CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761150Orig1s000

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)

Application Type	BLA
Application Number	761150
PDUFA Goal Date	December 18, 2020
OSE RCM #	2019-2354
Reviewer Name(s)	Leah Hart, PharmD
Team Leader	Naomi Boston, PharmD
Acting Deputy Division Director	Doris Auth, PharmD
Review Completion Date	December 4, 2020
Subject	Evaluation of Need for a REMS
Established Name	Margetuximab
Trade Name	Margenza
Name of Applicant	MacroGenics, Inc.
Therapeutic Class	HER2-targeted antibody indicated
Formulation(s)	Injection
Dosing Regimen	15 mg/kg over 120 minutes for the initial dose, then over a minimum of 30 minutes every 3 weeks for all subsequent doses.

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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 Margenza (margetuximab) is necessary to ensure the benefits outweigh its risks. MacroGenics, Inc. submitted a Biologic Licensing Application (BLA) 761150 for margetuximab with the proposed indication for, in combination with chemotherapy, the treatment of patients with metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. The risks associated with margetuximab include left ventricular dysfunction, and infusion-related reactions (IRRs). The applicant did not submit a proposed REMS or risk management plan with this application.

Should margetuximab be approved, DRM has concluded that a REMS is not needed to ensure the benefits of margetuximab outweigh its risks. The adverse events observed in the clinical trials are consistent with those known to occur with this class of biologic products. DRM and the Division of Oncology I (DO1) agree that the safety profile for margetuximab is acceptable for the patient population, and healthcare providers who prescribe and administer margetuximab are likely to be able to manage the margetuximab-related adverse events without additional risk mitigation measures beyond labeling.

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) Margenza (Margetuximab-cmkb) is necessary to ensure the benefits outweigh its risks. MacroGenics, Inc. submitted a Biologic Licensing Application (BLA) 761150 for margetuximab with the proposed indication for, use in combination with chemotherapy, for the treatment of adult patients with metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. 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

Margenza (margetuximab), a new molecular entity[a], is a HER2-targeted antibody, proposed for use, in combination with chemotherapy, for the treatment of patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

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

Margetuximab-cmkb binds to the extracellular domain of the HER2. Upon binding to HER2-expressing tumor cells, margetuximab-cmkb inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain and mediates antibody-dependent cellular cytotoxicity (ADCC).

Margetuximab will be supplied as 250 mg/10 mL (25 mg/mL) single-dose vials. Margetuximab will be administered as a 15 mg/kg intravenous infusion administered every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity[b]. Margetuximab will be administered over 120 minutes for the initial dose, then over a minimum of 30 minutes every 3 weeks for all subsequent doses. On days when both margetuximab and chemotherapy are to be administered, it may be administered immediately after chemotherapy completion. Margetuximab is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for BLA 761150 relevant to this review:

- 12/18/2020: BLA 761150 submission for the treatment of adult patients with metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease received
- 05/27/2020: 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 margetuximab

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death among females worldwide. Up to 30 percent of women with early-stage, non-metastatic breast cancer at diagnosis will develop distant metastatic disease.[1,2] Metastatic breast cancer (mBC) is unlikely to be cured, however meaningful improvements in survival have been seen. Median overall survival now is slightly over three years, with a range from a few months to many years.[c,3] The American Cancer Society estimates 279,100 new cases of breast cancer in the United States with approximately 42,690 deaths in 2020.[d,4] Patients face frequent medical procedures, chronic side effects and impacts to their work and family life. In cross-sectional studies, almost one-third of women with metastatic breast cancer met DSM-IV criteria for a depressive disorder and 6% met criteria for an anxiety disorder.[5,6]

3.2 Description of Current Treatment Options

[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 (B): *The seriousness of the disease or condition that is to be treated with the drug.*

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

Multiple HER2-directed agents are available for use in the treatment of HER2-positive breast cancer, either in the first line or later-line setting. For patients with metastatic breast cancer who progress on HER2- directed treatment, subsequent regimens of HER2-directed agents are continued as needed. The choice of subsequent therapy must be based on individualized assessment of treatment-related toxicity, prior treatments, and patient preferences. Table 1 summarizes the FDA approved treatments and their safety concerns and risk management approaches.

4 Benefit Assessment

The efficacy of margetuximab plus chemotherapy was evaluated in SOPHIA[7], a randomized, multicenter, open-label trial of 536 patients with IHC 3+ or ISH-amplified HER2+ metastatic breast cancer who had received prior treatment with other anti-HER2 therapies. Patients were randomized (1:1) to margetuximab plus chemotherapy or trastuzumab plus chemotherapy. Randomization was stratified by chemotherapy choice (capecitabine, eribulin, gemcitabine, or vinorelbine), number of lines of therapy in the metastatic setting (≤ 2, > 2), and number of metastatic sites (≤ 2, > 2). Patients were required to have progressed on or after the most recent line of therapy. Prior radiotherapy and hormonal therapy were allowed.

Patients received margetuximab intravenously at a dose of 15 mg/kg every 3 weeks administered over 120 minutes for the initial administration and then over 30 minutes thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg over 90 minutes, followed by 6 mg/kg over 30 minutes every 3 weeks thereafter. Patients were treated with margetuximab or trastuzumab in combination with chemotherapy until disease progression or unacceptable toxicity.

Major efficacy outcome measures were progression-free survival (PFS) by blinded independent central (BICR) review and overall survival (OS) of margetuximab plus chemotherapy, compared with trastuzumab plus chemotherapy. Additional efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) assessed by Blinded Independent Central Review (BICR).

The median age was 56 years (range: 27-86); 78% of patients were < 65 years. The majority of patients were female (99.4%), and the majority were White (80%). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (58%) or 1 (42%) at baseline. Forty seven percent had visceral disease, 57% had bone metastases, and 13% had brain metastases. Sixty percent were hormone receptor positive. The median number of prior lines of therapy in the locally advanced/metastatic setting was 2 (range: 1-4). All study patients had previously received trastuzumab, all but 1 patient had previously received pertuzumab, and 91% had previously received ado-trastuzumab emtansine.

The FDA agrees that the study met its primary endpoint of PFS by BICR. The OS data is immature (70% information) to provide a conclusive result. Refer to the benefit assessment in the Assessment Aid for additional information.[e]

[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.*

Table 2[7] Efficacy Results in SOPHIA

	MARGENZA + Chemotherapy (n = 266)	Trastuzumab + Chemotherapy (n = 270)
Progression-free Survival [a]		
Number of events (%)	130 (48.9)	135 (50.0)
Disease progression	118 (44.4)	125 (46.3)
Death	12 (4.5)	10 (3.7)
Median, months (95% CI) [b]	5.8 (5.5, 7.0)	4.9 (4.2, 5.6)
Hazard Ratio (HR) (95% CI) [c]	0.76 (0.59, 0.98)	
p-value [d]	0.033	
Objective Response for Patients with Measurable Disease [a]	**(n = 262)**	**(n = 262)**
Confirmed Objective Response Rate (95% CI)	22 (17, 27)	16 (12, 20)
Duration of Objective Response	**(n=58)**	**(n=42)**
Median (months) (95% CI) [b]	6.1 (4.1, 9.1)	6.0 (4.0, 6.9)

a Assessed per BICR.
b Based on Kaplan-Meier estimates.
c Based on stratified Cox Model.
d p-value based on 2-sided stratified log rank test.
CI: confidence interval; HR: (b) (4) N: number of patients in population; (b) (4)

5 Risk Assessment & Safe-Use Conditions

In Study 04 (data cutoff April 10, 2019), the most frequently reported AEs on margetuximab in combination with chemotherapy (incidence rate ≥ 20%) were fatigue, nausea, neutropenia/neutrophil count decreased, diarrhea, and vomiting. The most frequently reported (b) (4) .[7, f]

5.1 ADVERSE EVENTS OF SPECIAL INTEREST

5.1.1 Left Ventricular Dysfunction

In SOPHIA, left ventricular dysfunction occurred in 1.9% of patients treated with margetuximab and it has not been studied in patients with a pretreatment LVEF value of < 50%, a prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV. The boxed

[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.*

warning states: ***Margenza may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate cardiac function prior to and during treatment. Discontinue Margenza treatment for a confirmed clinically significant decrease in left ventricular function.***

Section 5.2 of the PI reiterates the boxed warning and recommends withholding margetuximab for ≥ 16% absolute decrease in LVEF from pre-treatment values or LVEF value below institutional limits of normal (or 50% if no limits are available) and ≥ 10% absolute decrease in LVEF from pretreatment values. This section in Warnings and Precautions also recommends permanently discontinuing margetuximab if LVEF decline persists for greater than 8 weeks, or if dosing is interrupted on greater than 3 occasions due to LVEF decline.

Conducting a thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan is recommended in the draft labeling. The following schedule is recommended:

- Baseline LVEF measurement within 4 weeks prior to initiation of margetuximab
- LVEF measurements (MUGA/echocardiogram) every 3 months during and upon completion of margetuximab
- Repeat LVEF measurement at 4-week intervals if margetuximab is withheld for significant left ventricular cardiac dysfunction.

5.1.2 Embryo-fetal Toxicity

In post-marketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death. In an animal reproduction study, margetuximab-cmkb given to pregnant cynomolgus monkeys starting at gestational day (GD) 20 until delivery also resulted in oligohydramnios, starting at GD 75. Animal exposures were (b) (4) greater than human exposures at the recommended dose, based on Cmax. There is a boxed warning for embryofetal toxicity, based on findings in animals and the mechanism of action. This risk will also be addressed in section 5.1 of the Prescribing Information (PI). The boxed warning states: ***Embryo-Fetal Toxicity: Exposure to MARGENZA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.***

In section 17 of the PI, prescribers are to advise pregnant women and females of reproductive potential that expose to margetuximab during pregnancy or within 4 months prior to conception can result in fetal harm. Females of reproductive potential are advised to use effective contraception during treatment and for 4 months following the last dose.

5.1.3 Infusion Related Reactions

In SOPHIA, infusion related reactions (IRRs) were reported by 13% of patients on margetuximab plus chemotherapy. Most of the IRRs occur during Cycle 1. Grade 3 IRRs were reported in 1.5% of margetuximab-treated patients. All IRRs resolved within 24 hours, irrespective of severity. In SOPHIA,

IRRs leading to interruption of treatment occurred in 9% in patients treated with margetuximab and chemotherapy. One patient (0.4%) on Margenza discontinued treatment due to IRR.

An infusion sub-study in 88 patients in SOPHIA evaluated margetuximab administered over 120 minutes for the initial dose, then 30 minutes from Cycle 2 forward. IRRs were ≤ Grade 2 and most occurred during the first (120 minutes) administration of margetuximab. From Cycle 2 onward, one patient (1.1%) had an IRR (Grade 1).

Section 5.3 in Warnings and Precautions of the PI informs prescribers to monitor patients for IRRs during MARGENZA administration and as clinically indicated after completion of infusion. Have medications and emergency equipment to treat IRRs available for immediate use. Monitor patients carefully until resolution of signs and symptoms.

In patients who experience mild or moderate IRRs, consider premedications, including antihistamines, corticosteroids, and antipyretics. Decrease the rate of infusion for mild or moderate IRRs. Interrupt MARGENZA infusion in patients experiencing dyspnea or clinically significant hypotension and intervene with medical therapy which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanently discontinue MARGENZA in all patients with severe or life-threatening IRRs.

6 Expected Postmarket Use

Margetuximab is likely to be used in healthcare settings capable of administering intravenous infusions. Likely settings of use include hospitals, outpatient clinics, and infusion centers. Prescribers will likely be oncologists or hematologists familiar with the class of drugs, including how to recognize and manage adverse events.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The Division has recommended approval based on a favorable risk-benefit profile for margetuximab when added to chemotherapy in patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. Refer to the Assessment Aid for additional information. The Division has advised that the data do not support the need for a REMS because the risks associated
with margetuximab are known effects of the class of drugs, and are consistent in incidence and severity with other drugs in the class. Labeling will include a boxed warning for left ventricular dysfunction and embryo-fetal toxicity. The label will also include infusion-related reactions (IRR) in the Warnings and Precautions section.

DRM recommends that, should margetuximab be approved, a REMS is not needed to ensure its benefits outweigh its risks. The risks associated with margetuximab are known effects of the class of drugs and are consistent in incidence and severity with other drugs in the class. The healthcare community has experience with identifying and managing these adverse events. The other drugs in the same class as margetuximab were approved without a REMS.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with margetuximab use are well documented and in general, healthcare providers who treat metastatic HER2-positive breast cancer are familiar with the risks of left ventricular dysfunction, embryo-fetal toxicity, and infusion related reactions and the importance of patient monitoring.

Should DO1 have any concerns or questions or if new safety information becomes available, please send a consult to the DRM.

10 Appendices

10.1 Summary of Treatment Options Relevant to Proposed Indication

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide (MG)
FDA Approved Treatments				
Herceptin[8] (trastuzumab) 1998	The treatment of HER2-overexpressing breast cancer and of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	4-8 mg/kg over 90 minutes followed by 2-6 mg/kg every week to every 3 weeks	Cardiomyopathy, infusion reactions, embryo-fetal toxicity, and pulmonary toxicity	Boxed Warning (BW) and Warnings and Precautions (W&P) for cardiomyopathy, infusion reactions, embryo-fetal toxicity, and pulmonary toxicity

Kadcyla[9] (Ado-trastuzumab emtansine) 2013	As a single agent, for: the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: -received prior therapy for metastatic disease, or -developed disease recurrence during or within six months of completing adjuvant therapy. -the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.	The recommended dose of KADCYLA is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity (metastatic breast cancer), or a total of 14 cycles (early breast cancer)	Hepatoxicity, left ventricular dysfunction, embryo-fetal toxicity, pulmonary toxicity, infusion reactions	BW and W&P for hepatotoxicity, cardiac toxicity, and embryo-fetal toxicity, and

Perjeta[10] (pertuzumab) 2012	Indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease In combination with trastuzumab and chemotherapy for -the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or nodepositive) as part of a complete treatment regimen for early breast cancer. -the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.	Initial dose is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion. (2.2) MBC: Administer pertuzumab, trastuzumab or trastuzumab hyaluronidaseoysk, and docetaxel every 3 weeks. Neoadjuvant: Administer pertuzumab, trastuzumab or trastuzumab hyaluronidase-oysk, and chemotherapy preoperatively every 3 weeks for 3 to 6 cycles. Adjuvant: Administer pertuzumab, trastuzumab or trastuzumab hyaluronidase-oysk, and chemotherapy postoperatively every 3 weeks for a total of 1 year (up to 18 cycles).	Left ventricular dysfunction, embryo-fetal toxicity, infusion-related reactions, hypersensitivity reactions/anaphylaxis	BW for left ventricular dysfunction and embryo-fetal toxicity. W&P for infusion-related reactions, and hypersensitivity reactions/anaphylaxis

Enhertu[11] (fam-trastuzumab deruxtecan) 2019	Indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting[g]	The recommended dosage is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.	Interstitial lung disease, embryo-fetal toxicity, neutropenia, and left ventricular dysfunction	BW for interstitial lung disease and embryo-fetal toxicity W&P for neutropenia, and left ventricular dysfunction MG
Tukysa[12] (tucatinib) 2020	Indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.	-Recommended dosage: 300 mg taken orally twice daily with or without food. -For patients with severe hepatic impairment, the recommended dosage is 200 mg orally twice daily.	Diarrhea, hepatotoxicity, and embryo-fetal toxicity	No BW W&P for diarrhea, hepatotoxicity, and embryo-fetal toxicity MG

Tykerb[13] (lapatinib) 2007	Indicated in combination with: --capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Limitations of Use: Patients should have disease progression on trastuzumab prior to initiation in combination with capecitabine. -letrozole for the treatment of postmenopausal women with hormone receptorpositive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.	The recommended dosage for advanced or metastatic breast cancer is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. The recommended dose for hormone receptor-positive, HER2-positivemetastatic breast cancer is 1,500 mg (6 tablets) given orally once daily continuously in combination with letrozole.	Hepatotoxicity, decreases in left ventricular ejection fraction, diarrhea, interstitial lung disease and pneumonitis, prolonged QT interval, severe cutaneous reactions, and fetal harm	BW for hepatotoxicity W&P for decreases in left ventricular ejection fraction, hepatotoxicity, diarrhea, interstitial lung disease and pneumonitis, prolonged QT interval, severe cutaneous reactions, and fetal harm MG

Nerlynx[14] (neratinib) 2017	As a single agent, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy. In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.	Extended Adjuvant Treatment of Early Stage Breast Cancer: 240 mg (6 tablets) given orally once daily, with food, continuously until disease recurrence for up to one year. Advanced or metastatic breast cancer: 240 mg (6 tablets) given orally once daily with food on Days 1–21 of a 21-day cycle plus capecitabine (750 mg/m2 given orally twice daily) on Days 1–14 of a 21-day cycle until disease progression or unacceptable toxicities.	Diarrhea, hepatotoxicity, and embryo-fetal toxicity	No BW W&P for diarrhea, hepatotoxicity, and embryo-fetal toxicity MG

10.2 REFERENCES

[1] Tevaarwerk AJ, Gray RJ, Schneider BP, et al. Survival in patients with metastatic recurrent breast cancer after adjuvant chemotherapy: little evidence of improvement over the past 30 years. Cancer 2013; 119:1140.

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[7] Macrogenics Inc. Proposed Prescribing Information for Margenza, updated October 15, 2020.

[8] Herceptin Prescribing Information (last updated November 29, 2018).

[9] Kadcyla Prescribing Information (last updated September 27, 2020).

[10] Perjeta Prescribing Information (last updated January 16, 2020).

[11] Enhertu Prescribing Information (last updated December 20, 2019).

[12] Tukysa Prescribing Information (last updated April 17, 2020).

[13] Tykerb Prescribing Information (last updated December 6, 2018).

[14] Nerlynx Prescribing Information (last updated July 29, 2020).

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