimab with C-terminal lysine residue truncation of heavy chains and intact disulfide bond structure is 143.9 kDa. Dostarlimab-gxly functions as an anti-tumor agent via binding to PD-1, blocking the interaction of PD-1 with its ligands PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of T cell proliferation and cytokine production.

Quality Assessment Team

Discipline	Assessor	Branch/Division
Drug Substance	Tracy Denison	CDER/OPQ/OBP/DBRR III
Drug Product	Tracy Denison	CDER/OPQ/OBP/DBRR III
Immunogenicity	Zhenzhen Liu	CDER/OPQ/OBP/DBRR III
Labeling	CAPT Vicky Borders Hemphill	CDER/OPQ/OBP
Facility	Michael Shanks	CDER/OPQ/OPMA/DBM
Microbiology	Madushini Dharmasena Reyes Candau-Chacon	CDER/OPQ/OPMA/DBM
Team Lead	Zhenzhen Liu (Product quality) Immunogenicity (Susan Kirshner)	CDER/OPQ/OBP/DBRR III CDER/OPQ/OBP/DBRR III

	Peter Qiu (Facilities) Reyes Candau-Chacon (Microbiology)	CDER/OPQ/OPMA/DBM CDER/OPQ/OPMA/DBM
Application Team Lead	Zhenzhen Liu	CDER/OPQ/OBP/DBRR III
OPQ RBPM	Teshara Bouie	CDER/OPQ/OPRO/DRBPMI/RBPMB2

Multidisciplinary Assessment Team

Discipline	Assessor	Office/Division
RPM	Amy Tilley	CDER/OND/OOD/DO1
Cross-disciplinary Team Lead	Gwynn Ison	CDER/OND/OOD/DO1
Medical Officer	Sakar Wahby	CDER/OND/OOD/DO1
Pharmacology/Toxicology	Tiffany Ricks Wimolnut Manheng	CDER/OND/OOD/DHOT
Clinical Pharmacology	Safaa Burns Pengfei Song Nan Zheng	CDER/OTS/OCP/DCPII CDER/OTS/OCP/DCPII CDER/OTS/OCP/DPM
Statistics	Hui Zhang Erik Bloomquist Shenghui Tang	CDER/OTS/OB/DBV

1. Names:

   a. Proprietary Name: Jemperli
   b. Trade Name: Jemperli
   c. Non-Proprietary Name/USAN: dostarlimab-gxly
   d. CAS Name: 2022215-59-2
   e. Common Name: TSR-042
   f. INN name: dostarlimab
   g. OBP systematic name: MAB HUMAN (IGG4) ANTI Q15116 (PDCD1_HUMAN) [TSR-042]

2. Pharmacological class: PD-1 targeted monoclonal antibody

Submissions Assessed

Submission(s) Assessed	Document Date	Review Completed by:
STN 761223/0001- BLA Original Application	12/18/2020	All

Quality Assessment Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

This is a second BLA submitted for the same product in BLA 761174 and all CMC information is cross-referenced to BLA 761174 which was approved on April 22, 2021. The Applicant is the same for both BLAs and no changes are made to the CMC information.

3. Consults: None

4. Environmental Assessment or Claim of Categorical Exclusion:

GSK requests a categorical exclusion for Jemperli under 21 CFR 25.31 (c) from preparation of an environmental assessment or an environmental impact statement.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Pharmaceutical Quality (OPQ), CDER, reviewed the product quality submission of BLA 761174 for Jemperli (dostarlimab-gxly) manufactured by GSK and approved this application on April 22, 2021. GSK indicated that information on product quality in Module 3 of BLA 761223 is incorporated by cross-reference to BLA 761174. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Letter Language:

- Manufacturing location:
  - Drug Substance (DS): (b) (4)
  - Drug Product (DP): (b) (4)
  - DP Vial Labeling and Secondary Packaging: (b) (4)
- Fill size and dosage form:
  - 500 mg solution in a 10 mL single-dose vial for infusion[1]
- Dating period:
  - Drug Product (DP): 30 months: 2-8 °C

[1] The applicant proposes that the vials are filled to a target fill volume of (b) (4) mL to allow for a delivered volume of 10 mL.

- Drug Substance (DS): (b) (4) months: ≤ (b) (4) °C

- Exempt from lot release:
  - Jemperli is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

The assessment of information provided in the cross-referenced application BLA 761174 concluded that the methodologies and processes used for dostarlimab-gxly DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to lead to a product that is safe, pure and potent.

The drug substance manufacturing site (b) (4) was evaluated by multiple tools including 704 (a)(4) record review, remote assessment, and on-site inspection to support approval of BLA761174. The on-site pre-license inspection resulted in a VAI recommendation (b) (4) (b) (4) The drug product manufacturing site (b) (4) was inspected by CDER/OPQ/OPMA and ORA during the review cycle of BLA 761174 (b) (4) and it was concluded as VAI to support approval of BLA 761174. (b) (4). was also inspected by ORA (b) (4) and the outcome of that inspection was VAI.

The immunogenicity assays are sufficiently specific and sensitive to detect anti-dostarlimab antibodies in presence of the expected level of dostarlimab-gxly in serum.

Individual assessments of BLA 761223 for each discipline, (1) product quality of DS and DP [OBP], (2) immunogenicity assay validation [OBP], (3) microbiology evaluation [OPMA/DBM], (4) facilities evaluation [OPMA/DBM] and [ORA]. Refer to the OPQ memoranda for BLA 761174, and any associated addenda, for more information.

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/

ZHENZHEN LIU
08/06/2021 04:16:36 PM

SUSAN L KIRSHNER
08/06/2021 04:17:49 PM