CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761163Orig1s000

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	761163
PDUFA Goal Date	August 30, 2020
OSE RCM #	2019-2676; 2019-2678
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 17, 2020
Subject	Review to determine if a REMS is necessary
Established Name	tafasitamab-cxix
Trade Name	Monjuvi
Name of Applicant	MorphoSys US Inc.
Therapeutic Class	Fc-modified CD19 target monoclonal antibody (mAb)
Formulation(s)	200mg of tafasitamab-cxix as lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	Administer 12mg/kg of tafasitamab-cxix in combination with lenalidomide for a maximum of 12 cycles

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Monjuvi (tafasitamab-cxix) is necessary to ensure the benefits outweigh its risks. MorphoSys US Inc. submitted a Biologic Licensing Application (BLA) 761163 for tafasitamab-cxix with the proposed indication in combination with lenalidomide, for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT). The serious risks associated with the use of tafasitamab-cxix are infusion-related reactions, myelosuppression, infections and embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information.

Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) have determined that if approved, a REMS is not necessary to ensure the benefits of tafasitamab-cxix outweigh its risks. DLBCL is the most common lymphoid malignancy in the United States. Despite overall improvements in outcomes of DLBCL, approximately one-third of patients will develop relapsed/refractory disease that remains a major cause of morbidity and mortality. DLBCL patients who progress or do not respond after two lines of treatment are unlikely to respond to further treatment with standard chemotherapy and have a dismal prognosis. Tafasitamab-cxix appeared efficacious in both its primary outcome of overall response rate and secondary outcome of duration of response and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of tafasitamab-cxix in combination in combination with lenalidomide, for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for ASCT. The most concerning adverse reactions observed with the use of tafasitamab-cxix are of infusion-related reactions, myelosuppression, infections and embryo-fetal toxicity. If tafasitamab-cxix is approved, labeling, including information in Warnings and Precautions and the Patient Counseling Information will be used to communicate the safety issues and management of toxicities associated with tafasitamab-cxix.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) tafasitamab-cxix is necessary to ensure the benefits outweigh its risks. MorphoSys US Inc. submitted a Biologic Licensing Application (BLA) 761163 for Monjuvi (tafasitamab-cxix) with the proposed indication in combination with lenalidomide (LEN), for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).[1] The applicant did not submit a REMS with this application but proposed the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information.

2 Background

2.1 PRODUCT INFORMATION

Tafasitamab-cxix is a NME BLA type 351(a) pathway application.[a] It is a is a Fc-modified CD19 targeting monoclonal antibody (mAb). Tafasitamab-cxix binds to CD19 expressed antigen expressed on the surface of pre-B and mature B lymphocytes and on several B-cell malignancies, including DLBCL. Tafasitamab-cxix acts by inducing B-cell lysis through apoptosis and immune effector mechanisms, including antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). The combination of tafasitamab-cxix and lenalidomide resulted in increased ADCC activity compared to tafasitamab-cxix or lenalidomide alone in DLBCL tumor cells.[1] Tafasitamab-cxix is prepared as 200 mg of lyophilized powder in a single-dose vial for reconstitution. The recommended dose of tafasitamab-cxix is 12 mg/kg intravenously in combination with lenalidomide for a maximum of 12 cycles (Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle; Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle; Cycle 4 and beyond: Days 1 and 15 of each 28-day cycle), then continue tafasitamab-cxix as monotherapy until disease progression or unacceptable toxicity.[b] Tafasitamab-cxix was granted fast track designation on October 29, 2014, orphan drug designation on December 1, 2014 and breakthrough therapy designation on October 23, 2017. Tafasitamab-cxix is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for tafasitamab-cxix (BLA 761163) relevant to this review:

- 09/21/2012: Investigation New Drug (IND) 114856 submission for tafasitamab-cxix (MOR00208) was received.
- 10/29/2014: Fast Track Designation granted
- 12/01/2014: Orphan Drug Designation granted
- 10/23/2017: Breakthrough Therapy Designation granted
- 12/30/2019: BLA 761163 submission for tafasitamab-cxix with the proposed indication in combination with lenalidomide, for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for ASCT, received.
- 04/29/2020: 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 tafasitamab-cxix.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Lymphomas are solid tumors of the immune system. Hodgkin's lymphoma accounts for about 10% of all lymphomas, and the remaining 90% are referred to as non-Hodgkin lymphoma (NHL).[2] Diffuse large B-

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

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

cell lymphoma (DLBCL) is the most common type of NHL worldwide, representing approximately 30-40%.[3] The expected number of new cases of NHLs in the United States in 2020 is 77,240[c], with 19,940 expected deaths due to the disease[d]. Five-year survival for patients diagnosed with NHL is approximately 72.7%.[4] DLBCL is an aggressive NHL that affects B-lymphocytes, and primarily develops in the lymph nodes, though the disease can spread to extranodal sites such as the gastrointestinal tract, testes, thyroid, skin, breast, bone, brain, or essentially any organ of the body. The incidence of DLBCL in the United States is approximately 7 cases per 100,000 person-years, with a male predominance. Incidence increases with age, with a median age of presentation of 64 years. DLBCL can occur de novo as well as through the transformation of many different types of low-grade B-cell lymphomas.[5]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The standard therapy for patients with DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Using this regimen, approximately 60–70% of patients with DLBCL are cured of disease. However, about 30–40% of patients will relapse or, in a small patient's subset, be refractory to R-CHOP therapy.[3] Patients with chemosensitive disease proceeding to autologous stem cell transplantation (ASCT) achieve long-term remission in 60% of cases. Patients with primary progressive DLBCL are less chemosensitive to conventional salvage chemotherapy and recommend investigational strategies in this population to increase the likelihood of proceeding to transplant.[6] Patients with disease that has relapsed or is refractory to R-CHOP have a poor prognosis with short survival times, ranging 6-12 months, with only a small number of patients achieving long-term disease-free survival.[7,8,9] Despite overall improvements in outcomes of DLBCL, approximately one-third of patients will develop relapsed/refractory disease that remains a major cause of morbidity and mortality. Ongoing efforts are exploring novel conditioning regimens and maintenance approaches, but these will have limited impact on the whole population of relapsed/refractory DLBCL, because only a minority of patients proceed to this treatment. [10] Salvage chemotherapy followed by ASCT is the standard second-line treatment for relapsed and refractory DLBCL. Recently, three new therapies have been approved for DLBCL patients who have progressed after second-line therapy. These comprise two chimeric antigen receptor (CAR) T-cell therapies (CAR-T therapies), axicabtagene ciloleucel (Yescarta)[11] and tisagenlecleucel (Kymriah)[12] as well as the antibody-drug conjugate polatuzumab vedotin (Polivy)[13], in combination with bendamustine and rituximab (Pola + BR). Both CAR-T cell therapies target CD19, the same antigen as tafasitamab, whereas polatuzumab vedotin targets the CD79b antigen. The CAR-T cell therapies may produce durable CRs, but their use has limitations because of the toxicity profile, which requires rigorous selection criteria and inpatient administration, and restricted availability in tertiary care facilities. Additionally, the waiting period associated with CAR-T manufacture may be prohibitive in patients with symptomatic or rapidly progressing disease.[14,15,16] Overall, DLBCL patients who progress or do not respond after two lines of treatment are unlikely to respond to further treatment with standard chemotherapy and have a dismal prognosis.[17] There is a clear need for therapeutic strategies that encompass multiple modes of action.

[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.*

4 Benefit Assessment

The efficacy of tafasitamab-cxix in combination with lenalidomide followed by tafasitamab-cxix as monotherapy was evaluated in patients who had relapsed or refractory DLBCL after 1 to 3 prior systemic therapies, including a CD20-directed cytolytic antibody, and were not candidates for high dose chemotherapy (HDC) followed by ASCT in an open label, multicenter, single arm trial (MOR208C203; L-MIND [NCT02399085]). A total of 71 patients with confirmed DLBCL received tafasitamab-cxix 12 mg/kg intravenously in combination with lenalidomide (25 mg orally on Days 1 to 21 of each 28-day cycle) for maximum of 12 cycles (Cycle 1: Days 1, 4, 8, 15 and 22 of the 28-day cycle; Cycles 2 and 3: Days 1, 8, 15 and 22 of each 28-day cycle; Cycle 4 and beyond: Days 1 and 15 of each 28-day cycle), followed by tafasitamab-cxix as monotherapy until disease progression or unacceptable toxicity.[1]

The following section is a summary of relevant efficacy information to date for tafasitamab-cxix. Efficacy was established on the basis of the best overall response rate (ORR), defined as the proportion of complete and partial responders and duration of response (DoR), as assessed by an Independent Review Committee (IRC). The best ORR based on IRC was 60% (95% CI: 48.4, 70.8), and complete response (CR) rate was 42.5% (95% CI: 31.5, 54.1); 30/34 CRs were PET confirmed is shown in Table 1.[1,14,e] A best response of partial response (PR) was observed in 17.5% (95% CI: 9.9, 27.6), stable disease (SD) in 11 (13.8%), progressive disease (PD) in 13 (16.3%) patients, and 8 (10.0%) patients were not evaluable. Median time to initial response was 2.0 months (range: 1.7–16.8); and median time to CR was 7.1 months (range: 1.7–17.0).[14]

Table 1: Efficacy Results in L-MIND [1,e]

	N = 71
Overall response rate, n (%)	48 (60%)
(95% C.I.)	(48.4%, 70.8%)
Complete response rate, n (%)	34 (42%)
Partial response rate, n (%)	14 (18%)
DoR	
Median, months [a]	21.7
[a] Kaplan Meier estimates	

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for tafasitamab-cxix. The safety of tafasitamab-cxix was evaluated in an open label, multicenter, single arm trial (L-MIND). A total of 81 patients received tafasitamab-cxix 12 mg/kg as intravenously in combination with lenalidomide for maximum of 12 cycles (see Section 4: Benefit Assessment). Among patients receiving tafasitamab-cxix, 57% were exposed for 6 months or longer and 42% were exposed for greater than one year, and 24% were exposed for greater than two years.[1]

[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*

The most frequently reported (incidence ≥20% of patients) hematological treatment-emergent adverse events (TEAEs) in the Combination Therapy phase in MOR208C203 (L-MIND) compared with the pooled monotherapy trials were noted as neutropenia (48.8% versus 12.8%), anemia (33.8% versus 10.6%) and thrombocytopenia (31.3% versus 10.6%).

Deaths

A total of 50 (22.5%) deaths was reported in the 222 patients in the primary safety analysis. Of 50 deaths reported the distribution was: 10 (10.9%) deaths out of 92 patients in MOR208C201, 6 (27.3%) deaths out of 22 patients in MOR208C202, and 34 (42.0%) deaths out of 81 patients in MOR208C203 (L-MIND). Of the 50 deaths, 38/222 (17.1%) deaths resulted from disease progression. There were four fatalities that were not related to disease progression and not caused by TEAE, which were occurred later than 30 days post last study drug administration and, 8/222 (3.6%) that were due to TEAEs. These 8 patients had 10 TEAEs with a fatal outcome assessed as not related to disease progression. All 10 TEAEs with fatal outcome except one event 'sclerosing cholangitis' were considered not related to study medication by both the investigator and applicant. The only death for which a causal relationship to tafasitamab-cxix could not be excluded was a case of sclerosing cholangitis confounded by acute hepatitis A and Graft versus Host Disease after bone marrow transplant that started approximately 3 months prior to start of study medication.[14]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 52% of patients who received tafasitamab-cxix. The most frequent serious adverse reactions were infections (26%), including pneumonia (7%) and febrile neutropenia (6%). Permanent discontinuation due to an adverse reaction occurred in 25% of patients who received tafasitamab-cxix. In the pivotal trial MOR208C203 (L-MIND), 55/81 (68.8%) patients experienced 184 TEAEs that resulted in study drug modification (i.e., study drug interruption or dose reduction) during the combination therapy phase. The most frequent TEAE resulting in study drug modification of either tafasitamab-cxix or lenalidomide was neutropenia (28 [35.0%]).[1]

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 INFUSION-RELATED REACTIONS

In the L-MIND Study in R/R DLBCL, 5 (6%) patients experienced an infusion reaction; all were Grade 1 and resolved on the same day of occurrence. The majority of these reactions occurred during the first infusion. Symptoms included chills, flushing, dyspnea, and hypertension. Tafasitamab-cxix infusion was interrupted then resumed for 3 patients and supportive treatment was required for 3 of these 5 patients.[14] Management of infusion-related reactions, including recommendations to premedicate patients prior to tafasitamab-cxix infusion with acetaminophen, histamine H_1 receptor antagonists, histamine H_2 receptor antagonists, and/or glucocorticosteroids as well as monitoring and infusion rate modifications address the adverse events will be included in in the Dosage and Administration sections of the label.[1]

5.2 MYELOSUPPRESSION

Treatment with tafasitamab-cxix can cause serious or severe myelosuppression including neutropenia, thrombocytopenia, and anemia. In patients treated with tafasitamab-cxix and lenalidomide (n = 81),

Grade 3 hematologic adverse reactions occurring in ≥5% of patients included neutropenia (25%), thrombocytopenia (12%), febrile neutropenia (10%), leukopenia (9%), and anemia (7%). Grade 4 hematologic adverse reactions occurring in ≥5% of recipients included neutropenia (25%) and thrombocytopenia (5%). Cytopenias were the most common reason for treatment discontinuation (1% of patients due to tafasitamab-cxix; 5% of patients due to lenalidomide). There were no fatal neutropenic events.[14] Labeling instructs to monitor complete blood counts throughout treatment and prior to administration of each treatment cycle and monitor patients with neutropenia for signs of infection. Monitoring and dose modifications for toxicities to address the safety issues with tafasitamab-cxix will also be included in both Warnings and Precautions and the Dosage and Administration sections of the label.[1]

5.3 INFECTION

Bacterial, fungal, and new or reactivated viral infections can occur during and following tafasitamab-cxix therapy. Grade 3 or higher infections occurred in 30% of patients treated with tafasitamab-cxix and lenalidomide (n=81). Pneumonia was the most frequently reported serious infection occurring in 7% (6/81) patients. Infections occurring in ≥5% of patients included bronchitis (16%), nasopharyngitis (10%), pneumonia (10%), respiratory tract infection (10%), upper respiratory tract infection (10%), urinary tract infections (10%), gastroenteritis (6%), escherichia urinary tract infection (5%), rhinitis (5%), sinusitis (5%), and lower respiratory tract infection (5%).[14] Labeling instructs to monitor patients for signs and symptoms of infection.[1]

5.4 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, tafasitamab-cxix can cause fetal B-cell depletion when administered to a pregnant woman. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception for females of reproductive potential during treatment with tafasitamab-cxix and for at least 3 months after the last dose will be communicated in the Use in Specific Populations section of the label. Labeling instructs that the combination of tafasitamab-cxix with lenalidomide is contraindicated in pregnant women because lenalidomide may cause birth defects and death of the unborn child.[1] Lenalidomide is approved with a REMS to mitigate the risk of teratogenicity.[18]

6 Expected Postmarket Use

According to the current proposed indication, if approved, tafasitamab-cxix will be used in both inpatient and outpatient settings such as oncology infusion centers. It is expected that oncologists/hematologists, who should be familiar with the management of toxicities such as infusion-related reactions, myelosuppression, infections and embryo-fetal toxicity, will be the likely prescribers of tafasitamab-cxix.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for tafasitamab-cxix beyond routine pharmacovigilance and labeling. The applicant proposed the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information to address the risks of infusion-related reactions, myelosuppression, infections and embryo-fetal toxicity.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for tafasitamab-cxix, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Tafasitamab-cxix is a Fc-modified CD19 targeting mAb, with the proposed indication in combination with lenalidomide, for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for ASCT.[1] At the time this review was completed , labeling negotiations were still ongoing with the Applicant. Based on the efficacy and safety information currently available, the clinical reviewers stated that tafasitamab-cxix shows clinically meaningful benefit, and recommends approval of tafasitamab-cxix in combination with lenalidomide, for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for ASCT.[14,19]

DLBCL is the most common lymphoid malignancy in the United States. Despite overall improvements in outcomes of DLBCL, approximately one-third of patients will develop relapsed/refractory disease that remains a major cause of morbidity and mortality. DLBCL patients who progress or do not respond after two lines of treatment are unlikely to respond to further treatment with standard chemotherapy and have a dismal prognosis. Tafasitamab-cxix appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.[14,19]

The likely prescribers for tafasitamab-cxix will be oncologists or hematologists. The risks identified are risks that these providers have likely encountered in their practice experience. The most concerning adverse reactions observed with the use of tafasitamab-cxix are of infusion-related reactions, myelosuppression, infections and embryo-fetal toxicity. If tafasitamab-cxix is approved, labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with tafasitamab-cxix, as well as information to be included in Patient Counseling Information to inform patients. Management and monitoring of infusion-related reactions and myelosuppression, as well as the infusion rate and dose modifications for toxicities to address the safety issues with tafasitamab-cxix will also be included in both Warnings and Precautions and the Dosage and Administration sections of the label. At this time, none of these risks will receive a boxed warning in the label. DRM and DMH2 have determined that if approved, a REMS is not necessary to ensure the benefits of tafasitamab-cxix outweigh its risks.

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of tafasitamab-cxix. The management of the risks associated with tafasitamab-cxix treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile, so that this recommendation can be reevaluated if necessary.

10 References

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[19] Schwarsin A. Clinical Review Presentation. Mid-Cycle Meeting, dated April 15, 2020.

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/s/

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