Summary Report of Benefit-Risk Assessment

ELREXFIO SOLUTION FOR INJECTION 44 MG/1.1 ML AND 76 MG/1.9 ML

NEW DRUG APPLICATION

Active Ingredient(s)	Elranatamab
Product Registrant	Pfizer Private Limited
Product Registration Numbers	SIN17155P and SIN17156P
Application Route	Full evaluation
Date of Approval	31 December 2024

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A INTRODUCTION

Elrexfio is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb).

The active substance, elranatamab, is a B-cell maturation antigen (BCMA)-directed and CD3directed bispecific antibody that binds BCMA on plasma cells, plasmablasts, and multiple myeloma cells and CD3-epsilon on T cells leading to selective cytolysis of the BCMAexpressing multiple myeloma cells.

Elranatamab is available as solution for injection containing 44 mg/1.1 ml or 76 mg/1.9 ml of elranatamab. Other ingredients in the vials are edetate disodium dihydrate, L-histidine, Lhistidine hydrochloride monohydrate, polysorbate 80, sucrose and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, elranatamab, is manufactured at Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC, Andover, USA. The drug products, Elrexfio Solution for Injection 44 mg/1.1 ml and 76 mg/1.9 ml, are manufactured at Pharmacia & Upjohn Company LLC, Kalamazoo, USA.

Drug substance:

Adequate controls have been presented for the reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on four consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 20°C with a shelf-life of 24 months. The packaging is 8.3 L or 16.6 L ethylene vinyl acetate bags.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. The manufacturing process utilises aseptic processing and is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B guideline and impurity limits were considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is a Type I borosilicate glass vial with chlorobutyl rubber vial stopper, aluminum seal and polypropylene flip-off cap. The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at 2-8°C, as well as inuse storage of the prepared syringe for up to 24 hours at 2-30°C.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of elranatamab in the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received three prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb was based primarily on an open-label, non-randomised, multicentre, Phase 2 study, referred to as the MagnetisMM-3 study.

MagnetisMM-3 was a single-arm, uncontrolled study with objective response rate (ORR) as the primary endpoint. The study design was considered reasonable as treatment for RRMM patients who were heavily pretreated was limited without a consensus on the appropriate standard of care. The approach was aligned with that for currently registered drugs for treatment of MM patients who had received at least three or four prior lines of therapy for which the clinical evidence was based on similar uncontrolled study designs.

The study enrolled two independent and parallel cohorts; one cohort with participants who had not previously received a BCMA-directed therapy (Cohort A) and one cohort with participants who had received previous treatment with a BCMA-directed therapy (antibody drug conjugate [ADC] or chimeric antigen receptor T cell therapy [CAR-T]) (Cohort B). Cohort A comprised patients who received at least three prior therapies including a PI, IMiD, and anti-CD38 mAb but not a BCMA-directed therapy and it was the primary efficacy population whereas Cohort B was considered the supportive population.

The participants in the study received step-up priming doses of subcutaneous elranatamab during the first week of treatment (12 mg on Day 1 and 32 mg on Day 4) followed by the first full dose (76 mg) on Day 8, then 76 mg weekly (QW) thereafter. After 24 weeks, for participants who achieved partial response (PR) or better persisting for ≥2 months, the dose interval was changed from QW to once every 2 weeks (Q2W). The participants received pre-medications (acetaminophen 650 mg or paracetamol 500 mg; diphenhydramine 25 mg; dexamethasone 20 mg) before administration of both priming doses and first full dose of elranatamab 76 mg. The participants could receive study drug treatment until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination.

The primary efficacy endpoint was ORR by blinded independent central review (BICR) based on the International Myeloma Working Group (IMWG) criteria. ORR was defined as having a

best overall response of confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR). The secondary efficacy endpoints included complete response rate (CRR) (sCR+CR), duration of response (DOR), time to response (TTR), and minimal residual disease (MRD) negativity rates in participants achieving sCR/CR. The endpoints were standard and considered to be appropriate for RRMM.

A sample size of 120 participants in Cohort A was required to provide 98% power to reject the null hypothesis (ORR by BICR of 30%), based on the response rates reported for patients with RRMM who had not received a BCMA-directed therapy. In addition, a sample size of 60 participants in Cohort B was required to provide 95% power to reject the null hypothesis (ORR by BICR of 15%). A total of 187 patients were included in the study: 123 patients in Cohort A and 64 patients in Cohort B.

Among the 123 patients treated in pivotal Cohort A, the median age was 68 (range: 36 to 89) years, with 19.5% of patients ≥75 years of age. A total of 44.7% of the patients were female; 58.5% were White and 13.0% were Asian. A total of 22.8% of the patients had Stage I, 55.3% had Stage II, and 15.4% had Stage III disease. The median time since initial diagnosis of MM to enrolment was 72.9 (range: 16 to 228) months and the median number of prior lines of therapy was 5 (range: 2 to 22), with 96.0% who had received ≥3 prior lines of therapy. A total of 96.7% of the patients were triple-class refractory, and 95.9% refractory to their last line of therapy. A total of 68.3% of the patients received prior autologous stem cell transplantation, and 5.7% received prior allogeneic stem cell transplantation. High-risk cytogenetics (t(4;14), t(14;16),or del(17p)) were present in 25.2% of patients. A total of 31.7% of patients had extramedullary disease (presence of any plasmacytoma (extramedullary and/ or para-medullary) with a soft-tissue component) at baseline. Among the 64 patients treated in supportive Cohort B (BCMA-exposed patients: BCMA-directed ADC and/or CAR T cell therapy), the median age was 67 (range: 41 to 84) years with 18.8% of patients ≥75 years of age. 53.1% were female; 68.8% were White, 10.9% were Hispanic/Latino, 3.1% were Black, and 1.6% were Asian. Disease stage (R-ISS) at study entry was 17.2% in Stage I, 56.3% in Stage II and 23.4% in Stage III. The median time since initial diagnosis of multiple myeloma to enrolment was 102.6 (range: 23 to 219) months. Patients had received a median of 7.5 prior lines of therapy (range: 3 to 19); 96.9% were triple-class refractory and 51.6% were penta-drug refractory (refractory to at least 2 PIs, 2 IMiDs, and 1 anti-CD38 antibody); 87.5% were refractory to their last line of therapy. 71.9% and 32.8% received prior ADC and CAR T cell therapy, respectively. 82.8% received prior autologous stem cell transplantation, and 3.1% received prior allogenic stem cell transplantation. High-risk cytogenetics (t(4;14), t(14;16),or del(17p)) were present in 20.3% of patients. 57.8% of patients had extramedullary disease at baseline by BICR.

Summary of key efficacy results

	Cohort A (N=123)	**Cohort B (N=64)**
Best overall response, n (%)		
Stringent complete response (sCR)	16 (13.0)	0 (0)
Complete response (CR)	18 (14.6)	5 (7.8)
Very good partial response (VGPR)	34 (27.6)	16 (25.0)
Partial response (PR)	7 (5.7)	1 (1.6)
ORR (sCR+CR+VGPR+PR), n (%)	75 (61.0)	22 (34.4)
(95% CI)	(51.8, 69.6)	(22.9, 47.3)
CRR (sCR+CR), n (%)	34 (27.6)	5 (7.8)

(95% CI)	(20.0, 36.4)	(2.6, 17.3)
Median DOR, months (95% CI)	NE (12.0, NE)	NE (NE, NE)
Median TTR, months (range)	1.22 (0.9 to 7.4)	1.92 (0.9 to 6.7)
MRD negativity rate in participants achieving CR or sCR and evaluable for MRD, n/N (%)	20/22 (90.9)	2/2 (100.0)
(95% CI)	(70.8, 98.9)	(15.8, 100.0)

NE = Not estimable

The results showed that the primary analysis of confirmed ORR per BICR in Cohort A was 61.0% (95% CI: 51.8, 69.6) after a median (range) follow-up since initial dose of 10.38 (0.23, 20.14) months. There were 27.6% of participants who achieved CR or better. In Cohort B, the confirmed ORR by BICR was 34.4% (95% CI: 22.9, 47.3) after a median (range) follow-up from initial dose of 9.22 (0.33, 12.32) months, and 7.8% of patients achieved CR or better.

In terms of the secondary endpoints, in Cohort A, the median DOR was not reached (95% CI: 12.0, NE), Kaplan-Meier probability of maintaining response at 9 months was 84.4% (95% CI: 72.7, 91.4), and the median TTR was 1.22 months (range: 0.9 to 7.4 months). Among 22 patients with an evaluable sample who achieved sCR or CR in Cohort A, 20 (90.9%) were MRD negative. In Cohort B, the median DOR was also not reached (95% CI: NE, NE), the Kaplan-Meier probability of maintaining response at 9 months was 85.1% (95% CI: 60.5, 95.0), and the median TTR was 1.92 months (range: 0.9 to 6.7 months).

Although the study was single-arm and uncontrolled, the ORR of 61.0% with a CR of 27.6% in patients who had not received a BCMA-directed therapy was within range of currently approved therapies in patients who had three or more lines of prior therapy. For patients who had taken a BCMA-directed therapy previously (ADC or CAR-T), the ORR was lower (34.4% vs 61.0%) compared to patients who were naïve to BCMA-directed therapy. Nonetheless, the ORR was also within the range reported with currently available therapies for this group of patients. Overall, the ORR results provided reasonable assurance that the drug would provide similar clinical benefit compared to currently approved therapies. However, given the limitations of the early phase study and the small sample size, results from the ongoing confirmatory Phase 3 study, MagnetisMM-5 evaluating elranatamab monotherapy versus daratumumab plus pomalidomide and dexamethasone in patients with RRMM, would be required to confirm the clinical benefit of elranatamab.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of elranatamab was based on safety data derived from the pivotal Phase 2 MagnetisMM-3 study and three other Phase 1 studies, comprising a total of 265 patients who received at least one dose of study treatment. The pivotal Phase 2 study comprising 183 patients treated for a median duration of 4.1 months was considered adequate to characterise common adverse events, while the overall pooled safety database of 265 patients provided additional data to identify adverse reactions that might occur at a lower incidence.

Overview of safety profile

AE	Elranatamab (N=265)
Any adverse event (AE), n (%)	265 (100%)
Serious adverse event (SAE), n (%)	183 (69.1%)

Grade 3-4 AE, n (%)	191 (72.1%)
Discontinuations due to AE, n (%)	41 (15.5%)
Deaths due to AE, n (%)	50 (18.9%)

All subjects experienced an AE. The types of AEs reported with elranatamab were generally in line with the known safety profile of bispecific antibodies. The most common AEs were cytokine release syndrome (CRS, 64.2%), anaemia (52.8%), neutropenia (51.3%), diarrhoea (37.7%), thrombocytopenia (33.6%), fatigue (31.3%), decreased appetite (29.8%), lymphopenia (28.3%), injection site reaction (27.9%), pyrexia (24.2%), nausea (23.4%), hypokalaemia (22.3%), and headache (20.0%).

A total of 72.1% of participants experienced at least one Grade 3-4 AE, and the most common Grade 3-4 AEs were neutropenia (49.4%), anaemia (41.1%), thrombocytopenia (24.5%), lymphopenia (26.8%), and leukopenia (12.8%).

Serious AEs (SAEs) leading to hospitalisation and deaths were reported in 69.1% of participants. The most frequently reported SAEs were CRS (15.8%), COVID-19 pneumonia (8.3%), pneumonia (7.5%), and disease progression (6.0%). Treatment-related SAEs were reported in 35.5% of participants, and the most frequently reported treatment-related SAE was CRS (15.8%).

Discontinuation due to AEs occurred in 15.5% of participants. The most frequently reported AEs leading to discontinuation were COVID-19 and septic shock (4 participants [1.5%] each); neutropenia, sepsis, and disease progression (3 participants [1.1%] each); and thrombocytopenia and immune effector cell-associated neurotoxicity syndrome (ICANS) (2 participants [0.8%] each). Death due to AE was reported in 50 (18.9%) participants. The most frequent causes of deaths were related to disease progression (9.8%). The deaths which were considered to be treatment-related were caused by adenovirus infection, failure to thrive, pneumonia pseudomonal, and septic shock.

The AEs of special interest reported with elranatamab and known to be associated with bispecific antibodies were CRS ICANS and neurological toxicities. The most frequently occurring AEs of special interest were infections (69.1%), CRS (64.2%), neurological toxicities (29.1%), and ICANS (6.0%). Neurologic toxicities included headache (18.0%), encephalopathy (13.6%), motor dysfunction (12.5%), and sensory neuropathy (6.4%). Guillain-Barre Syndrome was reported in 0.4% of patients. The AEs of special interest have been adequately described as warnings and precautions in the package insert.

Overall, the safety profile of elranatamab was similar to that of other bispecific antibodies used in the treatment of RRMM, characterised by high incidences of toxicities such as CRS, anaemia, neutropenia, thrombocytopenia, lymphopenia, injection site reaction, diarrhoea, decreased appetite and fatigue. Given the significant toxicities associated with the treatment, mitigation measures including dose modifications and delays, close monitoring and supportive care such as the administration of premedication have been incorporated in the package insert to guide clinicians in appropriate patient management.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Despite the availability of multiple treatments for MM, patients with relapsed or refractory disease who have received multiple lines of therapy and treated with the major classes of drugs, including a PI, IMiD and an anti-CD38 mAb, have poor outcomes. Hence, there remains a need for therapies that could improve outcomes in these patients.

Study MagnetisMM-3 showed that in patients who received at least three prior therapies including a PI, IMiD, and anti-CD38 mAb (Cohort A), the confirmed ORR per BICR was 61.0% (95% CI: 51.8, 69.6) and 27.6% of patients achieved complete response (CR) or better. In patients who received a previous BCMA-directed therapy including ADC or CAR-T (Cohort B), the confirmed ORR by BICR was 34.4% (95% CI: 22.9, 47.3), and 7.8% of patients achieved CR or better.

The median DOR was not reached in either Cohort. The median TTR was 1.22 months (range: 0.9 to 7.4 months) in Cohort A and 1.92 months (range: 0.9, 6.7 months) in Cohort B. Among patients who achieved sCR/CR and had an evaluable sample, 20 of 22 of evaluable patients (90.9%) in Cohort A and 2 of 2 (100.0%) in Cohort B were MRD negative. However, the results should be interpreted with caution given the small number of patients.

The study design was single-arm and non-comparative and had inherent limitations. Nonetheless, the observed efficacy based on ORR in both cohorts were within range of currently approved therapies in the respective groups of patients. Hence, the results provided reasonable assurance that the clinical benefit of elranatamab would be comparable to that of currently approved therapies.

Treatment with elranatamab is associated with high incidences of Grade ≥3 AEs, including neutropenia, anaemia, thrombocytopenia, lymphopenia and leukopenia. The key safety concerns for elranatamab were CRS and neurologic toxicities such as ICANS, headache, encephalopathy, motor dysfunction, sensory neuropathy and GuillainBarre Syndrome, as well as infections. These AEs have been adequately described in the package insert, and mitigation strategies such as dose modifications and treatment delays as well as recommendations for monitoring and premedication have been included to guide clinicians in managing patients and optimise the benefit-risk balance through careful monitoring and timely intervention.

Considering the poor prognosis and limited effective treatment options in patients with RRMM after at least three prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb, and that mitigation strategies are in place to manage the risks associated with elranatamab, the benefits of elranatamab were considered to outweigh the risks. Data from the ongoing Phase 3 confirmatory study MagnetisMM-5 evaluating elranatamab monotherapy versus daratumumab plus pomalidomide and dexamethasone in patients with RRMM would be required to confirm the efficacy and safety profile of Elrexfio.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Elrexfio for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies including a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody was deemed favourable and approval of the product

registration was granted on 31 December 2024. The approval of this application is subject to the submission of the final study report of the ongoing Phase 3 study MagnetisMM5 to confirm the clinical benefit and favourable overall risk-benefit profile.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

ELREXFIO SOLUTION FOR INJECTION 44 MG/1.1 ML
ELREXFIO SOLUTION FOR INJECTION 76 MG/1.9 ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ELREXFIO SOLUTION FOR INJECTION 44 MG/1.1 ML

Each single-dose vial contains 44 mg of elranatamab in 1.1 mL (40 mg/mL).

ELREXFIO SOLUTION FOR INJECTION 76 MG/1.9 ML

Each single-dose vial contains 76 mg of elranatamab in 1.9 mL (40 mg/mL).

Elranatamab is an IgG2 kappa bispecific antibody derived from two monoclonal antibodies (mAbs), an anti-B-cell maturation antigen (BCMA) mAb and an anti-CD3 mAb. Elranatamab is produced using two recombinant Chinese Hamster Ovary (CHO) cell lines.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is clear to slightly opalescent, colourless to pale brownish liquid solution with a pH of 5.8 and osmolarity of approximately 301 mOsm/L (40 mg/mL solution for injection).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ELREXFIO is a B-cell maturation antigen (BCMA)-directed and CD3-directed bispecific antibody indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

4.2. Posology and method of administration

Treatment with ELREXFIO should be initiated and supervised by physicians experienced in the treatment of multiple myeloma.

ELREXFIO should be administered by a healthcare provider with adequately trained medical personnel and appropriate medical equipment to manage severe reactions, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (see section 4.4).

Posology

Recommended dosing schedule
The recommended dosing schedule for ELREXFIO is provided in Table 1. The recommended doses of ELREXFIO subcutaneous (SC) injection are step-up doses of 12 mg on Day 1 and 32 mg on Day 4 followed by a full treatment dose of 76 mg weekly, from Week 2 to Week 24.

For patients who have received at least 24 weeks of treatment with ELREXFIO and have achieved a response, the dosing interval should transition to an every two-week schedule.

Continue treatment with ELREXFIO until disease progression or unacceptable toxicity.

Administer pre-treatment medications prior to the first three doses of ELREXFIO in the dosing schedule, which includes Step-up dose 1 (12 mg), Step-up dose 2 (32 mg), and the first full treatment dose (76 mg) as described in Table 1 (see below).

Administer ELREXFIO subcutaneously according to the step-up dosing schedule in Table 1 to reduce the incidence and severity of CRS and ICANS. Due to the risk of CRS and ICANS, monitor patients for signs and symptoms for 48 hours after administration of each of the 2 step-up doses within the ELREXFIO dosing schedule and instruct patients to remain within proximity of a healthcare facility (see section 4.4).

Table 1. ELREXFIO dosing schedule

Dosing schedule	Week/Day	Dose	
Step-up dosing[a,b]	Week 1: Day 1	Step-up dose 1	12 mg SC
	Week 1: Day 4	Step-up dose 2	32 mg SC
Weekly dosing[a,c,d]	Week 2-24: Day 1	Full treatment dose	76 mg SC once weekly
Every 2 weeks dosing[d,e]	Week 25 onward: Day 1	Full treatment dose	76 mg SC once every two weeks

Abbreviation: SC=subcutaneous.

a. Administer pre-treatment medications prior to the first three doses of ELREXFIO.
b. A minimum of 2 days should be maintained between Step-up dose 1 (12 mg) and Step-up dose 2 (32 mg).
c. A minimum of 3 days should be maintained between Step-up dose 2 (32 mg) and the first full treatment (76 mg) dose.
d. A minimum of 6 days should be maintained between doses.
e. For patients who have achieved a response.

Note: See Table 2 for recommendations on restarting ELREXFIO after dose delays.

Missed doses
If a dose of ELREXFIO is missed, administer the dose as soon as possible, and adjust the dosing schedule as needed to maintain the dosing interval (see Table 1).

Recommended pre-treatment medications
Administer the following pre-treatment medications approximately 1 hour before the first three doses of ELREXFIO in the dosing schedule, which includes Step-up dose 1, Step-up dose 2, and the first full treatment dose as described in Table 1 to reduce the risk of CRS (see section 4.4):

- paracetamol (or equivalent) 500 mg orally
- dexamethasone (or equivalent) 20 mg orally or intravenously
- diphenhydramine (or equivalent) 25 mg orally

Restarting ELREXFIO after dosage delay

If a dose of ELREXFIO is delayed, therapy should be restarted based on the recommendations listed in Table 2 and ELREXFIO resumed according to the dosing schedule (see Table 1). Pre-treatment medications should be administered as indicated in Table 2.

Table 2. Recommendations for restarting therapy with ELREXFIO after dosage delay

Last administered dose	Duration of delay from the last administered dose	Action
Step-up dose 1 (12 mg)	2 weeks or less (≤14 days)	Restart ELREXFIO at Step-up dose 2 (32 mg).[a] If tolerated, increase to 76 mg 4 days later.
	Greater than 2 weeks (>14 days)	Restart ELREXFIO step-up dosing schedule at Step-up dose 1 (12 mg).[a]
Step-up dose 2 (32 mg)	2 weeks or less (≤14 days)	Restart ELREXFIO at 76 mg.[a]
	Greater than 2 weeks to less than or equal to 4 weeks (15 days to ≤28 days)	Restart ELREXFIO at Step-up dose 2 (32 mg).[a] If tolerated, increase to 76 mg 1 week later.
	Greater than 4 weeks (>28 days)	Restart ELREXFIO step-up dosing schedule at Step-up dose 1 (12 mg).[a]
Any full treatment dose (76 mg)	6 weeks or less (≤42 days)	Restart ELREXFIO at 76 mg.[a]
	Greater than 6 weeks to less than or equal to 12 weeks (43 days to ≤84 days)	Restart ELREXFIO at Step-up dose 2 (32 mg).[a] If tolerated, increase to 76 mg 1 week later.
	Greater than 12 weeks (>84 days)	Restart ELREXFIO step-up dosing schedule at Step-up dose 1 (12 mg).[a]

a. Administer pre-treatment medications prior to the ELREXFIO dose.

Dosage modifications for adverse reactions

Dosage reductions of ELREXFIO are not recommended.

Dosage delays may be required to manage toxicities related to ELREXFIO (see section 4.4). Recommendations on restarting ELREXFIO after a dose delay are provided in Table 2.

See Tables 3 and 4 for recommended actions for adverse reactions of CRS and ICANS, respectively. See Table 5 for recommended actions for other adverse reactions following administration of ELREXFIO. Consider further management per current practice guidelines.

Management of CRS, neurologic toxicity including ICANS

Cytokine Release Syndrome (CRS)
Management recommendations for CRS are summarised in Table 3.

Identify CRS based on clinical presentation (see section 4.4). Evaluate and treat other causes of fever, hypoxia, and hypotension.

If CRS is suspected, withhold ELREXFIO until CRS resolves. Manage CRS according to the recommendations in Table 3 and consider further management per current practice guidelines. Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS. Consider laboratory testing to monitor for disseminated intravascular coagulation (DIC), haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

Table 3. Recommendations for management of CRS

Grade[a]	Presenting symptoms	Actions
Grade 1	Temperature ≥38 °C[b]	• Withhold ELREXFIO until CRS resolves[c].

Table 3. Recommendations for management of CRS

Grade 2	Temperature ≥38 °C with either: • Hypotension responsive to fluid and not requiring vasopressors, and/or • Oxygen requirement of low-flow nasal cannula[d] or blow-by	• Withhold ELREXFIO until CRS resolves[c]. • Monitor patients daily for 48 hours following the next dose of ELREXFIO. Instruct patients to remain within proximity of a healthcare facility.
Grade 3 (First occurrence)	Temperature ≥38 °C with either: • Hypotension requiring one vasopressor with or without vasopressin, and/or • Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	• Withhold ELREXFIO until CRS resolves[c]. • Provide supportive therapy, which may include intensive care. • Monitor patients daily for 48 hours following the next dose of ELREXFIO. Instruct patients to remain within proximity of a healthcare facility.
Grade 3 (Recurrent)	Temperature ≥38 °C with either: • Hypotension requiring one vasopressor with or without vasopressin, and/or • Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	• Permanently discontinue therapy with ELREXFIO. • Provide supportive therapy, which may include intensive care.
Grade 4	Temperature ≥38 °C with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), and/or • Oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation)	• Permanently discontinue therapy with ELREXFIO. • Provide supportive therapy, which may include intensive care.

a. Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS.
b. Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anti-cytokine therapy.
c. See Table 2 for recommendations on restarting ELREXFIO after dose delays.
d. Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

Neurologic toxicity, including ICANS
Management recommendations for ICANS are summarised in Table 4.

At the first sign of neurologic toxicity, including ICANS, withhold ELREXFIO and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS (see section 4.4). Manage ICANS according to the recommendations in Table 4 and consider further management per current practice guidelines.

Table 4. Recommendations for management of ICANS

Grade[a]	**Presenting symptoms[b]**	**Actions**
Grade 1	ICE score 7-9[c]	• Withhold ELREXFIO until ICANS resolves.[e]

	Or depressed level of consciousness[d]: awakens spontaneously.	• Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis.
Grade 2	ICE score 3-6[c] Or depressed level of consciousness[d]: awakens to voice.	• Withhold ELREXFIO until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis. • Monitor patients daily for 48 hours following the next dose of ELREXFIO[e]. Instruct patients to remain within proximity of a healthcare facility.
Grade 3 (First occurrence)	ICE score 0-2[c] or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local oedema on neuroimaging[d]	• Withhold ELREXFIO until ICANS resolves[e]. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy, which may include intensive care. • Monitor patients daily for 48 hours following the next dose of ELREXFIO[e]. Instruct patients to remain within proximity of a healthcare facility.

Grade 3 (Recurrent)	ICE score 0-2[c] or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local oedema on neuroimaging[d]	• Permanently discontinue ELREXFIO. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.
Grade 4	ICE score 0[c] Or, depressed level of consciousness[d] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[d], either: • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[d]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral oedema[d], with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilloedema, or • Cushing's triad	• Permanently discontinue ELREXFIO. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously for 3 days. • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.

a. Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.

b. Management is determined by the most severe event, not attributable to any other cause.
c. If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess:
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.
d. Not attributable any other cause.
e. See Table 2 for recommendations on restarting ELREXFIO after dose delays.
f. All references to dexamethasone administration are dexamethasone or equivalent medications.

Table 5. Recommended dosage modifications for other adverse reactions

Adverse reactions	Severity	Actions
Haematologic Adverse Reactions (see section 4.8)	Absolute neutrophil count less than 0.5 x 10^9/L	• Withhold ELREXFIO until absolute neutrophil count is 0.5 x 10^9/L or higher.[b]
	Febrile neutropenia	• Withhold ELREXFIO until absolute neutrophil count is 1 x 10^9/L or higher and fever resolves.[b]
	Haemoglobin less than 8 g/dL	• Withhold ELREXFIO until haemoglobin is 8 g/dL or higher.[b]
	Platelet count less than 25,000/mcL Platelet count between 25,000/mcL and 50,000/mcL with bleeding	• Withhold ELREXFIO until platelet count is 25,000/mcL or higher and no evidence of bleeding.[b]
Other Non-haematologic Adverse Reactions[a] (see section 4.8)	Grade 3 or 4	• Withhold ELREXFIO until recovery to ≤Grade 1 or baseline.[b] • Permanently discontinue if recovery does not occur.

a. Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0.
b. See Table 2 for recommendations on restarting ELREXFIO after dose delays (see section 4.2).

Special populations

Elderly (65 years of age and older)
No dose adjustment is necessary (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment is recommended in patients with mild to moderate renal impairment. ELREXFIO has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustments are required for mild hepatic impairment. The effects of moderate to severe hepatic impairment on the pharmacokinetics of elranatamab have not been studied (see section 5.2).

Paediatric population
There is no relevant use of ELREXFIO in the paediatric population (below 18 years of age) for the treatment of multiple myeloma.

Method of administration

ELREXFIO is for subcutaneous injection only.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Cytokine release syndrome (CRS)

CRS, including life-threatening or fatal reactions, may occur in patients receiving ELREXFIO.

Clinical signs and symptoms of CRS may include, but are not limited to, fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes.

Therapy should be initiated according to ELREXFIO step-up dosing schedule to reduce risk of CRS and patients should be monitored following administration of ELREXFIO accordingly. Pre-treatment medications should be administered prior to the first three doses of ELREXFIO in the dosing schedule to reduce risk of CRS (see section 4.2).

Patients should be counselled to seek medical attention should signs or symptoms of CRS occur.

Management of cytokine release syndrome
CRS should be identified based on clinical presentation. Patients should be evaluated and treated for other causes of fever, hypoxia, and hypotension.

At the first sign of CRS, ELREXFIO should be withheld and patients should be immediately evaluated for hospitalisation. CRS should be managed according to the recommendations in Table 3 and further management should be considered per local institutional guidelines (see section 4.2). Supportive therapy for CRS (including but not limited to anti-pyretic agents, intravenous fluid support, vasopressors, IL-6 or IL-6 receptor inhibitors, supplemental oxygen, etc.) should be administered as appropriate. Laboratory testing to monitor for disseminated intravascular coagulation (DIC), haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered.

Neurologic toxicities, including ICANS

Serious or life-threatening neurologic toxicities, including ICANS, may occur following treatment with ELREXFIO.

Patients should be monitored for signs and symptoms of neurologic toxicities during treatment with ELREXFIO.

Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicity occur.

Due to the potential for ICANS, patients should be advised not to drive or operate heavy or potential dangerous machinery during the ELREXFIO step-up dosing schedule and for 48 hours after completing each of the 2 step-up doses within the ELREXFIO dosing schedule and in the event of new onset of any neurological symptoms (see sections 4.2 and 4.7).

Management of neurologic toxicities, including ICANS
At the first sign of neurologic toxicity, including ICANS, ELREXFIO should be withheld and neurology evaluation should be considered. Other causes of neurologic symptoms should be ruled out. Patients should be immediately evaluated and treated based on severity. Supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, should be provided. General management for neurologic toxicity (e.g., ICANS) is summarised in Table 4 (see section 4.2). Patients who experience Grade 2 or higher ICANS with the previous dose of ELREXFIO should be instructed to remain within proximity of a healthcare facility and be monitored for signs and symptoms daily for 48 hours following the next dose.

Infections

Severe, life-threatening, or fatal infections have been reported in patients receiving ELREXFIO (see section 4.8). New or reactivated viral infections occurred during therapy with ELREXFIO. Progressive multifocal leucoencephalopathy (PML) has also occurred during therapy with ELREXFIO.

Treatment with ELREXFIO should not be initiated in patients with active infections. Patients should be monitored for signs and symptoms of infection prior to and during treatment with ELREXFIO and treated appropriately. ELREXFIO should be withheld based on severity as indicated in Table 5 (see section 4.2). Prophylactic antimicrobials and anti-virals should be administered according to local institutional guidelines. Treatment with subcutaneous or intravenous immunoglobulin (IVIG) should be considered, as appropriate.

Neutropenia

Neutropenia and febrile neutropenia have been reported in patients receiving ELREXFIO (see section 4.8).

Complete blood cell counts should be monitored at baseline and periodically during treatment. Supportive therapy should be provided according to local institutional guidelines. Patients with neutropenia should be monitored for signs of infection.

Treatment with ELREXFIO should be withheld as indicated in Table 5 (see section 4.2).

Hypogammaglobulinaemia

Hypogammaglobulinaemia has been reported in patients receiving ELREXFIO (see section 4.8).

Immunoglobulin levels should be monitored during treatment with ELREXFIO. Subcutaneous or intravenous or immunoglobulin (IVIG) therapy should be considered if IgG levels fall below 400 mg/dL and patients should be treated according to local institutional guidelines, including infection precautions and antimicrobial prophylaxis.

Concomitant use of live viral vaccines

The safety of immunisation with live viral vaccines during or following treatment with ELREXFIO has not been studied. Vaccination with live virus vaccines is not recommended within 4 weeks prior to the first dose of ELREXFIO and during treatment with ELREXFIO.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with ELREXFIO.

The initial release of cytokines associated with the start of ELREXFIO may suppress cytochrome P450 (CYP) enzymes. The highest risk of interaction is expected to occur during the step-up dosing schedule for ELREXFIO and up to 7 days after CRS. During this time period, toxicity or medicinal product concentrations (e.g., cyclosporine) should be monitored in patients who are receiving concomitant sensitive CYP substrates with a narrow therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

4.6. Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females

Women of child-bearing potential should use effective contraception during treatment with ELREXFIO and for 4 months after the last dose.

Pregnancy

There are no human or animal data to assess the risk of elranatamab use during pregnanacy. Human immunoglobulin (IgG) is known to cross the placenta after the first trimester of pregnancy. Based on the mechanism of action, elranatamab may cause foetal harm when administered to a pregnant woman and therefore ELREXFIO is not recommended for use during pregnancy.

ELREXFIO is associated with hypogammaglobulinaemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with ELREXFIO should be considered.

The pregnancy status of women of child-bearing potential should be verified prior to initiating treatment with ELREXFIO.

Breast-feeding

It is not known whether elranatamab is excreted in human or animal milk, affects breast-fed infants or affects milk production. Human IgGs are known to be excreted in breast milk. A risk to the breast-fed child cannot be excluded and therefore breast-feeding is not recommended during treatment with ELREXFIO and for 4 months after the last dose.

Fertility

There are no data on the effect of elranatamab on human fertility. Effects of elranatamab on male and female fertility have not been evaluated in animal studies.

4.7. Effects on ability to drive and use machines

ELREXFIO may have major influence on the ability to drive and use machines.

Due to the potential for ICANS, patients receiving ELREXFIO are at risk of depressed level of consciousness (see section 4.8). Patients should be instructed to refrain from driving or operating heavy or potential dangerous machinery during and for 48 hours after completing each of the 2 step-up doses within the ELREXFIO dosing schedule and in the event of new onset of neurologic toxicity until resolution of any neurological symptoms (see sections 4.2 and 4.4).

4.8. Undesirable effects

Summary of the safety profile

The safety of ELREXFIO was evaluated in MagnetisMM-3 (see section 5.1), which included 183 adult patients with multiple myeloma who received the recommended dosing regimen of ELREXFIO. The median duration of ELREXFIO treatment was 4.1 (range: 0.03 to 14.9) months.

The most frequent adverse reactions of any grade in patients were CRS (57.9%), anaemia (53.6%), neutropenia (44.3%), fatigue (42.6%), diarrhoea (35.5%), thrombocytopenia (35.0%), lymphopenia (29.5%), decreased appetite (26.2%), rash (25.7%), arthralgia (21.9%), nausea (21.3%), hypokalaemia (21.3%), pyrexia (21.3%), injection site reaction (21.3%), and dry skin (20.8%).

Serious adverse reactions were reported in 57.9% of patients who received ELREXFIO, including pneumonia (25.1%), sepsis (13.1%), CRS (12.6%), anaemia (5.5%), upper respiratory tract infection (4.4%), urinary tract infection (3.3%), dyspnoea (2.2%), and febrile neutropenia (2.2%).

Tabulated list of adverse reactions

Table 6 summarises adverse drug reactions reported in patients who received ELREXFIO at the recommended dosing regimen (N=183 including 64 patients with prior BCMA-directed antibody drug conjugate [ADC] or chimeric antigen receptor [CAR] T cell therapy [supportive Cohort B]). The safety data of ELREXFIO was also evaluated in the all-treated population (N=265) with no additional adverse drug reactions identified.

Adverse reactions observed during clinical studies are listed by frequency category. Frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

Within each frequency grouping, where relevant, adverse drug reactions are presented in order of decreasing seriousness.

Table 6. Adverse drug reactions

System Organ Class	Adverse Drug Reaction	Frequency Category	Incidence (%)
Infections and infestations	Upper respiratory tract infection[a]	Very Common	34.4
	Pneumonia[b]	Very Common	31.7
	Sepsis[c]	Very Common	15.3
	Urinary tract infection[d]	Very Common	12.0
Blood and lymphatic system disorders	Anaemia[e]	Very Common	53.6
	Neutropenia[f]	Very Common	44.3
	Thrombocytopenia[g]	Very Common	35.0
	Lymphopenia[h]	Very Common	29.5
	Leucopenia[i]	Very Common	15.8
	Febrile neutropenia	Common	2.2
Immune system disorders	Cytokine release syndrome	Very Common	57.9
	Hypogammaglobulinaemia[j]	Very Common	13.1
Metabolism and nutrition disorders	Decreased appetite	Very Common	26.2
	Hypokalaemia	Very Common	21.3
	Hypophosphataemia	Common	6.0
Nervous system disorders	Headache	Very Common	18.0
	Peripheral neuropathy[k]	Very Common	13.7
	Immune effector cell-associated neurotoxicity syndrome (ICANS)	Common	3.3

Table 6. Adverse drug reactions

System Organ Class	Adverse Drug Reaction	Frequency Category	Incidence (%)
Respiratory, thoracic and mediastinal disorders	Dyspnoea[l]	Very Common	15.8
Gastrointestinal disorders	Diarrhoea	Very Common	35.5
	Nausea	Very Common	21.3
Skin and subcutaneous tissue disorders	Rash[m]	Very Common	25.7
	Dry skin[n]	Very Common	20.8
Musculoskeletal and connective tissue disorders	Arthralgia[o]	Very Common	21.9
General disorders and administration site conditions	Fatigue[p]	Very Common	42.6
	Injection site reaction[q]	Very Common	37.2
	Pyrexia	Very Common	21.3
Investigations	Transaminases increased[r]	Very Common	15.8

Adverse events are coded using MedDRA Version 25.0.

a. Upper respiratory tract infection includes upper respiratory tract infection, sinusitis, acute sinusitis, pharyngitis, rhinitis, rhinovirus infection, viral upper respiratory tract infection, bronchitis viral, chronic sinusitis, nasopharyngitis, sinusitis bacterial, bronchitis, respiratory tract infection viral.
b. Pneumonia includes pneumonia, COVID-19 pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia influenzal, pneumonia pseudomonal, pneumonia viral.
c. Sepsis includes sepsis, bacteraemia, device related bacteraemia, device related sepsis, escherichia bacteraemia, escherichia sepsis, klebsiella sepsis, pseudomonal sepsis, septic shock, staphylococcal bacteraemia, staphylococcal sepsis, streptococcal sepsis, urosepsis.
d. Urinary tract infection includes urinary tract infection, cystitis, urinary tract infection bacterial, escherichia urinary tract infection, urinary tract infection enterococcal.
e. Anaemia includes anaemia, haemoglobin decreased, red blood cell count decreased, haematocrit decreased, normochromic anaemia, normocytic anaemia, normochromic normocytic anaemia, aplasia pure red cell.
f. Neutropenia includes neutropenia, neutrophil count decreased, neutrophil percentage decreased, cyclic neutropenia, agranulocytosis, granulocytopenia, granulocyte count decreased.
g. Thrombocytopenia includes thrombocytopenia, platelet count decreased.
h. Lymphopenia includes lymphopenia, lymphocyte count decreased, lymphocyte percentage decreased, CD4 lymphocytes decreased, CD4 lymphocyte percentage decreased, CD8 lymphocytes decreased, CD8 lymphocyte percentage decreased.
i. Leucopenia includes leucopenia, white blood cell count decreased.
j. Hypogammaglobulinemia includes participants with adverse events of blood immunoglobulin G decreased, hypogammaglobulinaemia, immunoglobulins decreased.
k. Peripheral neuropathy includes peripheral sensory neuropathy, paraesthesia, peripheral sensorimotor neuropathy, dysaesthesia, neuropathy peripheral, peripheral motor neuropathy, guillain-barre syndrome, hypoaesthesia, neuralgia, polyneuropathy.
l. Dyspnoea includes dyspnoea, dyspnoea exertional, respiratory distress.
m. Rash incudes dermatitis exfoliative, dermatitis exfoliative generalised, erythema, palmar-plantar erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash pustular, symmetrical drug-related intertriginous and flexural exanthema.
n. Dry skin includes dry skin, skin exfoliation.
o. Arthralgia includes arthralgia, pain in extremity.
p. Fatigue includes fatigue, asthenia, malaise.
q. Injection site reaction includes injection site reaction, injection site erythema, injection site pruritus, injection site rash, injection site induration, injection site pain, injection site urticaria, injection site dryness, injection site haemorrhage, injection site inflammation.
r. Transaminases increased includes alanine aminotransferase increased and aspartate aminotransferase increased.

Description of selected adverse reactions

Cytokine release syndrome (CRS)
CRS occurred in 57.9% of patients who received ELREXFIO at the recommended dosing schedule (see section 4.2), with Grade 1 CRS in 43.7% of patients, Grade 2 CRS in 13.7% of patients and Grade 3 CRS in 0.5% of patients. Most patients experienced CRS after the first step-up dose (43.2%) or the second step-up dose (19.1%), with 7.1% of patients having CRS after the first full treatment dose and 1.6% of patients after a subsequent dose. Recurrent CRS occurred in 13.1% of patients. The median time to onset of CRS was 2 (range:1 to 9) days after the most recent dose, with a median duration of 2 (range: 1 to 19 days) days.

Among patients who developed CRS, associated symptoms included fever (99.0%), hypoxia (11.4%), and hypotension (21.0%). Among patients who received ELREXFIO at the recommended dosing schedule, 19.1% received tocilizumab (or siltuximab) and 8.7% received corticosteroids for treatment of CRS.

Immune effector cell-associated neurotoxicity syndrome (ICANS)
ICANS occurred in 3.3% of patients following treatment with ELREXFIO at the recommended dosing schedule (see section 4.2). The majority of patients had 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 a subsequent dose. 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 onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. The symptoms of ICANS included a depressed level of consciousness and Grade 1 or Grade 2 changes in the Immune Effector Cell-Associated Encephalopathy (ICE) score. Among patients who received ELREXFIO at the recommended dosing schedule, 2.2% received corticosteroids, 1.1% received tocilizumab (or siltuximab), and 0.5% received anakinra for treatment of ICANS.

Immunogenicity

During treatment in the pooled safety data (up to 24 months), 20 out of 240 participants evaluable for immunogenicity (8.3%) treated with ELREXFIO at the recommended dose developed anti-elranatamab antibodies. There was no identified clinically significant effect of anti-drug antibodies (ADA) on the pharmacokinetics, safety, or effectiveness of elranatamab.

4.9. Overdose

No participant reported an elranatamab overdose in the clinical trial program and the maximum tolerated dose has not been determined. In clinical studies, doses up to 76 mg QW have been administered.

Treatment

In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse reactions and appropriate supportive treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

ELREXFIO is a bispecific B-cell maturation antigen (BCMA)-directed T-cell engaging antibody that binds BCMA on plasma cells, plasmablasts, and multiple myeloma cells and CD3-epsilon on T cells

leading to selective cytolysis of the BCMA-expressing cells. The anticancer activity of ELREXFIO involves selective therapeutic targeting and activation of T cells re-directed against BCMA-expressing malignant plasma cells. ELREXFIO activated T cells, caused proinflammatory cytokine release, and resulted in multiple myeloma cell lysis.

Pharmacodynamic effects

Exposure-response relationships
Serum concentrations of cytokines (IL-2, IL-6, IL-8, IL-10, TNF-α, and IFN-γ) were measured before and after administration of Step-up dose 1, Step-up dose 2, and the first three full treatment doses of ELREXFIO. Time of the maximum cytokine concentration generally occurred during the step-up dosing and concentrations continue to decrease over the course of the first month of treatment.

Clinical efficacy and safety

Relapsed or refractory multiple myeloma
The efficacy of ELREXFIO monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in an open-label, non-randomised, multi-centre, Phase 2 study (MagnetisMM-3). The study included patients who were refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and one anti-CD38 monoclonal antibody. MagnetisMM-3 included 123 patients naïve to prior BCMA-directed therapy (pivotal Cohort A) and 64 patients with prior BCMA-directed antibody drug conjugate (ADC) or chimeric antigen receptor (CAR) T cell therapy (supportive Cohort B). Patients had measurable disease by International Myeloma Working Group (IMWG) criteria at enrollment. The study included patients with an ECOG score of ≤2, adequate baseline bone marrow (absolute neutrophil count ≥1.0 x 10^9/L, platelet count ≥25 x 10^9/L, haemoglobin level ≥8 g/dL), renal (CrCL ≥30 mL/min), and hepatic (AST and ALT ≤2.5 x ULN, total bilirubin ≤2 x ULN) function, and left-ventricular ejection fraction ≥40%. Patients with a stem cell transplant within 12 weeks prior to enrollment and active infections were excluded from the study.

Eligible patients received subcutaneous administration of ELREXFIO at 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 ELREXFIO (76 mg) on Day 8 of treatment. Thereafter, patients received 76 mg once weekly. After 24 weeks, in patients who achieved an IMWG response category of PR or better with responses persisting for at least 2 months, the dosing interval was changed from every week to every 2 weeks (see section 4.2).

Among the 123 patients treated in pivotal Cohort A, the median age was 68 (range: 36 to 89) years with 20% of patients ≥75 years of age. 44.7% were female; 58.5% were White, 13.0% were Asian, 8.9% were Hispanic/Latino, and 7.3% were Black. Disease stage (R-ISS) at study entry was 22.8% in Stage I, 55.3% in Stage II, and 15.4% in Stage III. The median time since initial diagnosis of multiple myeloma to enrolment was 72.9 (range: 16 to 228) months. Patients had received a median of 5 prior lines of therapy (range: 2 to 22); with 96.0% who had received ≥3 prior lines of therapy. 96.7% were triple-class refractory, and 95.9% refractory to their last line of therapy. 68.3% received prior autologous stem cell transplantation, and 5.7% received prior allogenic stem cell transplantation. High-risk cytogenetics (t(4;14), t(14;16),or del(17p)) were present in 25.2% of patients. 31.7% of patients had extramedullary disease (presence of any plasmacytoma (extramedullary and/or paramedullary)) with a soft-tissue component) at baseline by Blinded Independent Central Review (BICR).

Efficacy results were based on response rate and duration of response (DOR), as assessed by BICR based on the IMWG criteria. Efficacy results from pivotal Cohort A are shown in Table 7. The median (range) follow-up for responders was 10.9 (3.6, 20.1) months.

Table 7. Efficacy results for MagnetisMM-3 in pivotal Cohort A

	BCMA-directed therapy naïve patients (pivotal Cohort A)
	All treated (N=123)
Objective Response Rate (ORR: sCR+CR+VGPR+PR), n (%) (95% CI)	75 (61.0%) (51.8, 69.6)
Stringent complete response (sCR)	16 (13.0%)
Complete response (CR)	18 (14.6%)
Very good partial response (VGPR)	34 (27.6%)
Partial response (PR)	7 (5.7%)
Complete Response Rate (sCR+CR), n (%) (95% CI)	34 (27.6%) (20.0, 36.4)
Time to First Response (months)	
Number of responders	75
Median	1.22
Range	(0.9, 7.4)
Duration of Response (DOR) (months)	
Number of responders	75
Median (95% CI)	NR (12.0, NE)
Rate at 6 months (95% CI)	90.0 (80.2, 95.1)
Rate at 9 months (95% CI)	84.4 (72.7, 91.4)
MRD-negativity rate[a] in patients achieving CR or sCR and evaluable for MRD [N=22] n (%) 95% CI (%)	 20 (90.9%) (70.8, 98.9)

Abbreviations: CI=Confidence interval; NR=Not reached; NE=Not estimable; MRD=Minimal residual disease.

a. By threshold 10^{-5}, Next Generation Sequencing clonoSEQ assay (Adaptive Biotechnologies).

Among the 64 patients treated in supportive Cohort B (BCMA-exposed patients: BCMA-directed ADC and/or CAR T cell therapy), the median age was 67 (range: 41 to 84) years with 18.8% of patients ≥75 years of age. 53.1% were female; 68.8% were White, 10.9% were Hispanic/Latino, 3.1% were Black, and 1.6% were Asian. Disease stage (R-ISS) at study entry was 17.2% in Stage I, 56.3% in Stage II and 23.4% in Stage III. The median time since initial diagnosis of multiple myeloma to enrolment was 102.6 (range: 23 to 219) months. Patients had received a median of 7.5 prior lines of therapy (range: 3 to 19); 96.9% were triple-class refractory and 51.6% were penta-drug refractory (refractory to at least 2 PIs, 2 IMiDs, and 1 anti-CD38 antibody); 87.5% were refractory to their last line of therapy. 71.9% and 32.8% received prior ADC and CAR T cell therapy, respectively. 82.8% received prior autologous stem cell transplantation, and 3.1% received prior allogenic stem cell transplantation. High-risk cytogenetics (t(4;14), t(14;16),or del(17p)) were present in 20.3% of patients. 57.8% of patients had extramedullary disease at baseline by BICR.

Efficacy results in supportive Cohort B include confirmed ORR by BICR of 34.4% (95% CI: 22.9, 47.3); 7.8% of patients achieved CR or better, and 32.8% achieved VGPR or better. Median TTR was 1.92 (range: 0.92, 6.74) months. After a median (range) follow-up of 10.2 (6.4, 12.3) months in responders, median DOR was not reached and the Kaplan-Meier DOR rate was 85.1% (95% CI: 60.5, 95.0) at 6 months and 85.1% (95% CI: 60.5, 95.0) at 9 months.

5.2. Pharmacokinetic properties

Pharmacokinetic parameters are presented as geometric mean (coefficient of variation [CV]%) and are based upon subcutaneously administered unless otherwise specified.

The C_{max} and AUC_{tau} of elranatamab after the first subcutaneous dose increased in a dose proportional manner over the evalutated dose range via SC administration (~ 6 to 76 mg). The median

accumulation ratio after 24 weeks of weekly dosing (steady state) relative to the first subcutaneous dose of elranatamab 76 mg for C_{max} and AUC_{tau} was 6.6-fold and 11.2-fold, respectively. The C_{max}, C_{trough}, and C_{avg} for the recommended dosage of elranatamab are presented in Table 8.

Table 8. Pharmacokinetic parameters of elranatamab in subjects with relapsed or refractory multiple myeloma

Timepoint	Parameters		
	C_{avg} (mcg/mL)	**C_{max} (mcg/mL)**	**C_{trough} (mcg/mL)**
First full 76 mg dose	3.1 (94%)	3.8 (94%)	3.3 (102%)
End of weekly dose (week 24)	32.7 (49%)	33.6 (48%)	31.2 (50%)
Steady state (every two weeks dosing)[a,b]	18.4 (57%)	20.1 (55%)	15.9 (64%)

a. In patients who have achieved a response.
b. Steady state exposure of elranatamab every two weeks dose is approximated at week 48.

Absorption

The predicted mean bioavailability of elranatamab was 56.2% when administered subcutaneously. The median T_{max} after elranatamab SC administration across all dose levels ranged from 3 to 7 days for both total and free serum concentrations.

Distribution

The mean (coefficient of variation [CV]%) central volume of distribution of elranatamab was 4.78 L (69%). The mean peripheral volume of distribution of elranatamab was 2.83 L.

Elimination

The predicted geometric mean half-life of elranatamab is 22, 64% (CV) days at week 24 following doses of 76 mg weekly. Based on the population pharmacokinetic model, the predicted mean elranatamab clearance was 0.324 L/day, 69% (CV).

Special populations

No clinically relevant differences in the pharmacokinetics of elranatamab were observed age (36 to 89 years), sex (167 male, 154 female), race (193 White, 49 Asian, 29 Black), and body weight (37 to 160 kg).

Renal impairment
No formal studies of elranatamab in patients with renal impairment have been conducted. Results of population pharmacokinetic analyses indicate that mild renal impairment (60 mL/min/1.73 m^2 ≤estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2) or moderate renal impairment (30 mL/min/1.73 m^2 ≤eGFR <60 mL/min/1.73 m^2) did not significantly influence the pharmacokinetics of elranatamab. Limited data are available from patients with severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment.

Hepatic impairment
No formal studies of elranatamab in patients with hepatic impairment have been conducted. Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal (ULN) and any aspartate aminotransferase (AST), or total bilirubin ≤ULN and AST>ULN) did not significantly influence the pharmacokinetics of elranatamab. No data

are available in patients with moderate (total bilirubin >1.5 to 3.0 x ULN and any AST) or severe (total bilirubin >3.0 x ULN and any AST) hepatic impairment.

5.3. Preclinical safety data

Carcinogenicity and mutagenicity

No animal studies have been performed to assess the carcinogenic and genotoxic potential of elranatamab.

Reproductive toxicology and fertility

No animal studies have been performed to evaluate the effects of elranatamab on fertility or reproduction and foetal development. In a 13-week repeat-dose toxicity study in sexually mature cynomolgus monkeys, there were no adverse effects on male and female reproductive organs following subcutaneous doses up to 6 mg/kg/week (approximately 6.5 times the maximum recommended human dose, based on AUC exposure) subcutaneously.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Edetate disodium dihydrate
L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 80
Sucrose
Water for injection

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medications.

6.3. Shelf life

Unopened vial

Refer to outer carton.

Prepared syringe

Chemical and physical stability has been demonstrated for the prepared syringe for up to 24 hours at 2 °C to 30 °C. From a microbiological point of view, the prepared syringe should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C.

6.4. Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).

Do not freeze. Do not shake.

Store in the original carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5. Nature and contents of container

ELREXFIO SOLUTION FOR INJECTION 44 MG/1.1 ML

1.1 mL solution in a single-dose vial (Type 1 borosilicate glass) with a stopper (chlorobutyl rubber) and an aluminium seal with a flip-off cap containing 44 mg of elranatamab.
Pack size of 1 vial.

ELREXFIO SOLUTION FOR INJECTION 76 MG/1.9 ML

1.9 mL solution in a single-dose vial (Type 1 borosilicate glass) with a stopper (chlorobutyl rubber) and an aluminium seal with a flip-off cap containing 76 mg of elranatamab.
Pack size of 1 vial.

Not all presentations may be available locally.

6.6. Special precautions for disposal and other handling

ELREXFIO is intended for subcutaneous use by a healthcare provider only.

ELREXFIO should be administered by a healthcare provider with adequate medical personnel and appropriate medical equipment to manage severe reactions, including CRS and neurologic toxicity, including ICANS (see section 4.4).

ELREXFIO 76 mg/1.9 mL (40 mg/mL) vial and 44 mg/1.1 mL (40 mg/mL) vial are supplied as ready-to-use solution that do not need dilution prior to administration.

ELREXFIO is a clear to slightly opalescent, and colourless to pale brown liquid solution. ELREXFIO should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should not be administered if it is discoloured or contains particulate matter.

Aseptic technique should be used to prepare and administer ELREXFIO.

Preparation instructions

ELREXFIO vials are single-dose and do not contain any preservatives.

ELREXFIO should be prepared following the instructions below (see Table 9) depending on the required dose. It is suggested to use a 44 mg/1.1 mL (40 mg/mL) single-dose vial for Step-up dose 1 or Step-up dose 2.

Table 9. Preparation instructions for ELREXFIO

Required dose	**Dose volume**
76 mg (Full treatment dose)	1.9 mL
32 mg (Step-up dose 2)	0.8 mL
12 mg (Step-up dose 1)	0.3 mL

Once punctured, the vial and dosing syringe should be used immediately. For storage conditions after first opening of the medicinal product, see section 6.3.

ELREXFIO is available as a single-dose vial. Any solution remaining in the vial should be discarded after single withdrawal.

Administration instructions

ELREXFIO should be administered by a healthcare provider.

The required dose of ELREXFIO should be injected into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, ELREXFIO may be injected into the subcutaneous tissue at other sites (e.g., thigh).

Disposal

The vial and any remaining contents after withdrawal of a single-dose should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

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