CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761345Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Oncologic Disease
Division of Hematology Malignancies 2 (DHM2)

NDA/BLA #s:	761345
Products:	Elrexfio (elranatamab) injection
APPLICANT:	Pfizer
FROM:	Shan M. Pradhan, M.D., Associate Director for Safety
DATE:	August 11, 2023

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(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;

(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for elrantatamab to ensure that the benefits of the drug outweigh the risks of Cytokine Release Syndrome (CRS) and neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). In reaching this determination, we considered the following:

A. Multiple myeloma (MM) is the second most common hematological malignancy in the United States (US). The estimated number of patients in the US with a new MM diagnosis in 2023 is 35,730 and 12,590 multiple myeloma-related deaths are expected to occur (American Cancer Society, 2023). These estimates are based on key statistics for MM from American Cancer Society's Cancer Statistics Center and the SEER (Surveillance, Epidemiology, and End Results) program of the National Cancer Institute.

B. Despite the availability of multiple treatments, MM remains an incurable disease, with a 5-year survival rate of 58%. Patients with recurrent MM become resistant to current standard of care options and patients who have received multiple lines of therapy and have been treated with major classes of drugs including proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies have poor outcomes.

C. Treatment with elranatamab at step-up doses of 12 mg on Day 1 and 32 mg on Day 4, followed by 76 mg once weekly (responders could switch to biweekly dosing week 25 onward) resulted in an objective response rate (ORR) of 57.7% (95% CI: 47.3%, 67.7%). With a median follow-up of 11.1 months (95% CI: 10.6, 12.0) among responders, the median duration of response (DOR) was not reached (NR). The DOR rate at 6 months was 90.4% (95% CI: 78.4%, 95.9%) and at 9 months was 82.3% (95% CI: 67.1%, 90.9%).

D. It is expected that adult patients with relapsed or refractory MM who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody would receive treatment with elranatamab until disease progression or unacceptable toxicity.

E. Elranatamab at the recommended step-up doses of 12 mg on Day 1 and 32 mg on Day 4, followed by 76 mg weekly (responders may switch to biweekly dosing week 25 onward) poses the serious risks of CRS and neurologic toxicity including ICANS. Elranatamab is administered via subcutaneous injection, and onset of CRS and neurologic toxicity may occur hours or days after elranatamab dosing. In the pivotal C1071003 study, hospitalization was required for at least 48 hours after the start of the injection for step-up dose one (C1D1), and for 24 hours after the start of the injection for step-up dose two (C1D4). CRS and neurologic toxicity were common, occurring in 58% and 59% of patients, respectively, treated with elranatamab at the recommended dose. Grade 1 CRS occurred in 44% of patients, Grade 2 CRS (IV fluids and/or supplemental oxygen needed for management) in 14% of patients, and Grade 3 CRS in 0.5% of patients. Recurrent CRS occurred in 13% of patients. Most patients experienced CRS after the first step-up dose (43%) or the second step-up dose (19%), with 7% of patients having CRS after the first treatment dose and 1.6% of patients after a subsequent dose. The overall incidence of CRS was high despite consistent use of pre-medications. Grade 3 or 4 neurologic toxicity occurred in 7% of patients; neurologic toxicities included headache (18%), encephalopathy (15%), motor

dysfunction (13%), sensory neuropathy (13%), and Guillain-Barré Syndrome (0.5%). ICANS occurred in 3.3% of patients treated at the recommended dose. Most patients experienced ICANS after the first step-up dose (2.7%), 1 (0.5%) patient had ICANS after the second step-up dose, and 1 (0.5%) patient had ICANS after subsequent dose(s). Recurrent ICANS occurred in 1.1% of patients. The median time to onset was 3 (range: 1 to 4) days after the most recent dose, with a median duration of 2 (range: 1 to 18) days. The most frequent clinical manifestations of ICANS included a depressed level of consciousness and Grade 1 or Grade 2 Immune Effector Cell-Associated Encephalopathy (ICE) scores. In the overall safety population with elranatamab, including four patients treated with a single step-up dose, two additional patients experienced ICANS, such that the overall incidence of ICANS in Study C1071003 was 4.3%. In addition to CRS and neurologic toxicities including ICANS, elranatamab has been associated with infections, neutropenia, and hepatotoxicity.

F. Elrexfio is a new molecular entity.

The elements of the REMS will be a communication plan, elements to assure safe use including ETASU A (healthcare providers who prescribe elranatamab are specially certified) and ETASU B (pharmacies and healthcare settings that dispense elranatamab are specially certified), an implementation system, and a timetable for submission of assessments of the REMS.

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/s/

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Division of Risk Management (DRM)
Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
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	761345
PDUFA Goal Date	August 9, 2023
OSE TTT #	2022-3130
Reviewer Names	Bob Pratt, PharmD, DRM Kate Oswell, MA, DRM Tim Lape, PharmD, DMAMES
Team Leaders	Naomi Boston, PharmD, DRM Barbara Bergquist, PharmD, DMAMES
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS, DRM
Review Completion Date	August 9, 2023
Subject	Evaluation of need for a REMS
Established Name	Elranatamab-bcmm
Trade Name	Elrexfio
Name of Applicant	Pfizer Inc.
Therapeutic Class	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Formulation(s)	76 mg/1.9 mL (40 mg/mL) single-dose vial 44 mg/1.1 mL (40 mg/mL) single-dose vial
Dosing Regimen	Subcutaneous injection of 12 mg on Day 1 and 32 mg on Day 4 followed by 76 mg weekly, from week 2 to week 24. Patients who have achieved a response after 24 weeks of treatment and maintained this response for at least two months should transition to biweekly (every two weeks) administration.

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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 Elrexfio (elranatamab) is necessary to ensure the benefits outweigh its risks. Pfizer, Inc. submitted Biologic Licensing Application (BLA) 761345 for elranatamab with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. This indication will be approved under accelerated approval based on overall response rate and the durability of response. Regular approval for elranatamab may be contingent upon verification and description of clinical benefit in a confirmatory trial. The serious risks associated with elranatamab include cytokine release syndrome (CRS), neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS), hepatotoxicity, infections, and neutropenia. The major safety concerns in considering the need for a REMS are CRS and neurologic toxicity including ICANS, and these risks will be labeled in a Boxed Warning. The Applicant submitted a proposed REMS that consists of a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

The efficacy and safety of elranatamab were evaluated in Study C1071003, an open-label, multicenter study of elranatamab monotherapy. Efficacy in the pivotal cohort, which includes 123 patients naïve to prior BCMA-directed therapy, was established based on an overall response rate (ORR) of 61%. The median duration of response (mDOR) was not reached. In a subgroup of patients who received at least four prior lines of treatment, the ORR was 58% and the mDOR was not reached. In the safety population of patients who received the recommended dosing regimen, 58% of patients (N=106/183) experienced CRS, with Grade 1 events in 44% of patients and Grade 2 in 14% of patients. Fifty-nine percent (59%) of patients experienced neurologic toxicity, of which 7% were Grade 3 or 4 events. In addition, 3.3% of patients experienced ICANS. Risk mitigation activities during the clinical study included use of pretreatment medications for step-up dosing, initiating step-up dosing in an inpatient setting, and baseline, pre-dose and post-dose neurologic exams according to protocol in each 28-day treatment period through Cycle 6.

DRM and the Division of Hematologic Malignancies 2 (DHM2) agree that a REMS is necessary to ensure the benefits of elranatamab outweigh the risks of CRS and neurologic toxicity, including ICANS. The REMS determination is supported by the rate of CRS and neurologic toxicity, including ICANS, seen in the clinical trial program for elranatamab, as well as the route of administration and the potential for use by prescribers who may not have experience managing these adverse events in an outpatient setting. Elranatamab is proposed to be administered via subcutaneous injection, and the onset of CRS and neurologic toxicity may occur hours or days after the elranatamab dose, therefore, a REMS is necessary to ensure all prescribers are trained and aware of the importance of monitoring patients and to counsel patients to seek prompt supportive care for CRS and neurologic toxicity including ICANS that might occur when a patient is outside of a treatment setting.

The goal of the Elrexfio REMS is to mitigate the risks of CRS and neurologic toxicity including ICANS, by ensuring prescribers are aware of the importance of monitoring for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to Elrexfio. The Elrexfio REMS includes the following elements: a communication plan, ETASU A (healthcare providers who prescribe elranatamab are specially certified), ETASU B (pharmacies and healthcare settings that dispense elranatamab are specially certified),

an implementation system, and a timetable for submission of assessments. The communication plan will be used to target prescribers and healthcare providers who may be involved in administration of elranatamab or care for patients treated with elranatamab. Prescribers must certify in the REMS to ensure they receive training about the risks, how to monitor for and manage the risks, and that they provide counseling to patients. Counseling includes providing a wallet card to patients so that patients are aware they should seek medical care if CRS or neurologic toxicity including ICANS symptoms develop outside of a healthcare setting. Pharmacies and healthcare settings must be certified to confirm that prescribers are certified prior to dispensing elranatamab.

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] elranatamab is necessary to ensure the benefits outweigh its risks. Pfizer, Inc. submitted Biologic Licensing Application (BLA) 761345 for elranatamab with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. This application is under review in the Division of Hematologic Malignancies 2 (DHM2). The Applicant's proposed REMS consists of a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments, to ensure the benefits of elranatamab outweigh the risks of cytokine release syndrome (CRS) and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS).

2. Background

2.1. Product Information

Elranatamab is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager with the proposed indication of the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. Elranatamab binds to the CD3 receptor expressed on T-cells and BCMA on multiple myeloma cells, plasma cells and plasmablasts. Binding results in T-cell activation, cell lysis, and release of pro-inflammatory cytokines.

Elranatamab is proposed to be available as 76 mg/1.9 mL single-dose vials and 44 mg/1.1 mL single-dose vials for subcutaneous (SC) injection. The recommended doses of elranatamab are step-up doses of 12 mg on Day 1 and 32 mg on Day 4, which are followed by a full treatment dose of 76 mg weekly from week 2 to week 24. Patients who have received at least 24 weeks of treatment and have achieved a response and maintained this response for at least two months should transition to a dose administration schedule of biweekly administration. Treatment is expected to be continued until disease progression or unacceptable toxicity.[b] Elranatamab is currently not marketed in any jurisdiction.

[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.*

2.2. REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761345 relevant to this review:

- 10/12/2021: Orphan product designation status granted for the treatment of multiple myeloma.
- 10/21/2022: pre-BLA submission content and format meeting. The Sponsor proposed a possible REMS with ETASU but asked if the Agency agreed that the safety profile of elranatamab does not warrant a REMS program. The Agency acknowledged the information submitted regarding a possible REMS and stated that in general the approach is reasonable. The Agency reiterated that a determination of whether a REMS is needed, and the adequacy of the proposed REMS would be determined during review of the BLA submission.
- 10/27/2022: Breakthrough Therapy designation granted for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
- 11/3/2022: Initial portion of elranatamab BLA rolling submission containing chemistry, manufacturing and controls and nonclinical sections received.
- 12/19/2022: Final portion of BLA received to complete elranatamab rolling submission for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. The submission included a proposed REMS that consisted of a communication plan, ETASU, an implementation system, and a timetable for submission of assessments, to ensure the benefits of elranatamab outweigh the risks of CRS and neurologic toxicity including ICANS.
- 4/12/2023: Mid-cycle communication meeting with the Applicant. The Agency informed the Applicant that the proposed REMS remains under review.
- 5/2/2023: Information Request sent to the Applicant to state the Agency has determined that the proposed REMS submitted on December 19, 2022, will be required to adequately mitigate the risk of CRS and neurologic toxicity including ICANS.
- 6/29/2023: Information Request sent to the Applicant that provided the Agency's edits and comments in redlined Word versions of the REMS document and REMS materials. Annotated comments were provided in PDF versions of the REMS program training materials. In addition, the Agency requested that the Applicant explain the model for distribution of elranatamab that will be used for each type of pharmacy or healthcare setting including physician offices that dispense the product.
- 7/13/2023: The Applicant submitted a REMS Amendment that included a REMS document, REMS supporting document, and REMS materials in response to the Information Request that was sent by the Agency on 6/29/2023.
- 7/19/2023: Information Request sent to the Applicant that provided the Agency's comments about the REMS assessment plan and Key Performance Indicators.
- 7/25/2023: The Applicant submitted a response to the 7/19/2023 Information Request. The response included updates to the REMS assessment plan and supporting document. The Applicant also included questions about authorization of dispensing and requested clarification about the assessment plan in their response.
- 7/28/2023: Information Request sent to the Applicant that provided the Agency's edits and comments in redlined Word versions of the REMS document and REMS materials and redlined PowerPoint versions of

the prescriber and pharmacy/healthcare setting training slides. Annotated comments were provided in a PDF version of the REMS website. In addition, the Agency responded to the issues related to dispensing and questions about the assessment plan that the Applicant raised in their July 25, 2023, submission.

- 7/31/2023: Information Request sent to the Applicant that clarified the requirement for pharmacies and healthcare settings related to the maintenance and provision of dispensing records.
- 8/1/2023: The Applicant submitted a REMS Amendment that included a REMS document, REMS supporting document, and REMS materials in response to the comments sent in the 7/28/2023 Information Request and the clarification of the request sent 7/31/2023.
- 8/2/2023: Information Request sent to the Applicant that stated the Agency did not agree with the Applicant's proposed changes to the audit plan submitted in the 8/1/2023 REMS Amendment.
- 8/3/2023: The Applicant submitted a response to the 8/2/2023 Information Request. The response included updates to the REMS document, supporting document, and assessment plan.
- 8/4/2023: Information Request sent to the Applicant that provided the Agency's comments on the REMS materials submitted 8/1/2023.
- 8/8/2023: The Applicant submitted a REMS Amendment that included a REMS document, REMS supporting document, and REMS materials in response to the comments sent in the 8/4/2023 Information Request.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Multiple myeloma is a heterogeneous disease characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. The disease accounts for 1% – 2% of all cancers and approximately 17% of all hematologic malignancies. The plasma cells proliferate in the bone marrow and can result in skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. The clinical presentation of multiple myeloma can include bone pain with lytic lesions, anemia, hypercalcemia, acute kidney failure, and increased total serum protein and/or monoclonal protein in the serum or urine.[1]

Multiple myeloma is generally a disease of older adults. The median age at diagnosis is 65 to 74 years and the disease occurs slightly more frequently in men than in women and among individuals of African American descent. The American Cancer Society estimates approximately 35,730 new cases of multiple myeloma and 12,590 deaths from multiple myeloma in the U.S. in 2023.[c] The adjusted 5-year survival rate for patients diagnosed with multiple myeloma over the period of 2012-2018 is reported to be 58%.[d,2]

Most patients with multiple myeloma will have an initial response to treatment, but patients typically experience serial relapses over time and ultimately receive most if not all available agents at some point during the course of their disease. In addition, a minority of patients will have primary refractory disease that does not respond to initial treatment. Refractory myeloma is defined as being non-responsive to therapy or disease that progresses within 60 days of the last line of therapy. Relapsed and refractory

[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.*

multiple myeloma (RRMM) is defined as disease nonresponsive to the chosen line of therapy in patients who had achieved a minimal response or better at some point previously in their disease.[3] A retrospective cohort study of patients with multiple myeloma refractory to anti-CD38 monoclonal antibody therapy found the median overall survival (OS) to be 8.6 months.[4]

3.2. DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are various combination treatment regimens for patients with relapsed and/or refractory multiple myeloma. The choice of therapy for relapsed disease must consider prior therapy and response and prioritize regimens that contain treatments the patient has not already been exposed to. For patients with third or later relapse, the most used classes of therapy are immunomodulatory agents including lenalidomide, pomalidomide, and thalidomide; the proteasome inhibitors bortezomib, carfilzomib, and ixazomib; and anti-CD38 monoclonal antibodies that include daratumumab and isatuximab. The term penta-refractory disease is used to describe multiple myeloma that is refractory to an anti-CD38 monoclonal antibody as well as lenalidomide, pomalidomide, bortezomib, and carfilzomib. Whether a patient has penta-refractory disease represents an important determinant of therapy in third or greater relapse; these patients may be treated with various regimens that contain alkylators, such as cyclophosphamide, melphalan, and bendamustine.[5] Selinexor, a selective inhibitor of nuclear export, is approved in combination with dexamethasone for the treatment of patients with RRMM who received at least four prior therapies and whose disease is refractory to multiple agents.[6] In addition, idecabtagene vicleucel and ciltacabtagene autoleucel are BCMA-directed chimeric antigen receptor (CAR)-T cell therapies approved for relapsed or refractory multiple myeloma following at least four lines of systemic therapy. The CAR-T therapies require REMS programs with ETASU to mitigate the risks of CRS and neurologic toxicities.[7,8] Similar to elranatamab, teclistamab is a bispecific monoclonal antibody T cell engager directed at both BCMA and CD3 on the patient's T-cells that was approved in October 2022. Teclistamab is approved for patients who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent, and the product requires a REMS with ETASU to mitigate the risks of CRS and neurologic toxicity, including ICANS. Teclistamab is administered as a subcutaneous injection in step-up doses on days 1, 4, and 7, followed by weekly dosing thereafter.[9] Talquetamab is another bispecific antibody T-cell engager directed at G protein-coupled receptor class C group 5 member D (GPRC5D) expressed on the surface of multiple myeloma cells and the CD3 receptor on T-cells. The BLA for talquetamab is currently under review. The proposed indication is for the treatment of patients who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and the product requires a REMS with ETASU to mitigate the risks of CRS and neurologic toxicity, including ICANS. Talquetamab is also administered as a subcutaneous injection in step-up doses on days 1, 4, and 7, followed by weekly or biweekly dosing thereafter.[10]

4. Benefit Assessment

The efficacy of elranatamab was evaluated in Study C1071003 [NCT04649359], a Phase 2, open-label, multicenter study of elranatamab monotherapy in patients with relapsed or refractory multiple myeloma. The study included patients who were refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody. The study included 123 patients naïve

to prior BCMA-directed therapy (Cohort A), which is considered the pivotal cohort. Sixty-four patients who were previously treated with a BCMA-directed antibody drug conjugate or CAR-T cell therapy comprised a second cohort (Cohort B), though the efficacy results for this cohort are considered supportive only and not otherwise described in this review.

Patients received elranatamab by subcutaneous injection with step-up doses of 12 mg on Day 1 and 32 mg on Day 4 of treatment, followed by the first full treatment dose of 76 mg on Day 8 of treatment. Thereafter, patients received 76 mg once weekly. After 24 weeks, in patients who achieved a partial response or better with responses persisting for at least 2 months, the dose interval was changed from every week to every 2 weeks. The primary endpoint was the objective response rate (ORR) assessed by blinded independent central review per the International Myeloma Working Group response criteria. Secondary endpoints included duration of response (DOR) as well as other endpoints.[11] The ORR in Cohort A was 61.0% (95% CI: 51.8, 69.6) and the median DOR (mDOR) (months) was not reached (95% CI: 12.0, [not estimable]) with a median follow-up among responders of 11.2 months. In a subgroup of 97 patients in Cohort A who received at least four prior lines of therapy, the ORR was 57.7% (95% CI: 47.3, 67.7). The mDOR (months) in this subgroup was also not reached (95% CI: 12.0, [not estimable]) and the median follow-up of responders was 11.1 months.[12,e]

The confirmatory study is an open-label, randomized Phase 3 study that is well underway to evaluate the efficacy and safety of elranatamab monotherapy and elranatamab in combination with daratumumab vs. daratumumab in combination with pomalidomide and dexamethasone.

The FDA review team concluded the trial supported the efficacy of elranatamab in patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies which included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. In this heavily pretreated population with limited available effective therapies, the magnitude of response with durability represents a clinically meaningful treatment effect and provides an advantage over available therapies.[13]

5. Risk Assessment & Safe-Use Conditions

The elranatamab safety population for this review consists of 183 patients in Cohorts A and B in Study C1071003. This includes 119 patients who were naïve to prior BCMA-directed therapy and who received the recommended step-up dosing regimen of 12 mg and 32 mg followed by the full treatment dose, and 64 patients previously treated with a BCMA-directed antibody drug conjugate or CAR-T cell therapy.

The most frequently reported treatment-emergent adverse events (TEAE) occurring in ≥ 30% of patients included CRS (58%), fatigue (43%), injection site reaction (37%), diarrhea (36%), upper respiratory tract infection (34%), musculoskeletal pain (34%), and pneumonia (32%).[12] Categorization of fatigue, injection site reaction, diarrhea, upper respiratory tract infection, musculoskeletal pain, and pneumonia were based on FDA grouping of related MedDRA preferred terms.

5.1. Serious Adverse Events

Deaths

[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.*

Deaths were reported in 73 of 183 (40%) patients and were primarily due to disease progression (N=53/73 [73%]). Fatal TEAEs were reported in 20% of patients and most of these adverse events were also related to disease progression. The majority of deaths not related to disease progression were due to infectious adverse events, including COVID-19/COVID-19 pneumonia (N=5), sepsis/septic shock (N=5), adenovirus infection/adenoviral pneumonia (N=2), and pseudomonal pneumonia (n=1). All other adverse events leading to death were reported in one patient only across several MedDRA System Organ Classes (SOCs).[14]

Other Serious or Severe Adverse Events [f]

Based on an evaluation of fatal and nonfatal serious adverse events (SAEs), serious events occurred in 125 of 183 patients (68%) who received elranatamab. Overall, the most frequently reported SAEs occurred in the Infections and Infestations SOC including pneumonia (25%), sepsis (13%), and urinary tract infection (3.3%). The SAEs of pneumonia, sepsis, and urinary tract infection were based on FDA grouping of related MedDRA preferred terms. The labeling includes a Warning and Precaution that states elranatamab can cause severe, life-threatening, or fatal infections including opportunistic infections, and that patients are to be monitored for signs and symptoms of infection prior to and during treatment with elranatamab and treated appropriately. Elranatamab can also cause neutropenia and febrile neutropenia. In patients who received the recommended dose in the clinical trial, decreased neutrophils occurred in 62% of patients, with Grade 3 or 4 decreased neutrophils in 51%. Febrile neutropenia occurred in 2.2% of patients. The labeling includes a Warning and Precaution to monitor complete blood cell counts at baseline and periodically during treatment, and to provide supportive care according to current practice guidelines.[12]

5.2. ADVERSE EVENTS OF SPECIAL INTEREST [g]

5.2.1. Cytokine Release Syndrome

CRS is a potentially life-threatening toxicity related to cell lysis and release of pro-inflammatory cytokines that has been observed following administration of immune-based therapies for cancer. Patients in Study C1071003 received dexamethasone, diphenhydramine, and acetaminophen as pretreatment medications prior to the step-up doses and the first full treatment dose of elranatamab. The study protocol required patients to be hospitalized for 48 hours after the first step-up dose and for 24 hours after the second step-up dose.

In the 183 patients receiving elranatamab, 106 (58%) experienced CRS events. In terms of the maximum toxicity grade experienced, most patients experienced Grade 1 events (44%), 14% of patients experienced Grade 2 CRS and 0.5% of patients Grade 3 CRS. There were no Grade 4 events or deaths from CRS reported. The most frequent clinical manifestations of CRS included fever, hypotension, and hypoxia. The majority of CRS events occurred after the first (43%) or second (19%) step-up dose; 7% of events occurred after the third dose (first full treatment dose) and 1.6% occurred after a later dose. Twenty-four patients (13%) experienced more than one CRS event. All CRS events resolved.[14]

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[f] The grading of adverse event severity was based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), with the exception of CRS and ICANS, which were graded based on the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 criteria.

[g] 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.*

Management of CRS during the clinical study was at the discretion of the Investigator. The interleukin-6 (IL-6) inhibitors tocilizumab and siltuximab were to be considered for the treatment of Grade 1-2 CRS and recommended for CRS that was Grade 3 and higher. Corticosteroids and other supportive care were also considered or recommended depending on the severity of symptoms.[15] In the 183 patients who received elranatamab, 36% of patients who developed CRS received tocilizumab or siltuximab, including 22% of patients with Grade 1 CRS events and 66% of patients with Grade 2 CRS events.[14]

Although tocilizumab has received approval for the treatment of CAR-T cell-induced severe or life-threatening CRS, tocilizumab is not approved for the treatment of CRS associated with BCMA-directed CD3 T-cell engagers. The review team concluded that there were no overall differences in outcomes among patients who received tocilizumab for the management of Grade 1-2 CRS in the clinical study compared to those who did not, therefore, its use will not be described in the Prescribing Information for elranatamab.[13] Recommendations in the Prescribing Information include initiating therapy according to the 12 mg and 32 mg step-up dosing schedule and administering pretreatment medications to reduce the risk of CRS. The draft labeling also advises that patients should be hospitalized for 48 hours after administration of the first step-up dose and for 24 hours after the second step-up dose.

5.2.2. Neurologic Toxicity including ICANS

The risk of neurologic toxicity including ICANS, a clinical and neuropsychiatric syndrome that may be life threatening, was identified as a serious risk in the clinical study. ICANS may manifest as aphasia, delirium, encephalopathy, tremor, seizures, and cerebral edema, among other symptoms. Neurotoxicity was monitored by baseline, pre-dose and post-dose neurologic exams of each 28-day treatment period according to protocol through Cycle 6.

In the clinical study, 59% of patients receiving elranatamab experienced neurologic toxicity. The most common symptoms of neurologic toxicity were headache (18%), motor dysfunction (14%), encephalopathy (14%), and sensory neuropathy (13%). Categorization of these four adverse events was based on FDA grouping of related MedDRA preferred terms. Most patients experienced either Grade 1-2 neurologic events, with Grade 3 or 4 neurologic events occurring in 7% of patients who experienced an event. One patient experienced a Grade 3 adverse event of Guillain-Barré syndrome concurrent with CMV infection.

ICANS was reported in 6 of 183 (3.3%) patients in the clinical study. The 6 cases occurred concurrently with CRS. Four of the 6 patients developed a maximum toxicity of Grade 1 or Grade 2 ICANS, and two patients developed Grade 3 ICANS. The most frequent clinical manifestations of ICANS included a depressed level of consciousness and Grade 1 or Grade 2 Immune Effector Cell-Associated Encephalopathy (ICE) scores.[h] Two patients experienced recurrent ICANS.

Recommendations in the Prescribing Information include monitoring of patients for signs and symptoms of neurologic toxicities during treatment. At the first sign of neurologic toxicity, including ICANS, evaluate and

[h] Immune Effector Cell-Associated Encephalopathy (ICE) scores are based on assessment of the following: orientation (oriented to year, month, city, hospital = 4 points); naming (name 3 objects, e.g., point to clock, pen, button = 3 points); following commands (e.g., “show me 2 fingers” or “close your eyes and stick out your tongue” = 1 point); writing (ability to write a standard sentence = 1 point); and attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points. [Elrexfio (elranatamab) Draft Prescribing Information. July 24, 2023]

treat patients immediately based on severity, and withhold or permanently discontinue elranatamab based on severity of symptoms.

The Prescribing Information also recommends that prescribers counsel patients to seek medical attention should signs or symptoms of neurologic toxicity occur, and to advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of the step-up dosing schedule, and in the event of new onset of any neurologic toxicity symptoms until symptoms resolve.

5.2.3. Hepatotoxicity

In the clinical study, elevated ALT occurred in 36% of patients, with Grade 3 or 4 ALT elevation occurring in 3.8%; elevated AST occurred in 40% of patients, with Grade 3 or 4 AST elevation occurring in 6%. Grade 3 or 4 total bilirubin elevations occurred in 0.5% of patients.[12] The Division of Hepatology and Nutrition evaluated the potential for drug-induced liver injury (DILI) and the overall risk of hepatotoxicity with Elrexfio. Three patients in the clinical study developed jaundice and elevated aminotransferases and thus met the criteria for Hy's law. The hepatology team concluded that two of the three cases were not DILI. Although the third case was considered possible DILI related to Elrexfio, the case was confounded by extramedullary disease in the liver.[16]

The Prescribing Information includes a Warning and Precaution for hepatotoxicity that states liver enzymes and bilirubin are to be monitored at baseline and during treatment as clinically indicated, and that elranatamab should be withheld or permanently discontinued based on severity.

6. Expected Postmarket Use

If approved, it is expected that elranatamab will be administered by a healthcare provider in hospital inpatient settings, hospital outpatient settings, physician office practices, and oncology infusion centers that administer subcutaneous anti-cancer therapy. It is expected that oncologists/hematologists will be the primary prescribers of elranatamab. Although some prescribers may be familiar with the risks and management of CRS and neurotoxicity including ICANS, there may also be prescribers (primarily those who treat patients in an outpatient setting) with limited or no experience in managing CRS and neurologic toxicity including ICANS. As such, some patients might not receive prompt supportive care for CRS or neurologic toxicity if prescribers are not trained and fully aware to monitor for these risks. Furthermore, the subcutaneous route of administration lends elranatamab to be accessible in a broader range of practice settings than for some of the other approved products for RRMM. Until additional evidence is available that shows the prescribing population has generally acceptable knowledge and understanding of the risks and management of CRS and neurotoxicity/ICANS associated with this new class of subcutaneously administered therapy, the review team finds it necessary to ensure all prescribers are trained and aware of the importance of monitoring for these risks and to counsel patients to seek prompt supportive care for CRS and neurotoxicity/ICANS that might occur outside of the treatment setting.

Although the patient population will have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, most of these products are not associated with CRS or neurologic toxicity, including ICANS. Therefore, patients may be unfamiliar with CRS and neurologic toxicity/ICANS. CRS associated with elranatamab presented with a fever in 98% of patients in the clinical study and we expect patients who are eligible for elranatamab therapy would be familiar with identifying and monitoring for fevers at home. Oncology patients are often

instructed to monitor themselves for fevers as a common symptom of infection due to known complications of cancer therapies such as febrile neutropenia.

7. Risk Management Activities Proposed by the Applicant

In the original BLA submission, the Applicant proposed a REMS for elranatamab that includes a communication plan, ETASU A (healthcare providers who prescribe elranatamab are specially certified), ETASU B (pharmacies and healthcare settings that dispense elranatamab are specially certified), an implementation system, and a timetable for submission of assessments to ensure the benefits of elranatamab outweigh the serious risks of CRS and neurologic toxicity, including ICANS.

7.1. REVIEW OF APPLICANT'S PROPOSED REMS

The Applicant submitted a complete REMS proposal including a REMS document, REMS materials, and REMS supporting document with the original BLA submission dated December 19, 2022, and amended July 13, July 25, August 1, August 3, and August 8, 2023. The final REMS document, REMS materials, and REMS supporting document were submitted August 8, 2023.

7.1.1. REMS Goal

The goal of the Elrexfio REMS is to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by:

- Ensuring prescribers are aware of the importance of monitoring for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to Elrexfio

Reviewer Comments:

The Applicant's proposed goal for the REMS as submitted on December 19, 2022, was as follows:

The goal of the Elrexfio REMS is to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by:

- *(b) (4) prescribers (b) (4) the importance of monitoring (b) (4) for signs and symptoms of CRS and neurologic toxicity including ICANS.*

After Agency review, it was determined the objective of the goal should be revised for clarity and to provide a quantifiable measure to track and assess the REMS as well as to reflect the Agency's current thinking to remove (b) (4) from the objective and instead (b) (4) which is ensuring the prescriber's awareness of the importance of monitoring. The Applicant updated the goal statement as requested by the Agency.

7.1.2. Communication Plan

The Applicant proposes to send a Healthcare Provider REMS Letter and a Professional Society REMS Letter, with a REMS Fact Sheet attached, to inform healthcare providers about the Elrexfio REMS. The letters and Fact Sheet will describe the approved indication, the serious risks of CRS and neurologic toxicity, including ICANS, and safe use requirements of elranatamab. The Healthcare Provider letter targets healthcare providers including oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, and oncology nurses. The REMS Letters to Professional Societies targets professional societies including the American Society of Clinical Oncology; American Society of Hematology; Advanced Practitioner Society for Hematology and Oncology; Oncology Nursing Society; National Comprehensive Cancer Network; Society of

Hematologic Oncology; Hematology Oncology Pharmacy Association; American Pharmacists Association; and American Society of Health-System Pharmacists. The Applicant proposes to send the Healthcare Provider REMS letter via email within 30 calendar days of the date elranatamab is first commercially distributed and again 12 months later. Sending the letter by postal mail and via additional emails will take place depending on whether the emails are undeliverable, unopened, or if the healthcare provider's email address is not available. The letter will also be disseminated through field-based sales and medical representatives. The Professional Society letter will be disseminated within 30 calendar days of the date elranatamab is first commercially distributed and again 12 months later with a request that the letter or content be provided to the society's members. The letter and Fact Sheet will also be disseminated at professional meetings where the Applicant has a presence and by field-based sales and medical representatives for 12 months.

Reviewer Comments:
We agree with the Applicant's proposal to communicate the serious risks of elranatamab and to inform healthcare professionals that elranatamab is only available through the REMS. The communication plan will inform prescribers and other healthcare providers about the risks and key REMS requirements. Information about the REMS in these communication materials will include the requirements that prescribers must certify in the REMS program prior to prescribing elranatamab; pharmacies and healthcare settings must certify in the REMS program prior to dispensing elranatamab; and the need to monitor for CRS and neurologic toxicity in patients taking elranatamab.

7.1.3. Elements to Assure Safe Use (ETASU)

The Applicant proposed the following ETASU as part of the REMS requirements:

- ETASU A, Prescriber certification
- ETASU B, Pharmacy and healthcare setting certification

ETASU A: Prescriber Certification

Prior to prescribing the product, the healthcare provider (HCP) must certify in the Elrexfio REMS. To become certified, the prescriber must review the Prescribing Information, the Prescriber Training Program, and the Adverse Reaction Management Guide. The HCP must then successfully complete the Knowledge Assessment and enroll in the REMS by completing the Prescriber Enrollment Form and submitting these to the REMS. As part of prescriber certification, the prescriber must agree to counsel the patient on how to recognize and respond to signs and symptoms of CRS and neurologic toxicity including ICANS, and the need to report all symptoms suggestive of CRS and neurotoxicity/ICANS to their HCP or emergency room provider immediately. The prescriber must also agree to complete and provide the Patient Wallet Card to the patient, and must report CRS and neurologic toxicity events including ICANS to the REMS program.

Reviewer comments:
We agree that prescriber training and certification is necessary to ensure the benefits of elranatamab outweigh the risks. Due to the subcutaneous route and ease of administration of elranatamab, we expect use of this product by outpatient clinic settings and physician office practices where prescribers may be less familiar with monitoring for and managing CRS and neurologic toxicities. Prescriber certification ensures prescribers are educated on the risks of CRS and neurologic toxicity associated with elranatamab, are aware of the importance of monitoring, and the need to counsel patients about the risks of CRS and neurologic

toxicity. We also agree with the requirements for certification listed above, which support the goal and objectives of the REMS.

The Agency conveyed to the Applicant on June 29 and July 28, 2023, that changes were necessary to the REMS document and REMS materials. These changes include edits to the REMS document to remove a (b) (4) *. This recommendation was removed from the Prescribing Information and changed to recommending that patients should be hospitalized for 48 hours after the first step-up dose and for 24 hours after the second step-up dose. Although this specific aspect of counseling is not a REMS requirement, it is clinically important and therefore is included in the REMS materials. The REMS document and materials were also inconsistent regarding when patients are to receive counseling and the patient wallet card from the prescriber. The proposed REMS document stated this requirement must occur "Before treatment initiation* (b) (4) *." The REMS document and REMS materials were changed to state this requirement must occur before the "first step-up dose," because patients should be informed prior to initiation of treatment about how to recognize and respond to signs and symptoms of the risks of CRS and neurotoxicity and the need to report such signs and symptoms to their HCP or emergency room provider.*

Additional edits and changes were made to the prescriber-directed REMS materials to include the clinical management of neurotoxicity other than ICANS; changes to the wording of certain answers to questions in the knowledge assessment that were misstated, and the replacement of a question (b) (4) *with a more clinically important question about neurologic toxicity. Several additional signs and symptoms of CRS and neurologic toxicity were added to the Patient Wallet Card so that it aligns with the Medication Guide. Other edits and changes were made for the overall purpose of alignment of the REMS materials with the Prescribing Information and Medication Guide.*

ETASU B: Pharmacy and Healthcare setting Certification

The Applicant proposed that elranatamab is dispensed only from certified pharmacies and healthcare settings. Certified pharmacies and healthcare settings will be required to verify that prescribers are certified by obtaining a REMS Dispense Authorization (RDA) prior to dispensing elranatamab. Pharmacies and healthcare settings must become certified by designating an authorized representative to complete the certification process and oversee implementation and compliance with the REMS program. To become certified, the authorized representative must review the Pharmacy and Healthcare Setting Training Program and enroll in the REMS by completing and submitting the Pharmacy and Healthcare Setting Enrollment Form to the REMS program. In addition, the authorized representative must train all relevant staff involved in dispensing elranatamab on the REMS requirements using the Pharmacy and Healthcare Setting Training Program. If the product is administered at a physician office practice, a certified prescriber cannot be designated as the authorized representative for that healthcare setting.

Reviewer's comments:
We agree with the Applicant's proposal for pharmacy and healthcare setting certification. The role of pharmacy and healthcare setting certification in the REMS is to verify that prescribers are certified prior to dispensing elranatamab.

The Agency conveyed to the Applicant on June 29 and July 28, 2023, that changes were necessary to the REMS document and REMS materials directed to pharmacies and healthcare settings. These changes included edits to the REMS document (b) (4) *. The Agency also requested the rationale for the Applicant's proposal* (b) (4) *The Applicant subsequently removed this proposed requirement and acknowledged that the requirement for obtaining authorization to dispense is adequate.*

In the REMS Amendment submitted July 13, 2023, the Applicant proposed to replace occurrences of the word "prescription" in the REMS (b) (4) *when referring to dispense authorization, and that the change was for the purpose of aligning with the Prescribing Information. In their submission of July 25, 2023, the Applicant also asserted that the term "prescription" may be interpreted as an authorization to dispense that can cover multiple doses. The Agency did not agree with this change because the REMS requirement specifies pharmacies and healthcare settings that dispense Elrexfio must, before dispensing, obtain authorization to dispense each prescription by contacting the REMS to verify the prescriber is certified. The intent of the requirement is not for the pharmacy or healthcare setting to obtain authorization to administer each dose to a patient, but to obtain authorization to dispense the product based on receipt of a prescription from a certified prescriber. In our response to the Applicant sent July 28, 2023, we noted that* (b) (4) *is not necessary. In addition, at this time, the REMS does not specifically limit the amount of product that can be dispensed; however, given the proposed distribution model and dosing schedule, it is unclear if more than one dose would typically be dispensed at a time.*

In the Information Request that was sent on July 28, 2023, we requested that pharmacies and healthcare settings be required to maintain and submit dispensing data to the REMS and wholesalers-distributors at all times. After further consideration of the burden on pharmacies and healthcare settings to comply with this requirement, it was determined that pharmacies and healthcare settings would, as proposed in the original submission, maintain the dispensing data and provide it to the REMS and wholesalers-distributors as requested.

Additional edits and changes were made to the pharmacy/healthcare setting materials to correct a (b) (4)

7.1.4. Implementation System

For successful implementation of the REMS, the Applicant proposes to maintain a REMS Coordinating Center, REMS Website, and validated secure database of all REMS participants to support patients, prescribers, healthcare providers, pharmacies and healthcare settings, and wholesaler-distributors to interface with the REMS. The Applicant will notify stakeholders of successful enrollment in the REMS within one calendar day. The Applicant will ensure elranatamab is only distributed to certified pharmacies or

healthcare settings by wholesaler-distributors who are compliant with the REMS requirements. To ensure compliance, the Applicant will ensure processes and procedures are in place to maintain adequate records that demonstrate the REMS requirements are being met through audits of certified pharmacies/healthcare settings and wholesaler-distributors.

Reviewer Comments:
We agree with the Applicant's proposal to include an implementation system. The Agency provided edits and comments to the Applicant on June 29, 2023, that changes were necessary to the REMS document related to the operationalizing of the REMS website. The Applicant's original proposal was to operationalize the REMS website (b) (4) *which was changed to the requirement that it is operational at the time the product first becomes commercially available. The Applicant clarified that Wholesalers-Distributors will either be accessing a secure file containing a list of all certified pharmacies and healthcare settings by File Transfer Protocol or will obtain verification by calling the REMS coordinating center; this proposal is acceptable. Additional edits were made to standardize the description, format, or terminology of the REMS document.*

In the REMS Amendment submitted on August 1, 2023, the Applicant proposed (b) (4) *The Agency disagreed with the change and on August 2, 2023, informed the Applicant that a robust level of audit information is required to ensure that all REMS processes and procedures are in place, functioning, support the REMS requirements, and are being implemented with fidelity. In their response on August 3, 2023, the Applicant revised the audit requirement to audit all pharmacies and healthcare settings, which is acceptable. The Applicant is to submit their full audit plan and noncompliance plan within 60 days post approval as a REMS Methodology for Agency review.*

7.1.5. Timetable for Submission of Assessment for the REMS

The Applicant must submit REMS assessments to the FDA annually from the date of the initial approval of the REMS.

Reviewer Comments:
We agree with the Applicant's proposal to submit REMS assessments annually from the date of initial approval. Evaluation of the REMS strategy to directly affect knowledge and awareness of the importance of patient monitoring will require submission of prescriber surveys. Submission of prescriber survey results with a post-approval 6-month assessment report would not be feasible due to the time needed for development of the survey protocol and instruments, as well as subsequent review of these by the Agency.

7.1.6. REMS Materials & Key Risk Messages

The Applicant included the following materials as part of the REMS submission:

- Prescriber Enrollment Form: mechanism for the prescriber to enroll and become certified in the REMS, and for the prescriber to agree to comply with all REMS requirements.
- Pharmacy and Healthcare Setting Enrollment Form: mechanism for the authorized representative of the pharmacy or healthcare setting to enroll and have the pharmacy or healthcare setting become certified in the REMS, and for the authorized representative to agree to their responsibilities required by the REMS.

- Prescriber Training Program: informs prescribers about the serious risks associated with elranatamab and the management of those risks, and the REMS requirements and responsibilities of the prescriber.
- Adverse Reaction Management Guide: provides an accessible summary for prescribers on how to manage the risks of CRS and neurologic toxicity including ICANS associated with elranatamab.
- Knowledge Assessment: successful completion is a prerequisite for prescriber certification and will help to ensure adequate understanding of the serious risks and key REMS requirements.
- Patient Wallet Card: informs patients about the signs and symptoms of the serious risks associated with elranatamab, when to seek immediate care, and instructs the patient to present the wallet card to any healthcare professional involved in their care and if they go to the emergency room.
- Training for Pharmacies and Healthcare Settings: informs pharmacy and healthcare setting authorized representatives and staff that dispense of the serious risks associated with elranatamab, the REMS requirements, and the responsibilities of the pharmacy/healthcare setting and authorized representative.
- Dear Healthcare Provider Letter: informs healthcare providers about the risks of CRS and neurologic toxicity associated with elranatamab and provides information about the REMS. The letter also invites healthcare providers to consider participating in future knowledge and behavior surveys to assist in determining if the REMS is meeting its goal.
- Dear Professional Society Letter: requests that healthcare providers who are members of these societies are informed by the societies of the risks of CRS and neurologic toxicity associated with elranatamab and provides information about the REMS.
- REMS Fact Sheet: provides an overview of the REMS, the serious risks and management of those risks, and key requirements of the REMS for prescribers, pharmacies and healthcare settings, and wholesaler-distributors.
- REMS Website: allows prescribers, pharmacies and healthcare settings to enroll in the REMS. Healthcare providers will be able to certify in the REMS by completing the prescriber training and submitting the Knowledge Assessment. Authorized representatives for pharmacies and healthcare settings will be able complete the pharmacy/healthcare setting training, receive certification, and manage staff privileges associated with the REMS. Pharmacies and healthcare settings will also be able to obtain authorization to dispense online. The REMS materials, Prescribing Information, and Medication Guide will be available on the website for review and download. The website will also include a REMS participant locator that identifies certified prescribers and certified pharmacies/ healthcare settings.

The Applicant identified the REMS Fact Sheet as providing the key risk messages for healthcare providers.

Reviewer Comments:
We agree with the proposed REMS materials. The Applicant's proposed key risk messages have been revised as described below.

Key Risk Messages for Prescribers

- *CRS, including life threatening and fatal reactions that can occur in patients receiving elranatamab. Initiate treatment with elranatamab step-up doing schedule to reduce risk of CRS. Closely monitor*

patients for signs or symptoms of CRS during treatment. Withhold elranatamab until CRS resolves or permanently discontinue based on severity.

- *Neurologic toxicity, including ICANS and serious life-threatening reactions can occur in patients receiving elranatamab. Monitor patients for signs or symptoms of neurologic toxicity including ICANS during treatment. Withhold elranatamab until neurologic toxicity resoles or permanently discontinue based on severity.*
- *Instruct the patient that they should be hospitalized for 48 hours after administration of the first step-up dose, and for 24 hours after administration of the second step up dose.*
- *Before treatment initiation, complete and provide the patient/caregiver with a Patient Wallet Card.*
- *Counsel the patient/caregiver on how to recognize and respond to signs and symptoms of CRS and neurologic toxicity, including ICANS, using the Patient Wallet Card, and having the card at all times.*

Key Risk Messages for Patients

- *There is a risk of CRS and neurologic problems with elranatamab.*
- *Carry the Patient Wallet Card with you at all times and show the card to any healthcare professional that treats you.*
- *If you are having any symptoms listed on the patient wallet card, call your doctor, or seek emergency medical attention right away.*

Key Risk Messages for Pharmacies and Healthcare Settings

- *All staff must be trained on dispensing using the Pharmacy and Healthcare Setting Training Program.*
- *Before dispensing elranatamab, staff must verify prescriber is certified in the elranatamab REMS.*

7.1.7. REMS Supporting Document

The REMS supporting document includes background information on the benefits and risks of elranatamab and the Applicant's rationale and goal for the REMS. The supporting document also contains information on the requirements of the REMS and the responsibilities of stakeholders as well as how the REMS will be implemented and assessed.

The Applicant described a Risk Management Framework based on RE-AIM principles (Reach, Effectiveness, Adoption, Implementation, Maintenance) in the supporting document. The framework proposes that successful maintenance of the REMS will be demonstrated by three consecutive years of successful prescriber knowledge surveys; inclusion of knowledge imparted by the REMS into clinical treatment practice guidelines; and inclusion of REMS key messages into representative institutional policies and/or insurance requirements. The Applicant opined that these findings could support elimination of the REMS.

Reviewer Comments:
The Agency sent an Information Request on June 29, 2023, that requested the Applicant submit the REMS website screenshots that demonstrate the process used by the pharmacy/healthcare setting for determining prescriber certification status, and the screenshots that demonstrate how a user sets up an account and logs

in as well as the screenshots that occur after login. Additionally, the Applicant was asked to explain the model for distribution of Elrexfio that will be used for each type of pharmacy or healthcare setting including physician offices that dispense Elrexfio. In their response, the Applicant provided the screenshots, which describe processes for prescriber and pharmacy/healthcare setting users to meet their responsibilities in the REMS. The Applicant also included a description of the distribution model, which involves wholesalers-distributors shipping the product directly to either a certified healthcare setting or to a certified specialty pharmacy that subsequently dispenses it to the healthcare setting, which is acceptable.

Key Performance Indicators (KPIs) are the primary metrics or measures that will be used to evaluate the REMS and are essential in determining if the REMS is functioning as designed and meeting its goal and objective. The Applicant proposed (b) (4) *The Agency issued an Information Request (IR) on July 19, 2023, requesting that the Applicant* (b) (4) *includes the KPIs, KPI thresholds and supporting rationale, and what actions will be taken if the KPI thresholds are not met. In the Applicant's response on July 25, 2023, their revised REMS supporting document included the Agency's request to incorporate the KPIs and associated language as a new section in the REMS supporting document.*

The Risk Management Framework submitted in the supporting document proposes criteria for defining successful outreach and communication, implementation and operations, safe use behaviors and knowledge, and health outcomes. However, the source data and methods of measurement for some of these criteria are unclear to this reviewer at this time, including calculation of the rate of CRS/ICANS outcomes; determining that a sufficient number of certified prescribers and pharmacy/healthcare settings are available for patient access; and future uptake of and adherence to REMS messaging into clinical practice guidelines and institutional settings.

7.1.8. REMS Assessment Plan

The assessment plan includes metrics to assess communication plan activities, program implementation and operations, utilization data, compliance data, REMS coordinating center data, knowledge assessments of prescribers, and an analysis of adverse event outcomes for the REMS-related risks.

Reviewer's Comments: *DRM and the Division of Mitigation and Medication Error Surveillance agree that the assessment plan submitted on August 8, 2023, is acceptable and captures all necessary metrics. We will use a composite of the KPIs as well as the safety-related outcomes to determine if the REMS is meeting its goal and objectives.*

7.1.9. Summary of OPDP Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on July 10, 2023, and completed a consult review on July 27, 2023.[17] DRM accepted most of OPDP's recommendations and made corresponding changes to the REMS materials, which were communicated to the Applicant in the Information Request sent on July 28, 2023. The changes include the following:

- Addition of information to the REMS Fact Sheet related to prescriber counseling.
- Clarification of one of the answer options for a question in the Knowledge Assessment.

- Addition of information to the Adverse Reaction Management Guide related to the associated signs and symptoms and management of CRS.
- Changes to slides in the Prescriber Training Program to align with the Boxed Warning and to provide additional information related to neurologic toxicity events.

OPDP had additional recommendations about the Adverse Reaction Management Guide and the Patient Wallet Card that DRM did not agree with. The comments were communicated to OPDP on July 28, 2023, as follows:

- OPDP recommended that the Adverse Reaction Management Guide include additional risk statements about withholding or permanently discontinuing Elrexfio based on the severity of neurologic toxicity, as well as information related to prescribers counseling patients about the risk of experiencing a depressed level of consciousness. DRM notes that the tables already present in the guide specifically include information about when to withhold or discontinue Elrexio based on neurological toxicity severity, and that the language preceding the tables aligns with the Prescribing Information. The inclusion of prescriber counseling recommendations for patients does not apply to the guide, which focuses on active management of the REMS-related risks.
- OPDP recommended that the Patient Wallet Card should include advice that patients should not drive or operate heavy or dangerous machinery during and for 48 hours after the step-up dosing schedule is completed, or with the development of any new neurologic symptoms until the symptoms go away. DRM notes that the purpose of the wallet card is for patients to inform healthcare providers, particularly medical staff at emergency facilities, that they are taking Elrexfio, and to remind patients of the symptoms of CRS and neurologic toxicity and to seek immediate medical assistance if they experience any symptoms. The wallet card is a physically small communication tool and content is limited to the most important information related to its purpose. In addition, there is no free space on the wallet card to include the information that OPDP is recommending.

8. Discussion of Need for a REMS

In the draft integrated review, the review team recommends accelerated approval of elranatamab based on the efficacy and safety information currently available, with a REMS to ensure the benefits of the product outweigh the risks.[13]

Multiple myeloma is an incurable disease. There is an unmet medical need for additional and improved treatment options. Patients with refractory disease do not respond to treatment and almost all patients relapse at some point in their disease course. Most patients experience multiple relapses, requiring multiple lines of treatment with different drug combinations. Patients with disease refractory to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody have a median overall survival of less than 12 months.[13]

The draft Prescribing Information describes the efficacy of elranatamab observed in a subgroup of 97 patients in the pivotal cohort of the open label study, which includes patients naïve to prior BCMA-directed therapy who received at least four prior lines of therapy. The ORR was 57.7% (95% CI: 47.3, 67.7) and the mDOR was not reached in the subgroup, with a median follow-up of 11.1 months among responders. When

compared to other treatments approved for patients who have received four prior lines of therapy, the ORR and mDOR observed with elranatamab is greater than that for selinexor in combination with dexamethasone (ORR 25.4%, mDOR 3.8 months) and similar to the efficacy of teclistamab (ORR 61.8%; mDOR not reached). The BCMA-directed CAR-T therapies have high response rates for this patient population. Idecabtagene vicleucel has an ORR of 72% with an mDOR of 11.0 months and ciltacabtagene autoleucel has an ORR of 97.9% with a median duration of response of 21.8 months. However, the CAR-T products have several limitations, such as the need for leukapheresis, administration of a lymphodepleting regimen, the time needed for manufacturing of the product, and a limited number of treatment centers and available patient slots.[13] Teclistamab and the CAR-T products mentioned above require REMS with ETASU to mitigate the risks of CRS and neurologic toxicities.

The most serious risks associated with elranatamab are CRS and neurologic toxicity including ICANS. In the clinical study, patients received step-up doses of elranatamab, initiation of treatment in the inpatient setting, and premedication for CRS for the step-up doses and first full treatment dose. The overall incidence of CRS for the 183 patients who received the recommended dosing regimen in the clinical study was 58%, with Grade 1 CRS occurring in 44% of patients, Grade 2 in 14% and Grade 3 in 0.5% of patients. Recurrent CRS occurred in 13% of patients. Anti-IL-6 therapy for the treatment of CRS was administered to 36% of patients, including 22% of patients with Grade 1 CRS events and 66% of patients with Grade 2 CRS events. The incidence of neurologic adverse events was 59% and the incidence of ICANS was 3.3%. The severity of neurologic events was relatively low, with only 1.1% of patients experiencing a Grade 3 event. Grade 4 seizure and Guillain-Barre syndrome events occurred in one patient each. The severity of ICANS was low as all ICANS events were either Grade 1 or Grade 2.

Elranatamab is associated with a relatively high incidence of CRS and neurologic toxicity. We expect that the ease of its administration will lead to increased use in community oncology practice settings where healthcare providers may be less familiar with the risks and patients may experience serious adverse events without access to prompt supportive care. In contrast to the CAR T-cell products, which are a one-time treatment and have a complex manufacturing process, elranatamab is a recurrent, subcutaneous, once weekly to biweekly administration. Although the risks were greatest in the first cycle of treatment with elranatamab, the risks of CRS and neurotoxicity also occurred in subsequent treatment cycles but with less frequency. Therefore, patients treated with elranatamab may be at risk for CRS and neurologic toxicities in both initial and later cycles.

In determining the need for a REMS for elranatamab, DRM and DHM2 considered a high-level comparison with teclistamab, which has a similar mechanism of action as elranatamab and was approved in October 2022 for the same indication. See Table 1 and Table 2 in the Appendix for comparisons of product characteristics and the risks and mitigation of CRS and neurotoxicity/ICANS for the two products. Based on response rate and the duration of response, the efficacy of the products appears to be very similar. Elranatamab and teclistamab share similar labeling recommendations for hospitalization during step-up dosing. The incidence and severity of CRS and neurotoxicity/ICANS, including the medians and range for the time to onset, are similar. The usage of anti-IL-6 therapy for the management of CRS in the clinical studies for the two products is also similar. Teclistamab required a REMS with ETASU for approval that consists of prescriber certification and pharmacy/healthcare setting certification to ensure the benefits outweigh the risks of CRS and neurologic toxicity including ICANS. At this time, DRM and DHM2 conclude there is

insufficient evidence that shows the prescribing population has acceptable knowledge and understanding of the risks and management of CRS and neurotoxicity/ICANS associated with bispecific antibodies for the treatment of RRMM in the expected treatment settings. Therefore, we believe it is necessary to continue to ensure all prescribers are aware of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS as well as the need for counseling patients to seek prompt supportive care for CRS and neurotoxicity/ICANS that might occur outside of a treatment setting. A REMS with ETASU for elranatamab that is similar to that for teclistamab is necessary to ensure that the benefits outweigh the risks.

The REMS Oversight Committee (ROC) reviewed a summary of the product background and risk findings for elranatamab in the context of other bispecific antibodies that are administered subcutaneously and approved for hematologic malignancies. The ROC agreed by email with the review team's recommendation that a REMS that includes prescriber certification and pharmacy/healthcare setting certification is necessary to ensure the benefits of elranatamab for the proposed indication outweigh the risks of CRS and neurologic toxicity.[18]

The minimum necessary REMS elements required include the following:

- Communication plan to target healthcare providers who are likely to prescribe and care for patients treated with elranatamab
- Prescriber certification to ensure prescribers are aware of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to elranatamab
- Pharmacy/Healthcare setting certification to ensure prescribers are certified prior to dispensing elranatamab

DRM concludes that based on the review of the proposed REMS received on August 8, 2023, the REMS will support actions that will mitigate the risks of CRS and neurologic toxicity, including ICANS. The REMS will ensure that all prescribers are trained on these risks and aware of the importance of monitoring patients to support safe use of the product.

An assessment of whether the strategy to directly affect knowledge was successful in achieving its intended objectives of ensuring prescribers are aware of the importance of monitoring patients will be done annually with submission of the REMS assessment report including results of prescriber knowledge, attitude, and behavior surveys. In addition, REMS assessment metric data are utilized to determine if the REMS is successfully being implemented and operating as intended.

Key Performance Indicators (KPIs) are measures that are essential in determining that the REMS is functioning as designed and whether the Elrexfio REMS is achieving its goal of mitigating the risks of CRS and neurologic toxicity including ICANS. KPIs have been established for the objective to help determine the success of the program and may also help determine if modifications to the REMS are necessary.

The KPIs that will be used to evaluate the REMS include a process indicator to evaluate REMS operations by determining the proportion of dispensed prescriptions that were authorized, and an outcome indicator to evaluate the objective to ensure prescribers are aware of the importance of monitoring patients for the serious risks via knowledge surveys. The KPIs and KPI thresholds have been determined based on experience

with other REMS with similar program design. For the process indicator, a target threshold of 99.9% has be set a priori for the proportion of dispensed prescriptions that were authorized by the REMS prior to dispense. REMS authorization for dispense requires both the prescriber and the pharmacy or healthcare setting to be certified. For this REMS, the key outcome indicator will measure the proportion of prescriber survey respondents that demonstrated knowledge on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS compared to all prescriber survey respondents. A target threshold of ≥80% of prescriber survey respondents demonstrating knowledge has been set a priori.

Health outcome data will include an analysis of all reported cases of CRS and neurologic toxicity including ICANs stratified by grade and severity. This analysis of reported adverse events can provide insight as to whether the risk was mitigated, if step-up dosing was initiated in the hospital setting and if pre-medication was administered. This data may also inform on whether patients who experienced an adverse event of interest were monitored as recommended in the Prescribing Information.

In addition, the REMS assessment plan was designed to include data collected by the REMS Coordinating Center that will identify and evaluate if the REMS had any unintended burden on the healthcare system and if there were any patient access issues associated with the REMS.

We anticipate that following education through the REMS program, prescribers and other healthcare providers will be more aware of the risks of CRS and neurologic toxicity including ICANS and will follow the monitoring recommendations in labeling. Based on the review of the proposed REMS received on August 8, 2023, the REMS will support actions to mitigate the risks of CRS and neurologic toxicity including ICANS associated with elranatamab. The REMS ensures all prescribers are educated to support awareness of the risks and supports safe use of these products.

9. Conclusion & Recommendations

The risk of CRS and neurologic toxicity, including ICANS are serious and potentially life threatening. Therefore, it is necessary for prescribers, pharmacies, health care providers, and patients to be aware of and understand these risks. Based on the incidence of CRS and neurologic toxicity and the potential for broader outpatient use of this product, DRM and DHM2 agree that a REMS consisting of a communication plan, prescriber certification, and pharmacy/healthcare setting certification is necessary to ensure that the benefits outweigh the risks of CRS and neurotoxicity including ICANS. The REMS will also include an implementation system and timetable for submission of assessments.

DRM finds the Applicant's amended proposed REMS received on August 8, 2023, to be acceptable. The REMS is appended to this review.

10. Appendices

10.1. REFERENCES

1. Laubach JP. Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis. In: Rajkumar SV, Connor RF, eds. *UpToDate*. UpToDate; 2023.
2. Siegel R, Miller K, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73:17-48.
3. Bhatt P, Kloock C, Comenzo R. Relapsed/Refractory Multiple Myeloma: A Review of Available Therapies and Clinical Scenarios Encountered in Myeloma Relapse. *Curr Oncol*. Feb 15 2023;30(2):2322-2347. doi:10.3390/curroncol30020179
4. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. Sep 2019;33(9):2266-2275. doi:10.1038/s41375-019-0435-7
5. Laubach JP. Multiple myeloma: Treatment of third or later relapse. In: Rajkumar SV, Connor RF, eds. *UpToDate*. UpToDate; 2023.
6. Karyopharm Therapeutics. Xpovio (selinexor). NDA 212306. Prescribing Information. July 2022.
7. Celgene Corp. Abecma (Idecabtagene vicleucel). BLA 125736. Prescribing Information. March 2021.
8. Janssen Biotech. Carvykti (ciltacabtagene autoleucel). BLA 125746. Prescribing Information. March 2022.
9. Janssen Biotech. Tecvayli (teclistamab). BLA 761291. Prescribing Information. October 2022.
10. Talvey (talquetamab). BLA 761342. Draft Prescribing Information. July 28, 2023.
11. Pfizer, Inc. Elrexfio (elranatamab). BLA 761345. Module 2.5 - Clinical Overview. December 19, 2022.
12. Elrexfio (elranatamab). BLA 761345. Draft Prescribing Information. July 24, 2023.
13. Food and Drug Administration. Elrexfio (elranatamab). BLA 761345. Integrated Review, draft. July 27, 2023.
14. Food and Drug Administration. Division of Hematology 2. Elrexfio (elranatamab) BLA 761345. Clinical REMS Discussion Slides. April 19, 2023.
15. Pfizer. Elrexfio (elranatamab). BLA 761345. Module 5.3.5.2 - An open-label, multicenter, non-randomized phase 2 study of elranatamab (PF-06863135) monotherapy in participants with multiple myeloma who are refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody. Study C1071003. July 29, 2022.
16. Hayashi P. Food and Drug Administration. Division of Hepatology and Nutrition. Elrexfio (elranatamab). BLA 761345. Drug-induced Liver Injury Consult Review. July 27, 2023.
17. Khashei M. Food and Drug Administration. Office of Prescription Drug Promotion. Elrexfio (elranatamab). BLA 761345. REMS Consult Review. July 27, 2023.
18. Food and Drug Administration. Elrexfio (elranatamab) BLA 761345. REMS Oversight Committee Meeting Minutes (email). July 4, 2023.
19. Food and Drug Administration. Tecvayli (teclistamab). BLA 761291. Integrated Review. October 24, 2022.

10.2. Elranatamab and Teclistamab Comparison Tables

Table 1. Comparison of product characteristics and efficacy

	Elranatamab	Teclistamab
BLA	761345	761291
Approval Date	Pending	10/25/2022
Indication	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody
Mechanism of Action	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager	Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Route of Administration	Subcutaneous	Subcutaneous
Premedication	Corticosteroid, H1-receptor antagonist, and antipyretic for step-up doses and the first full treatment dose	Corticosteroid, H_1-receptor antagonist, and antipyretic for step-up doses and the first full treatment dose
Dosing	• Step-up doses on Day 1 and 4 • Full treatment dose on Day 8 • Weekly dosing thereafter. May be switched to every 2 weeks depending on treatment response • Patients should be hospitalized for 48 hours after the first step-up dose, and for 24 hours after administration of the second step-up dose	• Step-up doses on Day 1 and 4 • Full treatment dose on Day (b) (4) • Weekly dosing thereafter • Patients should be hospitalized for 48 hours after administration of all doses within step-up dosing schedule including the first full treatment dose
Duration of Treatment	Continue treatment until disease progression or unacceptable toxicity	Continue treatment until disease progression or unacceptable toxicity
Efficacy	• Objective Response Rate (b) (4) • Complete Response Rate (b) (4) • Median Duration of Response (mos) NR (95% CI: 12.0, NE)	• Overall Response Rate 61.8% (95% CI: 52.1, 70.9) • Complete Response Rate 28.2% (95% CI: 20.0, 37.6) • Median Duration of Response (mos) NE (95% CI: 9.0, NE)

mos=months; NR=not reached; NE=not estimable

Source: Elranatamab Draft Prescribing Information[12]; Teclistamab Prescribing Information[9]

Table 2. Comparison of risks and mitigation of CRS and Neurotoxicity/ICANS

	Elranatamab	Teclistamab
CRS Incidence	**58%**	**72%**
Grade 1	43%	50%
Grade 2	14%	21%
Grade 3	0.5%	0.6%
Grade 4	0%	0%
Grade 5	0%	0%
CRS after step-up dose 1	43%	42%
CRS after step-up dose 2	19%	35%
CRS after first full dose	7.1%	24%
CRS after subsequent dose	1.6%	< 3%
Median time to onset CRS	2 days (range:1 to 9 days)	2 days (range:1 to 6 days)
Median duration CRS	2 days (range:1 to 19 days)	2 days (range:1 to 9 days)
Recurrent CRS	13%	33%
Anti-IL-6 therapy for CRS	36% Patients with Grade 1 events: 22% Patients with Grade 2 events: 66% Patients with Grade 3 events: 100%	36% Patients with Grade 1 events: 21% Patients with Grade 2 events: 88% Patients with Grade 3 events: 100%
Neurotoxicity Incidence	**59%** [Grade 3/4: 7%]	**57%** [Grade 3/4: 2.4%]
ICANS Incidence	**3.3%**	**6%**
Grade 1	0.5%	3.6%
Grade 2	1.6%	2.4%
Grade 3	1.1%	0%
Grade 4	0%	0%
Grade 5	0%	0%
Median time to onset ICANS	3 days (range:1 to 4 days)	4 days (range:2 to 8 days)
Median duration ICANS	2 days (range:1 to 18 days)	3 days (range:1 to 20 days)
Risk Mitigation	REMS with ETASU • Prescriber certification • Pharmacy/Healthcare setting certification	REMS with ETASU • Prescriber certification • Pharmacy/Healthcare setting certification

Source: Elranatamab Draft Prescr bing Information[12]; Teclistamab Prescribing Information[9]; Teclistamab Integrated Review[19]

10.3. REMS ASSESSMENT PLAN

The REMS assessment plan must include, but is not limited to, the following**:**

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Program Outreach and Communication

1. REMS communication plan activities (provide data for the 1-year and 2-year assessments only):
    a. Sources of the distribution lists for healthcare providers
    b. Number of healthcare providers targeted stratified by specialty if known
    c. Number of healthcare professional societies targeted, and which healthcare professional societies reported distribution of the REMS letter to their respective members
    d. The number of packets of REMS materials sent by date, attempt, and method of distribution
    e. The number and percentage of emails successfully delivered, opened, and unopened
    f. The number and percentage of mail successfully delivered and returned as undeliverable
    g. The number of REMS Fact Sheets distributed to targeted healthcare providers during the 12 months after ELREXFIO is commercially distributed
    h. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed

Program Implementation and Operations

2. Program Implementation (*provide data at 1 year assessment only):
    a. *Date of first commercial availability of ELREXFIO
    b. Date the REMS Website went live
        i. Number of total visits and unique visits to the REMS Website
        ii. Number and type of ELREXFIO REMS materials downloaded or accessed
    c. *Date the REMS Coordinating Center was fully operational
    d. Date prescribers and pharmacies/healthcare settings were able to complete the REMS certification process (online and by fax)
    e. *Date of the first prescriber certification
    f. *Date of the first pharmacy/healthcare setting certification
3. REMS Certification and Enrollment Statistics
    a. Healthcare Providers
        i. Number of newly certified healthcare providers and the number and percentage of active (i.e., who have prescribed ELREXFIO at least once during the reporting period) healthcare providers stratified by:

1. Credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, other)
2. Specialty (e.g., Oncology, Hematology, Internal Medicine/Family Medicine, Other). If "other" accounts for > 10% of respondents for specialties, provide the most common specialties identified.
3. Geographic region as defined by the US Census
4. Method of enrollment (e.g., online, fax, e-mail) for newly certified healthcare providers only

ii. Number of incomplete prescriber enrollments, and summary of reported reason(s) for not completing

b. Pharmacies and Healthcare Settings

i. Number of newly certified pharmacies/healthcare settings and the number and percentage of active (i.e., who have dispensed or ordered the drug at least once during the reporting period) pharmacies/healthcare settings stratified by:

1. Type of pharmacy/healthcare setting (e.g., Inpatient Hospital Pharmacy, Outpatient Hospital Pharmacy, Oncology Infusion Center, Community Oncology Physician Office, Other). If "other" accounts for > 10% of respondents for type, provide the most common type(s) identified.
2. Geographic region as defined by the U.S. Census
3. Method of enrollment (e.g., online, fax, e-mail) for newly certified pharmacies/healthcare settings only

ii. Number of incomplete pharmacy/healthcare setting enrollments, and summary of reported reason(s) for not completing

c. Wholesalers/distributors

i. Number of wholesalers/distributors contracted to ship and number of active (i.e., have shipped) wholesalers/distributors

4. Utilization Data

a. Number of vials sent to certified pharmacies/healthcare settings, stratified by type of pharmacy/healthcare setting

b. Number and percentage of healthcare providers who wrote/ordered prescriptions that were dispensed, stratified by medical specialty (e.g., oncology) and provider credentials (e.g., Doctor of Medicine)

c. Number of dispense authorizations stratified by pharmacy/healthcare setting type

d. Number of RDAs rejected, stratified by:

i. Reasons and number of denials (numerator) divided by all denials (denominator)

1. Healthcare provider not certified
2. Pharmacy or Healthcare Setting not certified
3. Other reasons for denial not categorized above

e. The percentage of dispensed prescriptions that were authorized by the REMS prior to dispense. REMS authorization for dispense requires both the prescriber and the pharmacy/healthcare setting be certified.

5. REMS Compliance

   a. Audits

      i. A copy of the audit plan

      ii. Report of audit findings for each stakeholder

      iii. Number of audits expected, and the number of audits performed

      iv. Documentation of completion of training for relevant staff

      v. Documentation of processes and procedures in place for complying with the ELREXFIO REMS

      vi. Verification for each audited stakeholder's site that the designated Authorized Representative remains the same. If different, include the number of new Authorized Representatives

      vii. Number and type of deficiencies (e.g., critical, major, or minor findings) noted for each group of audited stakeholders as a percentage of audited stakeholders

      viii. Confirmation of documentation of completion of training for relevant staff after audit findings indicated training was necessary

      ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

   b. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder (healthcare providers, pharmacies/healthcare settings and wholesalers-distributors), actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified from the REMS

      i. For those with deficiencies noted, report the number that successfully completed a Corrective and Preventive Actions (CAPA) plan within the timeframes specified in the Noncompliance Plan

      ii. For any that did not complete the CAPA within the timeframe specified in the Noncompliance Plan, describe actions taken

      iii. Number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

         1. Unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time

         2. Source of the noncompliance data

         3. Results of root cause analysis

         4. Action(s) that were taken in response

      iv. Pharmacies/healthcare settings

1. Number of pharmacies/healthcare settings for which non-compliance with the ELREXFIO REMS is detected (numerator) divided by all pharmacies/healthcare settings dispensing ELREXFIO (denominator)
2. Number and description of pharmacies/healthcare settings that dispensed ELREXFIO to non-certified prescribers, and any corrective and preventative actions taken to prevent future occurrences
3. Number of non-certified pharmacies/healthcare settings that dispensed ELREXFIO (numerator) divided by all pharmacies/healthcare settings that dispensed ELREXFIO
4. Number of prescriptions dispensed by non-certified pharmacies/healthcare settings (numerator) divided by all ELREXFIO prescriptions dispensed (denominator) and the actions taken to prevent future occurrences
5. Summary of audit findings and any action taken and outcome of actions to prevent future occurrences
6. Summary of findings for monitoring conducted during the reporting period, including any CAPA

v. Wholesalers/Distributors

1. Number and description of non-certified pharmacies/healthcare settings that were shipped ELREXFIO, and the number of these that subsequently became certified
2. The number of authorized wholesalers-distributors for which non-compliance with the REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)
3. The number and type of wholesalers-distributors not contracted with Pfizer Inc. that shipped ELREXFIO, the number of incidents for each, actions taken to remove Elrexfio from these entities, and actions taken to prevent future occurrences and outcome of such actions
4. The number of contracted wholesalers-distributors suspended and/or unauthorized to distribute for non-compliance with REMS requirements and reasons for such actions, and actions taken to prevent distribution or removal of Elrexfio from these entities

c. Any other ELREXFIO REMS noncompliance, source of report and resulting CAPA

6. REMS Coordinating Center Report

a. Number of contacts by stakeholder type (patient/caregiver, certified prescriber, pharmacy/healthcare setting authorized representative or staff, other HCP, wholesaler/distributor, other)

b. Summary of the reasons for the call(s) by stakeholder type. Limit the summary to the top five reasons for calls by stakeholder group

c. Description of each call, including stakeholder credentials, that may indicate an issue with product access due to the REMS, REMS burden or adverse event

d. If the summary reason for the call(s) indicates an adverse event related to CRS or neurologic toxicity including ICANS include details and the outcome of the call(s)

e. Provide an assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, health care availability, other

f. Summary of frequently asked questions (FAQ) by stakeholder credentials type. Limit the summary to the top five FAQs for calls by stakeholder group

g. Summary of any noncompliance that is identified through coordinating center contacts, source of report and resulting CAPA

h. Summary of CAPAs resulting from issues identified

i. Percentage of calls to the REMS Coordinating Center that were answered within 20 minutes

j. The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered

k. Percentage of calls to the REMS Coordinating Center where the caller abandoned the call before the call was answered

l. The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned

Knowledge

7. Knowledge Assessment

    a. Number of completed healthcare provider Knowledge Assessments, including the method of completion

    b. Summary statistics, including mean number of attempts, score, and range of scores and number of attempts to successfully complete the Knowledge Assessment

    c. Summary of most frequently missed questions on the Knowledge Assessment

    d. A summary of potential comprehension or perception issues identified with the Knowledge Assessment

8. Periodic Knowledge, Attitude, and Behavior (KAB) Survey of Certified Prescribers (beginning with the 1-Year REMS Assessment Report and thereafter with each assessment report)

    A KAB Survey will be conducted with random samples, if the population is large enough to randomize, of healthcare providers who prescribe ELREXFIO

    a. Evaluation of understanding of the risks of CRS and neurologic toxicity including ICANS associated with Elrexfio and mitigation strategies of the ELREXFIO REMS as well as compliance with the mitigation strategies

    b. An evaluation of the prescriber's knowledge on the importance of monitoring for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to ELREXFIO

    c. Provide the proportion of KAB prescriber survey respondents that demonstrated knowledge of the importance of monitoring for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to ELREXFIO

Health Outcomes and/or Surrogates of Health Outcomes (Safe Use Behaviors)

9. A summary analysis of all reported cases of CRS and neurologic toxicity, including ICANS, stratified by source of report (i.e., spontaneous).
    a. Include the following stratifications by grade/severity in the analysis (if available)
        i. Step-up dosing was initiated in the hospital setting. (For those reports that indicate initiation outside of the hospital setting provide the setting if known)
        ii. Pre-medication was administered

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

10.4. REMS

APPEARS THIS WAY ON ORIGINAL

66 Pages of REMS have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

*****This document may contain information that cannot be released to the public*****

Application Type	BLA
Application Number	761345
Submission Type/Number	Original-1/57
Submission Date	July 13, 2022
Reviewer	Tim Lape, PharmD (DMAMES)
Team Lead	Barbara Berquist, PharmD (DMAMES)
Review Completion Date	July 18, 2023
Subject	Interim Comments for the Elrexfio (elranatamab) Risk Mitigation Strategies (REMS) Assessment Plan for the Proposed New REMS
Established/Proper Name	elranatamab
Trade Name	Elrexfio
Applicant	Pfizer Inc.
Therapeutic Class	Bispecific CD3/CD20-directed T-cell engager
Formulation	Solution for injection
Nexus REMS TTT#	2023-4546

1 Introduction

This review provides our findings and recommendations for the proposed Elrexfio (elranatamab) Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan included in the REMS Supporting Document that was submitted on December 19, 2022[a] and amended July 13, 2023[b].

We initiated this review in response to a consult request from the Division of Risk Management (DRM) to review the proposed assessment plan included in the REMS Supporting Document for the new Elrexfio (elranatamab) REMS. The Applicant did not include an audit plan or noncompliance plan in their submission. The Supporting Document was submitted by the Applicant on December 19, 2022.

2 Background

This section provides relevant regulatory history and the Elrexfio REMS proposed goal, elements, and timetable for submission of assessments.

2.1. Relevant Regulatory History

- December 19, 2022: Applicant submitted a proposed REMS for elranatamab, a bispecific B-cell maturation antigen (BCMA), with an indication for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
- July 13, 2023: Applicant submitted an amended version of its proposed REMS for elranatamab following an Agency's June 29, 2023 Information Request.[c] Changes made by the Applicant to the Assessment Plan were for the addition of the (b) (4) (b) (4) the deletion of the (b) (4) and the addition of the (b) (4)

2.2. REMS Goal and Objective

The proposed goal of the Elrexfio REMS is to mitigate the risk of Cytokine Release Syndrome (CRS) and neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) by:

- Ensuring prescribers are aware of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS in patients exposed to ELREXFIO

2.3 Proposed REMS Elements

1. Communication Plan

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[a] The proposed REMS assessment plan was included in the Supporting Document submitted on December 19, 2023 is available at: \\CDSESUB1\EVSPROD\bla761345\0002\m1\us\riskmgt-draft-rems-supporting-document.docx
[b] The amended REMS assessment plan was included in the Supporting Document submitted on July 13, 2023 is available at: \\CDSESUB1\EVSPROD\bla761345\0058\m1\us\riskmgt-draft-rems-supporting-document-track.docx
[c] The Agency's June 29, 2023 Information Request to the Applicant is available at: https://darrts fda.gov/darrts/ViewDocument?documentId=090140af806d9bfa

2. Elements to Assure Safe Use
    - Health care providers who prescribe drug are specially certified
    - Pharmacies and health care settings that dispense drug are specially certified
3. Implementation System
4. Timetable for Submission of Assessments
    - The Applicant must submit REMS Assessments to the FDA annually from the date of the initial approval of the REMS

3 Review of the REMS Assessment Plan

We reviewed the amended proposed Elrexfio REMS Assessment Plan for BLA 761345 that the Applicant included in the REMS Supporting Document submission on July 13, 2023.[b]

The proposed REMS Assessment Plan includes metrics under the following categories: Program Outreach and Communication, Program Implementation and Operations, Knowledge, and Health Outcomes and/or Surrogates of Health Outcomes. Appendix A provides a copy of the Applicants' proposed Elrexfio REMS Assessment Plan with our suggested edits.

Reviewer Comments:

- *The Applicant's proposed Elrexfio Assessment Plan was comparable to the assessment plan for Tecvayli (teclistamab; BLA 761291), another REMS whose goal is to mitigate the risk of CRS and neurologic toxicity including ICANS.*
- *We provide our comments to the Applicant regarding the proposed Elrexfio REMS Assessment Plan in section 5 below. The comments include requested editorial changes, revisions to existing metrics, and additional metrics.*

4 Conclusions and Recommendations

The Applicant's proposed Elrexfio REMS Assessment Plan, included in the REMS Supporting Document, needs revision to inform on the REMS goal and objective and to ensure that the REMS is functioning as intended. Of note, the table of contents referred to an audit and noncompliance plan in the appendix of the REMS Supporting Document, however, these plans were not included in the submission. The Applicant will be required to submit their full audit and noncompliance plans 60 days after receiving the approval letter. We recommend sending the comments in Section 5 and the revised assessment plan to the Applicant.

5 Comments To The Applicant

We have the following comments on the proposed Elrexfio REMS Supporting Document, including your REMS Assessment Plan, submitted on July 13, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final.

<u>REMS Supporting Document Comments</u>

- Key Performance Indicators (KPI) (b) (4). Add a new section, titled "Key Performance Indicators" before Section 3.6 (REMS Assessment Plan) in the REMS Supporting Document. The section should include the updated KPIs,

KPI thresholds, along with your supporting rationale, and plans to evaluate the REMS if the KPI is not met.

- Refer to your July 13, 2023 submission [redacted (b) (4)]

[redacted (b) (4)]

REMS Assessment Plan Comments

REMS Assessment Plan revisions are needed to inform on the goal and objectives of the proposed REMS. We have the following comments for your Elrexfio REMS Assessment Plan:

- Revise the metrics for the following assessment plan categories: REMS Implementation and Operations, Knowledge, and Health Outcomes and/or Surrogates of Health Outcomes to provide the two previous, current, and cumulative reporting periods, where applicable, unless otherwise noted.
- Make minor changes (e.g., removal of language [redacted (b) (4)] throughout the Assessment Plan to improve clarity.
- **Metric 1: REMS Communication activities**: No changes.
- **Metric 2: REMS Program and Implementation**: No changes.
- **Metric 3: REMS Certification and Enrollment Statistics:** Remove language [redacted (b) (4)]. Add percentage metric for active and Healthcare Providers, pharmacies, and healthcare settings.
- **Metric 4: Utilization Data**: Remove language for [redacted (b) (4)] Add metrics to included data for the numbers of pharmacies and healthcare settings not certified and the percentage of dispensed prescriptions that were authorized by the REMS prior to dispense to inform if this REMS authorization process is working as intended.
- **Metric 5: REMS Compliance**: Remove language [redacted (b) (4)] Add classification examples for the types of audit deficiencies to clarify the level of noncompliance. Add a summary of the actions taken to prevent the distribution or removal of Elrexfio by noncontracted, suspended, or unauthorized wholesalers/distributors to ensure only authorized Wholesaler/Distributors distribute Elrexfio.

- **Metric 6: REMS Coordinating Center Report:** Remove language f [redacted]
- **Metric 7: Knowledge:** Remove language [redacted]
- **Metric 8: Periodic KAB Survey of Certified Prescribers**: Add language for the specific risks associated with Elrexfio use. Add the proportion of KAB prescriber survey respondents that demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS.
- [redacted]
- **Metric 10: Health Outcomes and/or Surrogated of Health Outcomes:** Revise numbering of Metric 10 to be Metric 9. Remove language [redacted] Add metric for stratification by step-up initial dosing setting to inform on the settings associated with reported cases of CRS and neurologic toxicity, including ICANS.
- **[Add New Metric] Metric10: Overall Assessment of REMS Effectiveness:** Add the heading "Overall Assessment of REMS Effectiveness" and the requirement for assessments under section 505-1(g)(3) to include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

Resubmission Instructions

Submit a REMS amendment within three business days that addresses these comments. Include in your response an updated REMS Supporting Document, including the REMS Assessment Plan, in Word tracked changes, Word clean, and a clean PDF version.

The revised REMS assessment plan for Elrexfio must include, but is not limited to, the following (additions are noted by underline and deletions are noted by ~~strikethrough~~):

REMS Assessment Plan

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Program Outreach and Communication

1. REMS communication plan activities (provide data for the 1-year and 2-year assessments only):

a. Sources of the distribution lists for healthcare providers

b. Number of healthcare providers targeted stratified by specialty if known

c. Number of healthcare professional societies targeted, and which healthcare professional societies reported distribution of the REMS letter to their respective members

d. The number of packets of REMS materials sent by date, attempt, and method of distribution

e. The number and percentage of emails successfully delivered, opened, and unopened

f. The number and percentage of mail successfully delivered and returned as undeliverable

g. The number of REMS Fact Sheets distributed to targeted healthcare providers during the 12 months after ELREXFIO is commercially distributed

h. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed

Program Implementation and Operations

2. Program Implementation (*provide data at 1 year assessment only):

   a. *Date of first commercial availability of ELREXFIO

   b. Date the REMS Website went live

      i. Number of total visits and unique visits to the REMS Website

      ii. Number and type of ELREXFIO REMS materials downloaded or accessed

   c. *Date the REMS Coordinating Center was fully operational

   d. Date prescribers and pharmacies/healthcare settings were able to complete the REMS certification process (online and by fax)

   e. *Date of the first prescriber certification

   f. *Date of the first pharmacy/healthcare setting certification

3. REMS Certification and Enrollment Statistics [redacted] (b) (4)

   a. Healthcare Providers

      i. Number of newly certified healthcare providers and the number and percentage of active (i.e., who have prescribed ELREXFIO at least once during the reporting period) healthcare providers stratified by:

         1. Credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, other)

2. Specialty (e.g., Oncology, Hematology, Internal Medicine/Family Medicine, Other). If "other" accounts for > 10% of respondents for specialties, provide the most common specialties identified.
3. Geographic region as defined by the US Census
4. Method of enrollment (e.g., online, fax, e-mail) for newly certified healthcare providers only

ii. Number of incomplete prescriber enrollments, and summary of reported reason(s) for not completing

b. Pharmacies and Healthcare Settings

i. Number of newly certified pharmacies/healthcare settings and the number and percentage of active (i.e., who have dispensed or ordered the drug at least once during the reporting period) pharmacies/healthcare settings stratified by:

1. Type of pharmacy/healthcare setting (e.g., Inpatient Hospital Pharmacy, Outpatient Hospital Pharmacy, Oncology Infusion Center, Community Oncology Physician Office, Other). If "other" accounts for > 10% of respondents for type, provide the most common type(s) identified.
2. Geographic region as defined by the U.S. Census
3. Method of enrollment (e.g., online, fax, e-mail) for newly certified pharmacies/healthcare settings only

ii. Number of incomplete pharmacy/healthcare setting enrollments, and summary of reported reason(s) for not completing

c. Wholesalers/distributors

i. Number of wholesalers/distributors contracted to ship and number of active (i.e., have shipped) wholesalers/distributors

4. Utilization Data (b) (4)

a. Number of vials sent to certified pharmacies/healthcare settings, stratified by type of pharmacy/healthcare setting

b. Number and percentage of healthcare providers who wrote/ordered prescriptions (b) (4) that were dispensed, stratified by medical specialty (e.g., oncology) and provider credentials (e.g., Doctor of Medicine)

c. Number of dispense authorizations stratified by pharmacy/healthcare setting type

d. Number of RDAs rejected, stratified by:

i. Reasons and number of denials (numerator) divided by all denials (denominator)

1. Healthcare provider not certified
2. Pharmacy or Healthcare Setting not certified
3. Other reasons for denial not categorized above

e. The percentage of dispensed prescriptions (b) (4) authorized by the REMS (b) (4). REMS authorization for dispense requires both the prescriber and the pharmacy/healthcare setting be certified.

5. REMS Compliance (b) (4)

a. Audits

i. A copy of the audit plan

ii. Report of audit findings for each stakeholder

iii. Number of audits expected, and the number of audits performed

iv. Documentation of completion of training for relevant staff

v. Documentation of processes and procedures in place for complying with the ELREXFIO REMS

vi. Verification for each audited stakeholder's site that the designated Authorized Representative remains the same. If different, include the number of new Authorized Representatives

vii. Number and type of deficiencies (e.g., critical, major, or minor findings) noted for each group of audited stakeholders as a percentage of audited stakeholders

viii. Confirmation of documentation of completion of training for relevant staff after audit findings indicated training was necessary

ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

b. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder (healthcare providers, pharmacies/healthcare settings and wholesalers-distributors), actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified from the REMS

i. For those with deficiencies noted, report the number that successfully completed a Corrective and Preventive Actions (CAPA) plan within the timeframes specified in the Noncompliance Plan

ii. For any that did not complete the CAPA within the timeframe specified in the Noncompliance Plan, describe actions taken

iii. Number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

1. Unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
2. Source of the noncompliance data
3. Results of root cause analysis
4. Action(s) that were taken in response

iv. Pharmacies/healthcare settings

1. Number of pharmacies/healthcare settings for which non-compliance with the ELREXFIO REMS is detected (numerator) divided by all pharmacies/healthcare settings dispensing ELREXFIO (denominator)
2. Number and description of pharmacies/healthcare settings that dispensed ELREXFIO to non-certified prescribers, and any corrective and preventative actions taken to prevent future occurrences
3. Number of non-certified pharmacies/healthcare settings that dispensed ELREXFIO (numerator) divided by all pharmacies/healthcare settings that dispensed ELREXFIO
4. Number of prescriptions (b) (4) dispensed by non-certified pharmacies/healthcare settings (numerator) divided by all ELREXFIO prescriptions (b) (4) dispensed (denominator) and the actions taken to prevent future occurrences
5. Summary of audit findings and any action taken and outcome of actions to prevent future occurrences
6. Summary of findings for monitoring conducted during the reporting period, including any CAPA

v. Wholesalers/Distributors

1. Number and description of non-certified pharmacies/healthcare settings that were shipped ELREXFIO, and the number of these that subsequently became certified
2. The number of authorized wholesalers-distributors for which non-compliance with the REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)
3. The number and type of wholesalers-distributors not contracted with Pfizer Inc. that shipped ELREXFIO, the number of incidents for each, actions taken to remove Elrexfio

from these entities, and actions taken to prevent future occurrences, and outcome of such actions

4. The number of contracted wholesalers-distributors suspended and/or unauthorized to distribute for non-compliance with REMS requirements and reasons for such actions, and actions taken to prevent distribution or removal of Elrexfio from these entities

c. Any other ELREXFIO REMS noncompliance, source of report and resulting CAPA

6. REMS Coordinating Center Report (b) (4)

a. Number of contacts by stakeholder type (patient/caregiver, certified prescriber, pharmacy/healthcare setting authorized representative or staff, other HCP, wholesaler/distributor, other)

b. Summary of the reasons for the call(s) by stakeholder type. Limit the summary to the top five reasons for calls by stakeholder group

c. Description of each call, including stakeholder credentials, that may indicate an issue with product access due to the REMS, REMS burden or adverse event

d. If the summary reason for the call(s) indicates an adverse event related to CRS or neurologic toxicity including ICANS include details and the outcome of the call(s)

e. Provide an assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, health care availability, other

f. Summary of frequently asked questions (FAQ) by stakeholder credentials type. Limit the summary to the top five FAQs for calls by stakeholder group

g. Summary of any noncompliance that is identified through coordinating center contacts, source of report and resulting CAPA

h. Summary of CAPAs resulting from issues identified

i. Percentage of calls to the REMS Coordinating Center that were answered within 20 minutes

j. The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered

k. Percentage of calls to the REMS Coordinating Center where the caller abandoned the call before the call was answered

l. The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned

Knowledge

7. Knowledge Assessment [redacted] (b) (4)

    a. Number of completed healthcare provider Knowledge Assessments, including the method of completion

    b. Summary statistics, including mean number of attempts, score, and range of scores and number of attempts to successfully complete the Knowledge Assessment

    c. Summary of most frequently missed questions on the Knowledge Assessment

    d. A summary of potential comprehension or perception issues identified with the Knowledge Assessment

8. Periodic KAB Survey of Certified Prescribers (beginning with the 1-Year REMS Assessment Report and thereafter with each assessment report)

    A KAB Survey will be conducted with random samples, if the population is large enough to randomize, of healthcare providers who prescribe ELREXFIO

    a. Evaluation of understanding of the risks of CRS and neurologic toxicity including ICANS associated with Elrexfio and mitigation strategies of the ELREXFIO REMS as well as compliance with the mitigation strategies

    b. An evaluation of the prescriber's knowledge on the importance of monitoring [redacted] (b) (4) for signs and symptoms of CRS and neurologic toxicity including ICANS

    c. Provide the proportion of KAB prescriber survey respondents that demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

[redacted] (b) (4)

Health Outcomes and/or Surrogates of Health Outcomes (Safe use Behaviors)

~~10.~~ 9. A summary analysis of all reported cases of CRS and neurologic toxicity, including ICANS, stratified by source of report (i.e., spontaneous). (b) (4)

a. Include the following stratifications by grade/severity in the analysis

i. Step-up dosing was initiated in the hospital setting. (For those reports that indicate initiation outside of the hospital setting provide the setting if known)

ii. Pre-medication was administered (b) (4)

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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.

/s/

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