

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761174Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Reviewer Name(s)	Brad Moriyama, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 23, 2020
Subject	Evaluation of Need for a REMS
Established Name	dostarlimab-gxly
Trade Name	Jemperli
Name of Applicant	GlaxoSmithKline LLC
Therapeutic Class	programmed death receptor-1 (PD-1) blocking antibody
Formulation(s)	500 mg vial
Dosing Regimen	dostarlimab-gxly 500 mg intravenous infusion every 3 weeks (dose 1 to 4), then 1000 mg intravenous infusion every 6 weeks (subsequent dosing beginning 3 weeks after dose 4, dose 5 onwards)

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Jemperli (dostarlimab-gxly) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline LLC submitted a Biologic Licensing Application (BLA) 761174 for dostarlimab-gxly with the proposed indication for the 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. The serious risks associated with dostarlimab-gxly include immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT) after PD-1/L-1 blocking antibody, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Oncology 1 (DO1) agree that a REMS is not necessary to ensure the benefits of dostarlimab-gxly outweigh its risks. The efficacy of dostarlimab-gxly was supported by the GARNET study cohort A1, in which the dostarlimab-gxly group had a confirmed overall response rate of 42.3%. DO1 recommends accelerated approval based on the currently available data. The serious risks associated with dostarlimab-gxly of immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT after PD-1/L-1 blocking antibody, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with dostarlimab-gxly.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)^a Jemperli (dostarlimab-gxly) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline LLC submitted a Biologic Licensing Application (BLA) 761174 for dostarlimab-gxly with the proposed indication for the 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.¹ This application is under review in the Division of Oncology 1 (DO1). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Jemperli (dostarlimab-gxly), a NME, is a programmed death receptor-1 (PD-1) blocking antibody, proposed for the treatment of adult patients with 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. Dostarlimab-gxly is supplied as a 500 mg vial for IV injection. The proposed dosing regimen is dostarlimab-gxly 500 mg intravenous infusion every 3 weeks (dose 1 to 4),

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

then 1000 mg intravenous infusion every 6 weeks (subsequent dosing beginning 3 weeks after dose 4, dose 5 onwards).^b Dostarlimab-gxly is not currently approved in any jurisdiction. Dostarlimab-gxly was designated as breakthrough therapy. If approved, the indication will be approved under accelerated approval based on tumor response rate and durability of response.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for dostarlimab-gxly BLA 761174 relevant to this review:

- 05/06/2019: Breakthrough therapy designation granted
- 12/19/2019: BLA 761174 submission for the treatment of adult patients with 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
- 03/12/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for dostarlimab-gxly

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Endometrial cancer is the most common cause of cancer in the genital system of women in the United States.^{2,3} The estimated number of new cases and the estimated number of deaths of uterine cancer in the United States in women is 65,620 and 12,590, respectively.^{3,c} The five year relative survival of localized, regional and distant uterine cancer is 95%, 69.4%, and 17.3%, respectively.⁴ Furthermore, the median survival of patients with metastatic/recurrent endometrial cancer with measurable disease is approximately 12 to 15 months.^{5,d}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Current guidelines from the National Comprehensive Cancer Network (NCCN) for uterine neoplasms list carboplatin/paclitaxel and carboplatin/paclitaxel/trastuzumab in the "Preferred Regimens" section for systemic therapy of endometrial carcinoma for recurrent, metastatic, or high-risk disease.² A number of regimens are also listed in the "Other Recommended Regimens" section. In the "Useful in Certain Circumstances" section, the NCCN guidelines recommend pembrolizumab for microsatellite instability-high (MSI-H)/dMMR tumors. Deficiencies in DNA mismatched repair have been reported with genomic

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): *The expected or actual duration of treatment with the drug.*

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

and transcriptomic analysis in 25% to 30% of tumors in endometrial cancer.⁶ Deficiencies in DNA mismatched repair lead to chromosomal changes called MSI-H.

Pembrolizumab, a PD-1 blocking antibody, was approved under accelerated approval by the FDA in 2017 for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.^{6,7} The serious risks associated with pembrolizumab include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis (Keytruda) and hepatotoxicity (Keytruda in combination with axitinib), immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated skin adverse reactions, other immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), increased mortality in patients with multiple myeloma when Keytruda is added to a thalidomide analogue and dexamethasone, and embryo-fetal toxicity. Pembrolizumab does not have a boxed warning in its label and is not approved with a REMS.

4 Benefit Assessment

The pivotal trial NCT 02715284 (GARNET) supporting this application for efficacy and safety consisted of a Phase 1 multicenter, multiple cohort, open-label trial.^{1,8} In the GARNET study cohort A1, there was 71 patients with dMMR, recurrent or advanced endometrial cancer who had progressed on or after treatment with a platinum-containing regimen. Patients received dostarlimab-gxly 500 mg intravenously every 3 weeks for 4 doses, followed by 1000 mg intravenously every 6 weeks. The primary endpoints were overall response rate (ORR) and duration of response (DOR). The dostarlimab-gxly treatment group had a confirmed ORR of 42.3% (95% CI 30.6% to 54.6%) with a duration of response that was not reached (range 2.6 to 22.4+ months). The FDA clinical reviewer recommended accelerated approval based on the currently available data.^e

5 Risk Assessment & Safe-Use Conditions

The safety of dostarlimab-gxly was evaluated in study NCT 02715284 (GARNET).^{1,8,f} In the safety population from the GARNET study in patients with advanced or recurrent dMMR endometrial cancer, 104 patients received dostarlimab-gxly. However, the safety population for the serious risk in section 5.1 to section 5.4 below included 444 patients in the GARNET study with advanced or recurrent solid tumors (268 patients with endometrial cancer and 176 patients with other solid tumors). Discontinuation due to an adverse event occurred in 5/104 (4.8%) of the dostarlimab-gxly group.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Common adverse reactions reported with dostarlimab-gxly included fatigue/asthenia, nausea, diarrhea, anemia, and constipation.

Five deaths due to an adverse event were reported in the GARNET study in the dostarlimab-gxly group. The causes of death due to an adverse event included bronchitis, gastroenteritis, sepsis, bronchial aspiration, and pleural effusion.⁸

The serious risks⁹ associated with dostarlimab-gxly which include immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT after PD-1/L-1 blocking antibody, and embryo-fetal toxicity are summarized in the sections below.

5.1 IMMUNE-MEDIATED ADVERSE REACTIONS

Section 5.1 of the draft labeling describes the risk of immune-mediated adverse reactions which include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and other immune-mediated adverse reactions. These immune-mediated adverse reactions are summarized below.

Immune-mediated pneumonitis

An adverse event of immune-mediated pneumonitis occurred in 1.1% of patients receiving dostarlimab-gxly, with Grade 2 immune-mediated pneumonitis reported in 0.9% of patients and Grade 3 immune-mediated pneumonitis reported in 0.2% of patients.

Immune-mediated colitis

An adverse event of immune-mediated colitis occurred in 1.4% of patients receiving dostarlimab-gxly, with Grade 2 immune-mediated colitis reported in 0.7% of patients and Grade 3 immune-mediated colitis reported in 0.7% of patients.

Immune-mediated hepatitis

An adverse event of immune-mediated hepatitis (Grade 3) occurred in 0.2% of patients receiving dostarlimab-gxly.

Immune-mediated endocrinopathies

An adverse event of adrenal insufficiency occurred in 0.9% of patients receiving dostarlimab-gxly, with Grade 2 adrenal insufficiency reported in 0.5% of patients and Grade 3 adrenal insufficiency reported in 0.5% of patients.

An adverse event of thyroiditis (Grade 2) occurred in 0.5% of patients receiving dostarlimab-gxly and an adverse event of hypothyroidism (Grade 2) occurred in 5.6% of patients receiving dostarlimab-gxly. In

⁹ Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

addition, an adverse event of hyperthyroidism occurred in 1.8% of patients receiving dostarlimab-gxly, with Grade 2 hyperthyroidism reported in 1.6% of patients and Grade 3 hyperthyroidism reported in 0.2% of patients.

Section 5.1 of the draft labeling also states that immune-mediated hypophysitis and Type 1 diabetes mellitus which can present as diabetic ketoacidosis may occur with dostarlimab-gxly.

Immune-mediated nephritis with renal dysfunction

An adverse event of immune-mediated nephritis (Grade 2) occurred in 0.5% of patients receiving dostarlimab-gxly.

Immune-mediated dermatologic adverse reactions

Section 5.1 of the draft labeling states that immune-mediated rash may occur with dostarlimab-gxly. In addition, bullous and exfoliative dermatitis, including Stevens Johnson Syndrome and toxic epidermal necrolysis, have been reported with PD-1/L1 blocking antibodies.

Other immune-mediated adverse reactions

Section 5.1 of the draft labeling also describes other immune-mediated adverse reactions that were reported in < 1% of patients receiving dostarlimab-gxly.

The proposed label recommends monitoring for symptoms and signs of immune-mediated adverse reactions. It also contains recommendations for supportive care of immune-mediated adverse reactions including administering systemic corticosteroids if interruption or discontinuation of dostarlimab-gxly is required. If approved, the risk of immune-mediated adverse reactions will be communicated in the warnings and precautions section of the label.

5.2 INFUSION-RELATED REACTIONS

[REDACTED] (b) (4)
[REDACTED] and

Grade 3 infusion-related reactions reported in 0.2% of patients. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3 COMPLICATIONS OF ALLOGENEIC HSCT AFTER PD-1/L-1 BLOCKING ANTIBODY

Allogeneic HSCT complications, including hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome, have been reported in allogeneic HSCT patients treated with PD-1/L-1 blocking antibody. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4 EMBRYO-FETAL TOXICITY

Dostarlimab-gxly may cause fetal harm based on the mechanism of action of the drug. Inhibition of the PD-1/PD-L1 pathway in animal studies has been reported to increase the risk of immune-mediated rejection of the developing fetus and fetal death. [REDACTED] (b) (4)

[REDACTED] The proposed label states advise patients of the risk of embryo-fetal harm and need for effective contraception. The proposed label recommends in females of reproductive potential

to verify pregnancy status before starting dostarlimab-gxly and that effective contraception be used during treatment and for 4 months after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

6 Expected Postmarket Use

If approved, dostarlimab-gxly will primarily be used in both inpatient and outpatient (such as infusion centers) settings. The likely prescribers will be oncologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for dostarlimab-gxly beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of dostarlimab-gxly on the basis of the efficacy and safety information currently available. The indication will be approved under accelerated approval based on tumor response rate and durability of response. The efficacy of dostarlimab-gxly was supported by the GARNET study cohort A1, in which the dostarlimab-gxly group had a confirmed ORR of 42.3%. The serious risks associated with dostarlimab-gxly of immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT after PD-1/L-1 blocking antibody, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label.

Endometrial cancer is the most common cause of cancer in the genital system of women in the United States. The estimated number of new cases and the estimated number of deaths of uterine cancer in the United States in women is 65,620 and 12,590, respectively. The median survival of patients with metastatic/recurrent endometrial cancer with measurable disease is approximately 12 to 15 months. Based on the GARNET study, treatment with dostarlimab-gxly offers a treatment option to patients with dMMR recurrent or advanced endometrial cancer for which there are limited other therapies. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with dostarlimab-gxly. If approved, based on the efficacy and risks associated with dostarlimab-gxly for the treatment of adult patients with 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, the DRM and DO1 agree that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for dostarlimab-gxly to ensure the benefits outweigh the risks. At the time of this review, evaluation of

safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

- ¹ Proposed prescribing information for dostarlimab-gxly as currently edited by FDA, June 30, 2020.
- ² National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Uterine Neoplasms (version 1.2020 – March 6, 2020). https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf (accessed 2020 June 18).
- ³ Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
- ⁴ Cancer Stat Facts: Uterine Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. <https://seer.cancer.gov/statfacts/html/corp.html> (accessed 2020 June 18)
- ⁵ Brooks RA, Fleming GF, Lastra RR, et al. Current recommendations and recent progress in endometrial cancer. *CA Cancer J Clin.* 2019;69(4):258-279.
- ⁶ Arora S, Balasubramaniam S, Zhang W, et al. FDA Approval Summary: Pembrolizumab plus Lenvatinib for Endometrial Carcinoma, a Collaborative International Review under Project Orbis. *Clin Cancer Res.* 2020; [published online ahead of print, 2020 Apr 15]
- ⁷ Keytruda (pembrolizumab) package insert. Whitehouse Station, NJ: Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc., 2020 June.
- ⁸ Wahby S, Bloomquist E, Zhang H, Ison G. Division of Oncology 1 (DO1). Dostarlimab. Mid-Cycle Meeting, clinical and statistics reviewer slides. February 27, 2020.

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