CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761171Orig1s000

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	761171
PDUFA Goal Date	October 30, 2020
OSE RCM #	2020-664
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Acting Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	September 10, 2020
Subject	Evaluation of Need for a REMS
Established Name	Naxitamab
Trade Name	Danyelza
Name of Applicant	Y-mAbs Therapeutics
Therapeutic Class	GD2 antibody
Formulation(s)	4mg/mL 10-mL vials
Dosing Regimen	3 mg/kg/day on Days 1, 3, 5 of treatment cycle

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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 (NME) naxitamab is necessary to ensure the benefits outweigh its risks. Y-mAbs Therapeutics submitted a Biologics License Application (BLA) 761171 for naxitamab with the proposed indication for the treatment of patients with refractory or relapsed high-risk neuroblastoma in bone (b) (4) or bone marrow in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF). Following a review of the data, the indication statement has been changed to the treatment, in combination with GM-CSF of (b) (4) patients with relapsed or refractory high-risk neuroblastoma in bone or bone marrow who have demonstrated (b) (4)

Naxitamab has risks of serious infusion-related reactions, neurotoxicity, hypertension, and embryo-fetal toxicity. A boxed warning has been proposed for serious infusion-related reactions and neurotoxicity.

The applicant did not propose a REMS or a risk management program for naxitamab. DRM agrees that a REMS is not needed to ensure the benefits of naxitamab outweigh its risks for the proposed indication. The risks of serious infusion-related reactions, neurotoxicity, hypertension, and embryo-fetal toxicity can be adequately described in the labeling, including the risks to be described in the boxed warning. DRM agrees with this analysis; healthcare providers who will prescribe and administer naxitamab are expected to be able to manage the naxitamab-emergent adverse events without additional risk mitigation measures beyond labeling.

1 Introduction

This review by the DRM evaluates whether a REMS for the NME naxitamab is needed to ensure its benefits outweigh its risks. Y-mAbs Therapeutics submitted a Biologics License Application (BLA 761171) for naxitamab with the proposed indication for the treatment of patients with refractory or relapsed high-risk neuroblastoma in bone (b) (4) or bone marrow in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF). Following a review of the data, the indication statement has been changed to the treatment, in combination with GM-CSF of (b) (4) patients with relapsed or refractory high-risk neuroblastoma in bone or bone marrow who have demonstrated a (b) (4)

2 Background

2.1 PRODUCT INFORMATION

Naxitamab, a new molecular entity[a], is to be supplied as 4mg/mL 10-mL vials. The proposed dose is 3mg/kg (max 150 mg) on Days 1, 3, and 5 of each 4-week treatment cycle. Treatment continues until complete or partial response, followed by 5 additional cycles every 4 weeks. Subsequent cycles are repeated every 8 weeks until disease progression, (b) (4) [b]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA (b) (4) relevant to this review:

- 6/24/2013: Orphan Drug Designation granted for naxitamab for the treatment of neuroblastoma.
- 3/2018: Memorial Sloan Kettering Cancer Center (MSKCC) transferred the Orphan Drug Designation to Y-mAbs
- 8/20/2018: naxitamab granted Breakthrough Therapy Designation (BTD) for the following indication: "naxitamab in combination with GM-CSF, for the treatment of high-risk neuroblastoma refractory to initial therapy or with incomplete response to salvage therapy in patients > 12 months of age with persistent, refractory disease limited to bone marrow with or without evidence of concurrent bone involvement.
- 6/26/2019: Pre-BLA meeting; applicant advised that a REMS was not needed (DRM did not participate in the meeting)
- 3/31/2020: BLA submitted
- 6/30/2020: Mid-cycle meeting held

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Neuroblastoma develops from immature nerve cells in several areas of the body. Neuroblastoma frequently arises in and around the adrenal glands; however, neuroblastoma can also develop in other areas of the abdomen and in the chest, neck and near the spine. The American Cancer Society states there are about 800 cases of neuroblastoma annually, occurring

[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.*

most often in children younger than 5 years of age. Overall, the 5-year survival rate is 81%, but drops to 40-50% in patients with high-risk disease.[c,1]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment options include surgery, radiation, and chemotherapy. Induction therapies for high-risk neuroblastoma includes surgery and treatment with agents such as cisplatin, cyclophosphamide, doxorubicin, etoposide, topotecan, or vincristine. Consolidation therapy includes treatment with carboplatin-etoposide-melphalan, busulfan melphalan, or thiotepa-cyclophosphamide. Stem cell transplantation and external-beam radiotherapy can be used. Post-consolidation therapy to treat minimal residual disease includes immunotherapy and cytokines, plus isotretinoin.[2]

4 Benefit Assessment

Study 12-230

Study 12-230 examined the efficacy of naxitamab in combination with GM-CSF in a single center, open-label, single arm trial, in patients who had relapsed or refractory high-risk neuroblastoma in bone or bone marrow and demonstrated a response of stable disease or better following initial or subsequent therapy.[3]

Patients received naxitamab 3 mg/kg/cycle on Days 1, 3 and 5 in the first week of each cycle. Patients received GM-CSF subcutaneously at 250 µg/m^2/day on Days -4 to 0 and at 500 µg/m^2/day on Days 1 to 5. The major efficacy outcome measures were overall response rate and duration of response.

Of the 39 patients included in the efficacy analysis, 54% had relapsed neuroblastoma and 46% had refractory disease; 51% were male, the median age was 5 years (range 2 to 21 years), 74% were White, 8% Asian and 5% were Black, 5% Native American/American Indian/Alaska Native, 3% other races and 5% was not available.

The overall response rate was 38% (95% CI, 23%, 55%). Twenty-seven percent of patients had a duration of response of 6 months or longer.

Study 201

Study 201 examined the efficacy of naxitamab in combination with GM-CSF in a multi-center, open label, single arm trial in patients who had relapsed or refractory high risk neuroblastoma

[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.*

in bone or bone marrow and demonstrated a response of stable disease or better following initial or subsequent therapy.[4] All patients received at least one systemic therapy to treat disease outside of the bone or bone marrow prior to patient enrollment. Patients received naxitamab 3 mg/kg on Day 1, 3 and 5 in the first week of a 4-week cycle. Patients received GM-CSF subcutaneously at 250 µg/m^2/d on days -4 to 0 and at 500 µg/m^2/d on Days 1 to 5. The major efficacy outcome measure was overall response rate.

Of the 22 patients included in the efficacy analysis, 64% had refractory disease and 36% had relapsed disease; the median age was 5 years (range 3 to 10 years), 59% were male; 45% were White, 50% were Asian and 5% were Black.

The overall response rate was 64% (95% CI, 41%, 83%), with 50% of patients having a complete response.

5 Risk Assessment & Safe-Use Conditions

The safety database comprises 77 patients. The safety issues in the draft *Warnings and Precautions* section of the labeling include serious infusion-related reactions, neurotoxicity, hypertension, and embryo-fetal toxicity. A boxed warning has been proposed for serious infusion-related reactions and neurotoxicity.[d]

5.1 Serious Infusion-Related Reactions

Naxitamab can cause serious infusion reactions. Infusion-related reactions included hypotension, bronchospasm, hypoxia, wheezing, and stridor. Infusion-related reactions of any Grade occurred in most patients (100% of patients in Study 201 and 94% of patients in Study 12-230). In Study 201, 68% of patients experienced a Grade 3 infusion reaction; while in Study 12-230, 29% of patients experienced a Grade 3 infusion reaction and 1.4% experienced a Grade 4 infusion reaction. One patient in Study 12-230 (1.4%) experienced a cardiac arrest 1.5 hours following completion of the infusion.

In Study 201, 80% of patients required a reduction in infusion rate for at least one infusion-related reaction. Anaphylaxis occurred in 12% of patients in Study 201 and two patients (8%) permanently discontinued DANYELZA due to anaphylaxis.

Infusion reactions occurred most often within 30 minutes of initiation of naxitamab. Infusion reactions were most frequent during the first infusion in each cycle.

[d] 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 premedicate patients with an antihistamine, acetaminophen, an H_2 antagonist and a corticosteroid. Patients should be monitored for at least 2 hours following completion of each infusion. Based on severity of the reaction, the rate of the infusion should be reduced, interrupted, or permanently discontinued.

5.2 NEUROTOXICITY

Neurotoxic effects include neuropathic pain, peripheral neuropathy, visual disturbances, urinary retention, transverse myelitis, and reversible posterior leukoencephalopathy syndrome (RPLS).

Pain included abdominal pain, bone pain, neck pain, and extremity pain. Pain occurred in 100% of patients in Study 201 and 94% of patients in Study 12-230. Grade 3 pain occurred in 72% of patients in Study 201. One patient in Study 201 (4%) required interruption of an infusion due to pain. Pain typically began during the infusion of naxitamab and lasted a median of less than one day (range less than one day and up to 62 days). Draft labeling advises to premedicate patients with drugs that treat neuropathic pain (e.g., gabapentin) and oral opioids, and to administer intravenous opioids as needed for breakthrough pain. Naxitamab should be discontinued (b) (4)

Peripheral neuropathy including peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, and neuralgia occurred in 32% of patients in Study 201 and in 24% of patients in Study 12-230. Most signs and symptoms of neuropathy began on the day of the infusion and lasted a median of 5.5 days (range 0 to 22) in Study 201 and 1 day (range 0 to 22) in Study 230. Draft labeling advises to permanently discontinue naxitamab if neuropathy is severe.

Visual disturbances including unequal pupils, blurred vision, accommodation disorder, optic nerve disorder, mydriasis, visual impairment, photophobia and mydriasis occurred in 19% of patients in Study 12-230 and 24% of patients in Study 201. Neurological disorders of the eye lasted a median of 17 days (range 0 – 84 days) in Study 201 with 8% of patients experiencing an event that had not resolved, and a median of 1 day (range less than one day to 21 days) in Study 12-230. Draft labeling advises to permanently discontinue naxitamab if severe.

Urinary retention occurred in 4% of patients in Study 201 and Study 12-230. All events in both studies occurred on the day of an infusion of naxitamab and lasted up to 24 days. Draft labeling advises to permanently discontinue naxitamab if urinary retention persists after opioids are discontinued.

Reversible posterior leukoencephalopathy syndrome (RPLS) occurred in 2 patients in Study 12-230. Events occurred 2 days and 7 days following completion of the first cycle of naxitamab. Draft labeling advises prescribers to monitor blood pressure and assess for neurologic symptoms following the infusion, and to permanently discontinue naxitamab should symptomatic RPLS occur. One case of transverse myelitis occurred in clinical testing of

naxitamab. Draft labeling advises to permanently discontinue naxitamab if patients develop transverse myelitis.

5.3 HYPERTENSION

Hypertension occurred in 44% of patients in Study 201 and 28% of patients in Study 12-230 who received naxitamab. Grade 3 hypertension occurred in 4% of patients in Study 201 and 7% of patients in Study 12-230. Four patients (6%) in Study 12-230 permanently discontinued naxitamab due to hypertension. In both studies, most events occurred on the day of a naxitamab infusion and occurred up to 9 days after the infusion.

Draft labeling advises the prescriber to withhold naxitamab in patients with uncontrolled hypertension, and to monitor blood pressure during infusion, and at least daily on Days 1 to 8 of each cycle of naxitamab. The infusion should be interrupted and resumed at a reduced rate. Naxitamab should be permanently discontinued in the case of severe hypertension.

5.4 EMBRYO-FETAL TOXICITY

Based on the mechanism of action, it is believed that naxitamab can cause embryo-fetal toxicity. The draft labeling advises that females of reproductive potential should use effective contraceptive during treatment with naxitamab and for two months after the final dose.

6 Expected Postmarket Use

Naxitamab would likely be used by oncology infusion centers and hospitals.

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 the data support a favorable benefit:risk assessment for naxitamab for the treatment of patients the treatment, in combination with GM-CSF of (b) (4) patients with relapsed or refractory high-risk neuroblastoma in bone or bone marrow who have demonstrated a (b) (4) Data submitted for Study 12-230 showed an overall response rate of 38% (95% CI, 23%, 55%). Twenty-seven percent of patients had a duration of response of 6 months or longer. Data submitted for Study 201 showed an overall response rate was 64% (95% CI, 41%, 83%), with 50% of patients having a complete response.

The clinical team's preliminary findings are that the application is appropriate for accelerated approval and the risks of serious infusion-related reactions, neurotoxicity, hypertension, and embryo-fetal toxicity will be included in *Warnings and Precautions.* Serious infusion-related reactions, and neurotoxicity will be included in a boxed warning.[e] The clinical reviewers believe the adverse events are manageable with dose reduction, interruption, or discontinuance, and the events are appropriately handled with labeling alone.

This reviewer recommends that, should naxitamab be approved, a REMS is not needed to ensure its benefits outweigh its risks. The risks of serious infusion-related reactions, neurotoxicity, hypertension, and embryo-fetal toxicity can be adequately described in the labeling, including the risks to be described in the boxed warning. DRM agrees with this analysis, healthcare providers who will prescribe and administer naxitamab are expected to be able to manage the naxitamab-emergent adverse events without additional risk mitigation measures beyond labeling.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of naxitamab outweigh its 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] https://www.ncbi.nlm.nih.gov/pubmed/31912902. Accessed September 6, 2020.

[2] American College of Clinical Oncology. https://www.cancer.net/cancer-types/neuroblastoma-childhood/types-treatment. Accessed September 6, 2020.

[3] NCT 01757626

[4] NCT 03363373

[e] The clinical review was ongoing at the time of this review.

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.

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