CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761208Orig1s000

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	761208
PDUFA Goal Date	October 10, 2021
OSE RCM #	2021-284
Reviewer Name(s)	Joyce Weaver, Pharm.D.[a]
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	September 15, 2021
Subject	Evaluation of the Need for a REMS
Established Name	Tisotumab vedotin
Trade Name	Tivdak
Name of Applicant	Seagen Inc
Therapeutic Class	Tissue Factor directed antibody drug conjugate
Formulation(s)	40mg lyophilized powder for reconstitution and infusion
Dosing Regimen	2mg/kg (max 200mg) via intravenous infusion every 3 weeks

[a] Dr. Weaver contributed to this review but was no longer with the FDA at the time of completion.

Table of Contents

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 (NME) tisotumab vedotin is necessary to ensure the benefits outweigh its risks. Seagen (the Applicant) submitted a Biologics License Application (BLA) 761208 for tisotumab vedotin with the proposed indication (b) (4) The FDA approved indication will be for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. This indication will be approved under accelerated approval based on tumor response rate and durability of response. Continued approval for tisotumab vedotin will be contingent upon verification and description of clinical benefit in the Applicant's confirmatory trials.

Tisotumab vedotin has risks of ocular toxicity, peripheral neuropathy, pneumonitis, and embryo-fetal toxicity.

The applicant did not propose a REMS or a risk management program for tisotumab vedotin. DRM and the Division of Oncology Products 1 (DOP1) agrees that a REMS is not needed to ensure the benefits of tisotumab vedotin outweigh its risks for the proposed indication. The risks of ocular toxicity will be described in a boxed warning while peripheral neuropathy, pneumonitis, and embryo-fetal toxicity can be adequately described in the warnings and precautions section of the labeling. In the 60% of patients who had occurrence of ocular toxicity, 85% of these patients either had complete resolution (55%) or partial improvement (30%) in these cases. Partial improvement was defined as a decrease in severity by one or more grades from the worst grade at last follow-up. In addition, in the 4% of patients who experienced visual acuity changes, 75% of these cases resolved, including the one patient who experienced decreased visual acuity to 20/200. Recommendations in the box warning include instructing healthcare providers to conduct an ophthalmic exam at baseline, prior to each dose, and as clinically indicated; adhering to premedication and required eye care before, during and after infusion; withholding tisotumab vedotin until improvement and resume, reduce the dose, or permanently discontinue based on the severity. It appears that the risk of ocular toxicity resolved with mitigation efforts outlined in labeling, which were to some extent found in the safety protocol in the clinical trial. Therefore, at this time, DRM does not believe a REMS is necessary to mitigate the risk of ocular toxicity since this risk was mitigated and resolved with the efforts outlined above.

1 Introduction

This review by the DRM evaluates whether a REMS for the NME tisotumab vedotin is needed to ensure its benefits outweigh its risks. Seagen submitted a BLA 761208 for tisotumab with the

proposed indication [redacted] (b) (4) The FDA approved indication will be for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. This indication will be approved under accelerated approval based on tumor response rate and durability of response. Continued approval for tisotumab vedotin will be contingent upon verification and description of clinical benefit in the Applicant's confirmatory trials. The Applicant did not propose a REMS or risk management plan for this NME.

2 Background

2.1 PRODUCT INFORMATION

Tisotumab vedotin, a new molecular entity[b], is a tissue factor (TF)-directed antibody drug conjugate (ADC) produced as a monoclonal antibody in a mammalian cell line (Chinese hamster ovary).[1] Nonclinical data suggests that the anticancer activity of tisotumab vedotin is due to the binding of the ADC to TF expressing cells, followed by internalization of the ADC-TF complex, and release of a small compound, MMAE, via proteolytic cleavage. This release of MMAE disrupts the microtubule network of actively dividing cancerous cells, leading to cell cycle arrest and apoptotic cell death.[1] Tisotumab vedotin will be supplied as 40 mg lyophilized powder for reconstitution and infusion. The proposed dose is 2 mg/kg (max 200 mg) once every 3 weeks. Treatment continues until disease progression or unacceptable toxicity.[c] Tisotumab vedotin is not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761208 relevant to this review:

- 01/17/2019: Breakthrough Therapy Designation denied for indication.
- 8/31/2020: Pre-BLA meeting; REMS not discussed (DRM did not participate in the meeting)
- 02/10/2021: BLA submitted
- 5/27/2021: Mid-cycle meeting held with applicant

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

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

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results Program (SEER) estimates that in 2021 there will be about 14,480 new cases of cervical cancer and 4,290 deaths from the disease.[d,2] As of 2018, there were an estimated 293,000 women living with a cervical cancer diagnosis in the United States. The relative five-year survival rate after being diagnosed with cervical cancer is 66.3%, however factors such as age at diagnosis and staging of the cancer (specifically whether the disease is localized or metastasized) largely determine the mortality rate for any given patient.[2]

3.2 Description of Current Treatment Options

The treatment of recurrent cervical cancer depends on the extent of the disease as well as options that may be available for the patient, which may include hysterectomy, chemoradiation, or a combination of both, particularly for women with localized disease.[3] Chemotherapeutic options may include platinum-based chemotherapy, with fluorouracil. Radiation options include external beam radiation and brachytherapy. Bevacizumab, an anti-VEGF drug has shown in its clinical trial program to extend overall survival beyond 12 months in patients with metastatic or recurrent disease. However, prognosis is poor in women with metastatic or recurrent disease.[3]

4 Benefit Assessment

The efficacy of tisotumab vedotin was evaluated in a multicenter, open-label, single arm trial. The trial included 101 patients with recurrent or metastatic cervical cancer who had received one (70%) or two (30%) previous systemic therapy regimens. The median age of the patients was 50 years (range, 31 to 78 years), 95% were White, 2% were Asian, and 1% were Black. Six percent of patients were Hispanic or Latino.[1] Patients were excluded if they had active ocular surface disease, any prior episode of cicatricial conjunctivitis or Stevens Johnson Syndrome, grade 2 or greater peripheral neuropathy or known coagulation defects leading to an increased risk of bleeding. Prior to enrolling in this trial, 70% of patients had received 1 prior line of systemic therapy, and 30% had received 2 prior lines; 69% of patients previously received bevacizumab as part of their prior systemic therapy. Patients received 2 mg/kg tisotumab vedotin intravenously every 3 weeks until disease progression or unacceptable toxicity. Tumor response assessments were performed every 6 weeks for the first 30 weeks and every 12 weeks thereafter. The median duration of treatment was 4.2 months (range 0.7-16). Efficacy was measured by overall response rate and duration of response. The overall response was 24%

[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.*

(95% confidence interval, 15.9%, 33%); of these 7% of patients had a complete response rate and 17% of patients had a partial response. The duration of response was 8.3 months (4.2, NR).

5 Risk Assessment & Safe-Use Conditions

The safety database for tisotumab includes data from 158 patients who received one or more doses of tisotumab for the stated indication. A subset of these patients comprises the 101 patients who received tisotumab in the efficacy trial described above. The median duration of treatment was 4.2 months (range: 0.7-16).

Serious adverse reactions occurred in 43% of patients. The most frequently occurring serious adverse reactions were ileus (6%), hemorrhage (5%), and pneumonia (4%). Fatal adverse reactions occurred in 4% of patients who received tisotumab, including septic shock (1%), pneumonitis (1%), sudden death (1%), and multisystem organ failure (1%).

Adverse reactions leading to permanent discontinuation occurred in 13% of patients receiving tisotumab and included peripheral neuropathy (5%) and corneal adverse reactions (4%).

Adverse reactions leading to dose interruption occurred in 47% of patients; the most frequently occurring adverse reactions leading to dose interruption were peripheral neuropathy (8%), conjunctival adverse reactions (7%), and hemorrhage (4%).

Dose reduction occurred in 23% of patients. The most common adverse reactions that led to dose reduction were conjunctival adverse reactions (9%) and corneal adverse reactions (8%).

The risk of ocular toxicity will be included as a boxed warning, while peripheral neuropathy, hemorrhage, pneumonitis, and embryo-fetal toxicity will be described in the warnings and precautions section of the prescribing information.[e]

5.1 Ocular Adverse Reactions

Ocular adverse reactions occurred in 60% of patients receiving tisotumab vedotin, including conjunctival reactions (25%), corneal reactions (21%), and blepharitis (8%). The median time to onset was 1.2 months (range, 0-6.5), and led to discontinuation of therapy in 6% of patients. Fifty-five percent of patients that experienced ocular events had complete resolution, and 30% of patients had partial improvement (defined as a decrease in severity by one or more grades from the worst grade). Four percent of patients experienced visual acuity changes to 20/50 or worse including 1% of patients who experienced a visual acuity change to 20/200. These visual acuity changes resolved in seventy-five percent of the patients, including in the patient who experienced decreased visual acuity to 20/200.

[e] 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.*

The draft labeling advises healthcare providers to refer patients for an eye exam prior to commencing therapy. Patients should be monitored and referred for eye care for new or worsening ocular signs and symptoms. Prior to prescribing an ocular steroid for ocular symptoms, a slit lamp examination should be performed. Depending on the severity of an ocular reaction, therapy can be reduced, interrupted, or discontinued. Adherence to these recommendations are outlined in the prescribing information (Dosage and Administration and Warnings and Precautions) to reduce the risk of ocular adverse events. Recommendations in draft labeling also advise healthcare providers (HCPs) to refer patients to an eye care provider for any new or worsening ocular signs and symptoms.

5.2 PERIPHERAL NEUROPATHY

Peripheral neuropathy occurred in 42% of patients, and Grade 3 reactions occurred in 8% of patients. The median time to onset was 2.4 months (range, 0-11.3). Peripheral neuropathy led to discontinuation of therapy in 8% of patients. Of the patients who experienced peripheral neuropathy, 17% had complete resolution and 17% had partial improvement.

The draft labeling advises HCPs to monitor patients for peripheral neuropathy. Tisotumab vedotin should be withheld, the dose reduced, or discontinued for peripheral neuropathy if necessary.

5.3 HEMORRHAGE

Hemorrhage occurred in 62% of patients receiving tisotumab, including epistaxis (44%), hematuria (10%), and vaginal hemorrhage (10%). Grade 3 hemorrhage occurred in 8% of patients.

The draft labeling advises HCPs to withhold therapy for any pulmonary or CNS hemorrhage and for any hemorrhage grade 2 or above. Tisotumab can be restarted in some patients after resolution of the event.

5.4 PNEUMONITIS

Two patients had pneumonitis in clinical testing, including one patient with a fatal outcome. The draft labeling advises HCPs to withhold treatment and consider dose reduction for patients with persistent or recurrent Grade 2 pneumonitis. Tisotumab should be permanently discontinued for patients with Grade 3 or 4 pneumonitis.

5.5 EMBRYO-FETAL TOXICITY

Based on the mechanism of action and findings from animal models, it is believed that tisotumab can cause embryo-fetal toxicity. MMAE, a small molecule component of tisotumab vedotin administered to rats caused adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities at exposures below the clinically recommended doses.

Draft labeling recommends effective pregnancy contraceptive inpatients who can get pregnant during treatment with tisotumab vedotin, and for two months after the lase dose.

6 Expected Postmarket Use

Tisotumab vedotin would likely be used by hospitals and oncology infusion centers with the experience and equipment to administer infusions.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or other risk mitigation measures.

8 Discussion of Need for a REMS

The clinical team has concluded that at this time, the data support a favorable benefit:risk assessment for tisotumab vedotin with the proposed indication (b) (4) The Applicant's clinical trial data submitted showed an overall response rate of 24% (95% confidence interval, 15.9%, 33.3%). The median duration of response was 8.3 months (4.2, NR). This indication will be approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication for tisotumab vedotin may be contingent upon verification and description of clinical benefit in confirmatory trials.

The serious risks of ocular toxicity, which is labeled as a boxed warning, and other adverse reactions such as peripheral neuropathy, hemorrhage, pneumonitis, and embryo-fetal toxicity which are described in warnings and precautions, can be managed through labeling. In the 60% of patients who had occurrence of ocular toxicity, 85% of these patients either had complete resolution (55%) or partial improvement (30%) in these cases. Partial improvement was defined as a decrease in severity by one or more grades from the worst grade at last follow-up. There were only three corneal adverse events that were classified as grade 3. In addition, in the 4% of patients who experienced visual acuity changes, 75% of these cases resolved, including the one patient who experienced decreased visual acuity to 20/200. Recommendations in the box warning include instructing HCPs to conduct an ophthalmic exam at baseline, prior to each dose, and as clinically indicated; adhere to premedication and required eye care before, during and after infusion; withhold tisotumab vedotin until improvement and resume, reduce the dose, or permanently discontinue based on the severity. It appears that the risk of ocular toxicity resolved with mitigation efforts outlined in labeling, which were to some extent found in the safety protocol in the clinical trial. Therefore, at this time, DRM and DOP1 do not believe

a REMS is necessary to mitigate the risk of ocular toxicity since this risk can be mitigated and resolved with efforts outlined above which will be described in the label.

Of note, in the Applicant's clinical trial program, patients were excluded if they had active ocular surface disease, any prior episode of cicatricial conjunctivitis or Stevens Johnson Syndrome. The risk of ocular toxicity may be increased in the post-market setting. This risk must be continually evaluated in the Applicant's ongoing clinical trial, that will be required as a Post marketing Requirement: "Conduct the clinical trial innovaTV 301 titled, "Tisotumab Vedotin versus Chemotherapy in Recurrent or Metastatic Cervical Cancer" and provide the final overall survival and progression-free survival analyses to describe and verify the clinical benefit of tisotumab vedotin in patients with recurrent or metastatic cervical cancer. Mitigation requirements may change based on whether there is new or worsening safety information related to ocular toxicity.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of tisotumab vedotin outweigh its risks. 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] Tisotumab Vedotin draft Prescribing Information, September 10, 2021

[2] https://seer.cancer.gov/statfacts/html/cervix.html. Accessed July 1, 2021.

[3] Cohen P, Jhingran A, Oaknin A, et al. Cervical Cancer. *Lancet*. 2019 Jan 12;393(10167):169-182

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