1. NAME OF THE MEDICINAL PRODUCT

ELREXFIO®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ELREXFIO 40 mg/mL solution for injection

One vial contains 44 mg of elranatamab in 1.1 mL (40 mg/mL).

ELREXFIO 40 mg/mL solution for injection

One 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). 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).

Clear to slightly opalescent, colourless to pale brownish solution, pH of 5.8, and osmolarity of approximately 301 mOsm/L.

Patient safety information Card

The marketing of ELREXFIO is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELREXFIO is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

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

ELREXFIO should be administered via subcutaneous injection by a healthcare professional 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).

Prior to initiating treatment, complete blood count should be performed. Any possibility of active infections and/or pregnancy in women of child-bearing potential should be ruled out (see sections 4.4 and 4.6).

Posology

Recommended dosing schedule
The recommended doses 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 (see Table 1).

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

ELREXFIO should be administered 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, patients should be monitored for signs and symptoms for 48 hours after administration of each of the 2 step-up doses and instructed 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
	Week 1: day 4	Step-up dose 2	32 mg
Weekly dosing[a,c,d]	Week 2-24: day 1	Full treatment dose	76 mg once weekly
Every 2 weeks dosing[d,e]	Week 25 onward: day 1	Full treatment dose	76 mg once every two weeks

a. Pre-treatment medicinal products should be administered 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 5 for recommendations on restarting ELREXFIO after dose delays.

Recommended pre-treatment medicinal products
The following pre-treatment medicinal products should be administered approximately 1 hour prior to the first three doses of ELREXFIO, 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 500 mg orally (or equivalent)
- dexamethasone 20 mg orally or intravenously (or equivalent)
- diphenhydramine 25 mg orally (or equivalent)

Prophylactic antimicrobials and anti-virals should be considered according to local institutional guidelines (see section 4.4).

Dose modifications based on toxicity

Dose reductions of ELREXFIO are not recommended. Dose delays may be required to manage toxicities (see section 4.4).

See Tables 2 and 3 for recommended actions for adverse reactions of CRS and ICANS, respectively.

See Table 4 for recommended actions for other adverse reactions.

Cytokine release syndrome (CRS)

CRS should be identified based on clinical presentation (see section 4.4). Patients should be evaluated and treated for other causes of fever, hypoxia, and hypotension. 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.

Table 2. Recommendations for management of CRS

Grade[a]	Presenting symptoms	Actions
Grade 1	Temperature ≥ 38 °C[b]	• Withhold treatment until CRS resolves.[c] • Provide supportive therapy.
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 treatment until CRS resolves.[c] • Provide supportive therapy. • 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 treatment until CRS resolves.[c] • Provide supportive therapy, which may include intensive care. • Administer pre-treatment medicinal products prior to the next dose of ELREXFIO. • 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. • 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. • 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 5 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 toxicities, including ICANS

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. 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.

Table 3. Recommendations for management of ICANS

Grade[a]	Presenting symptoms[b]	Actions
Grade 1	ICE score 7-9[c] Or depressed level of consciousness[d]: awakens spontaneously.	• Withhold treatment until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with a neurologist for further evaluation and management. • Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.
Grade 2	ICE score 3-6[c] Or depressed level of consciousness[d]: awakens to voice.	• Withhold treatment 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 medicinal products (e.g., levetiracetam) for seizure prophylaxis. • 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)	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 treatment 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 medicinal products (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. 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	• Permanently discontinue treatment. • 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.

	electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local oedema on neuroimaging[d]	• Consider non-sedating, anti-seizure medicinal products (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 treatment. • 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 medicinal products (e.g., levetiracetam) for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.

Abbreviations: Immune effector cell-associated encephalopathy (ICE).

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 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 to any other cause.

e. See Table 5 for recommendations on restarting ELREXFIO after dose delays.

f. All references to dexamethasone administration are dexamethasone or equivalent medicinal products.

Table 4. Recommended actions for other adverse reactions

Adverse reactions	Severity	Actions
Haematologic adverse reactions (see section 4.8)	Absolute neutrophil count less than 0.5×10^9/L	• Withhold treatment until absolute neutrophil count is 0.5×10^9/L or higher.[b]
	Febrile neutropenia	• Withhold treatment until absolute neutrophil count is 1×10^9/L or higher and fever resolves.[b]

	Haemoglobin less than 8 g/dL	• Withhold treatment 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 treatment 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 treatment until recovery to Grade 1 or less 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 5 for recommendations on restarting ELREXFIO after dose delays (see section 4.2).
* Other than CRS and ICANS.

Restarting ELREXFIO after dose delay

If a dose is delayed, therapy should be restarted based on the recommendations listed in Table 5, and therapy should be resumed according to the dosing schedule (see Table 1). Pre-treatment medicinal products should be administered as indicated in Table 5.

Table 5. Recommendations for restarting therapy with ELREXFIO after dose 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 at step-up dose 2 (32 mg).[a] If tolerated, increase to 76 mg 4 days later.
	Greater than 2 weeks (> 14 days)	Restart 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 at 76 mg.[a]
	Greater than 2 weeks to less than or equal to 4 weeks (15 days and ≤ 28 days)	Restart at step-up dose 2 (32 mg).[a] If tolerated, increase to 76 mg 1 week later.
	Greater than 4 weeks (> 28 days)	Restart 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 at 76 mg.
	Greater than 6 weeks to less or equal to 12 weeks (43 days to ≤ 84 days)	Restart at step-up dose 2 (32 mg).[a] If tolerated, increase to 76 mg 1 week later.
	Greater than 12 weeks (> 84 days)	Restart step-up dosing schedule at step-up dose 1 (12 mg).[a]

a. Administer pre-treatment medicinal products prior to the ELREXFIO dose.

Duration of treatment
Treatment should be continued until disease progression or unacceptable toxicity.

Missed doses
If a dose is missed, the dose should be administered as soon as possible, and the dosing schedule should be adjusted to maintain the dosing interval as needed (see Table 1).

Special populations

Elderly
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 (estimated glomerular filtration rate [eGFR] > 30 mL/min/1.73 m^2). Limited data are available from patients with severe renal impairment, see section 5.2).

Hepatic impairment
No dose adjustments are required for mild hepatic impairment (total bilirubin > 1 to 1.5 × ULN and any AST, or total bilirubin ≤ ULN and AST > ULN, see section 5.2).

Paediatric population
ELREXFIO is indicated for adult patients. There is no relevant use of ELREXFIO in the paediatric population for the treatment of multiple myeloma.

Method of administration

ELREXFIO is for subcutaneous injection only and should be administered by a healthcare professional.

The required dose should be injected into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue of the thigh.

ELREXFIO should not be injected into areas where the skin is red, bruised, tender, hard, or areas where there are scars.

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

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 (see section 4.8).

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

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

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 section 4.2, and further management should be considered per local institutional guidelines. 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 (see section 4.8). Patients should be monitored for signs and symptoms (e.g., decrease level of consciousness, seizures and/or motor weakness) of neurologic toxicities during treatment.

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

At the first sign of neurologic toxicity, including ICANS, ELREXFIO should be withheld and neurology evaluation should be considered. General management for neurologic toxicity (e.g., ICANS) is summarised in Table 3 (see section 4.2).

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

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, including cytomegalovirus infection/reactivation. Progressive multifocal leukoencephalopathy (PML), which can be fatal, has also occurred during therapy with ELREXFIO.

Treatment 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 the severity of the infection as indicated in Table 4 for other non-haematologic adverse reactions (see section 4.2).

Prophylactic antimicrobials (e.g., prevention of pneumocystis jirovecii pneumonia) and anti-virals (e.g., prevention of herpes zoster reactivation) should be administered according to local institutional guidelines.

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. Treatment with ELREXFIO should be withheld as indicated in Table 4 (see section 4.2). Patients with neutropenia should be monitored for signs of infection. Supportive therapy should be provided according to local institutional guidelines.

Hypogammaglobulinaemia

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

Immunoglobulin levels should be monitored during treatment. Treatment with subcutaneous or intravenous immunoglobulin (IVIG) 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 the 4 weeks prior to the first dose, during treatment, and at least 4 weeks after treatment.

Excipients

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free.'

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 and up to 14 days after the step-up dosing as well as during and up to 14 days after CRS. During this time period, toxicity or medicinal product concentrations should be monitored in patients who are receiving concomitant sensitive CYP substrates with a narrow therapeutic index (e.g., cyclosporine, phenytoin, sirolimus, and warfarin). The dose of the concomitant medicinal product should be adjusted as needed.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception

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

Women of child-bearing potential should use effective contraception during treatment with ELREXFIO and for 6 months after the last dose.

Pregnancy

There are no human or animal data to assess the risk of elranatamab use during pregnancy. 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.

Breast-feeding

It is not known whether elranatamab is excreted in human or animal milk, affects breastfed infants or affects milk production. Human IgGs are known to be excreted in breast milk. A risk to the breastfed

child cannot be excluded and therefore breast-feeding is not recommended during treatment with ELREXFIO and for 6 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 has 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 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 most frequent adverse reactions are CRS (57.9%), anaemia (54.1%), neutropenia (45.94%), fatigue (44.8%), upper respiratory tract infection (43.2%), injection site reaction (38.3%), diarrhoea (42.1%), pneumonia (38.3%), thrombocytopenia (36.6%), lymphopenia (30.1%), decreased appetite (27.3%), pyrexia (29.0%), rash (27.9%), arthralgia (26.8%), hypokalaemia (23.5%), nausea (21.9%), dry skin (21.9%) and dyspnoea (20.8%).

Serious adverse reactions are pneumonia (31.7%), sepsis (15.8%), CRS (12.6%), anaemia (5.5%), upper respiratory tract infection (5.5%), urinary tract infection (3.8%), febrile neutropenia (3.3%), diarrhoea (2.7%), dyspnoea (2.7%), and pyrexia (2.2%).

Tabulated list of adverse reactions

Table 6 summarises adverse 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 median duration of treatment was 4.1 (range: 0.03 to 35.9) months. The safety data of ELREXFIO was also evaluated in the all-treated population (N=265) with no additional adverse reactions identified.

Adverse reactions are listed according to the MedDRA system organ classification and by frequency. 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), very rare (< 1/10 000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 6. Adverse reactions in multiple myeloma patients treated with ELREXFIO in MagnetisMM-3 at the recommended dose

System organ class	Adverse reaction	Frequency (All grades)	N=183	
			Any grade (%)	Grade 3 or 4 (%)
Infections and infestations	Pneumonia[a]	Very common	38.3	25.7
	Sepsis[b]	Very common	18.6	13.1
	Upper respiratory tract infection	Very common	43.2	6.0
	Urinary tract infection	Very common	13.7	6.0

Table 6. Adverse reactions in multiple myeloma patients treated with ELREXFIO in MagnetisMM-3 at the recommended dose

	Cytomegalovirus infection[c]	Common	9.3	2.2
	Progressive multifocal leukoencephalopathy	Uncommon	0.5*	0
Blood and lymphatic system disorders	Neutropenia	Very common	45.9	44.3
	Anaemia	Very common	54.1	42.6
	Thrombocytopenia	Very common	36.6	26.2
	Lymphopenia	Very common	30.1	27.9
	Leukopenia	Very common	18.6	13.1
	Febrile neutropenia	Common	3.3	3.3
Immune system disorders	Cytokine release syndrome	Very common	57.9	0.5
	Hypogammaglobulinaemia	Very common	16.9	2.7
Metabolism and nutrition disorders	Decreased appetite	Very common	27.3	1.1
	Hypokalaemia	Very common	23.5	9.3
	Hypophosphataemia	Common	6.6	0.5
Nervous system disorders	Peripheral neuropathy[d]	Very common	17.5	1.1
	Headache	Very common	19.7	0
	Immune effector cell-associated neurotoxicity syndrome (ICANS)	Common	3.3	1.1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	20.8	4.9
Gastrointestinal disorders	Diarrhoea	Very common	42.1	2.7
	Nausea	Very common	21.9	0
Skin and subcutaneous tissue disorders	Rash[e]	Very common	27.9	0
	Dry skin	Very common	21.9	0
Musculoskeletal and connective tissue disorders	Arthralgia	Very common	26.8	1.6
General disorders and administration site conditions	Injection site reaction	Very common	38.3	0
	Pyrexia	Very common	29.0	3.3
	Fatigue	Very common	44.8	6.0
Investigations	Transaminases increased	Very common	17.5	5.5

* Fatal (Grade 5) case reported.

a. Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, coronavirus pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection fungal, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia haemophilus, pneumonia influenzal, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia viral.

b. Sepsis includes bacteraemia, campylobacter bacteraemia, device related bacteraemia, device related sepsis, escherichia bacteraemia, escherichia sepsis, klebsiella sepsis, pseudomonal sepsis, sepsis, septic shock, staphylococcal bacteraemia, staphylococcal sepsis, streptococcal sepsis, urosepsis.

c. Cytomegalovirus infection includes cytomegalovirus chorioretinitis, cytomegalovirus gastroenteritis, cytomegalovirus infection, cytomegalovirus infection reactivation, cytomegalovirus viraemia.

d. Peripheral neuropathy includes dysaesthesia, Guillain-Barre syndrome, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy.

e. Rash includes dermatitis exfoliative, dermatitis exfoliative generalised, epidermolysis, erythema, palmar-plantar erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash pustular, symmetrical drug-related intertriginous and flexural exanthema.

Description of selected adverse reactions

Cytokine release syndrome (CRS)
CRS occurred in 57.9% of patients who received ELREXFIO at the recommended dosing schedule, with Grade 1 CRS in 43.7%, Grade 2 in 13.7% and Grade 3 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 (98.1%), hypotension (20.8%), and hypoxia (11.3%) and 34.0% received tocilizumab (or siltuximab) and 15.1% 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, with Grade 1 ICANS in 0.5%, Grade 2 in 1.6% and Grade 3 in 1.1% of patients. 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 most frequent symptoms of ICANS included a depressed level of consciousness and Grade 1 or Grade 2 Immune Effector Cell-Associated Encephalopathy (ICE) scores (see Table 3). Among patients who developed ICANS, 66.7% received corticosteroids, 33.3% received tocilizumab (or siltuximab), 33.3% received levetiracetam and 16.7% received anakinra for treatment of ICANS.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Symptoms and signs

There has been minimal experience of overdose in clinical studies. The maximum tolerated dose of elranatamab has not been determined. In clinical studies, doses up to 76 mg once weekly 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

Pharmacotherapeutic group: Monoclonal antibodies and antibody drug conjugates, ATC code: L01FX32

Mechanism of action

Elranatamab is a bi-specific T-cell engaging antibody that binds CD3-epsilon on T cells and B-cell maturation antigen (BCMA) on plasma cells, plasmablasts, and multiple myeloma cells. Binding of elranatamab to BCMA on tumour cells and CD3 on T cells is independent of native T cell receptor (TCR) specificity or reliance on major histocompatibility (MHC) Class 1 molecules. Elranatamab activated T cells, led to proinflammatory cytokine release, and resulted in multiple myeloma cell lysis.

Pharmacodynamic effects

Immunogenicity
During treatment with elranatamab at the recommended dose in the MagnetisMM-3 study, anti-drug antibodies (ADA) were detected in 9.5% participants. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed; however, data are still limited.

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). Patients had measurable disease by international myeloma working group (IMWG) criteria at enrolment. The study included patients with an ECOG score of ≤ 2, adequate baseline bone marrow (absolute neutrophil count ≥ 1.0×10^9/L, platelet count ≥ 25×10^9/L, haemoglobin level ≥ 8 g/dL), renal (CrCL ≥ 30 mL/min), and hepatic [aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 2.5 × upper limit of normal (ULN)], total bilirubin ≤ 2 × ULN] function, and left-ventricular ejection fraction ≥ 40%. Patients with smouldering multiple myeloma, active plasma cell leukaemia, amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) syndrome, stem cell transplant within 12 weeks prior to enrolment, active infections, and clinically significant neuropathies and cardiovascular disease, were excluded from the study.

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 partial response 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 19.5% 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 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] by blinded independent central review (BICR) at baseline.

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 from initial dose for responders was 27.9 (3.6, 36.8) 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)	20 (16.3%)
Complete response (CR)	26 (21.1%)
Very good partial response (VGPR)	23 (18.7%)
Partial response (PR)	6 (4.9%)
Complete response rate (sCR+CR), n (%) (95% CI)	46 (37.4%) (28.8, 46.6)
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)	NE (NE, NE)
Rate at 12 months (95% CI)	73.4 (61.4, 82.1)
Rate at 24 months (95% CI)	66.9 (54.4, 76.7)
MRD-negativity rate[a] in patients achieving CR or sCR and evaluable for MRD (31 of the 46 patients who reached CR/sCR were evaluable for MRD) n (%) 95% CI (%)	 28 (90.3%) (74.2, 98.0)

Abbreviations: CI=confidence interval; NE=not estimable; MRD=minimal residual disease.

a. By threshold 10^{-5}, next generation sequencing clonoSEQ assay (Adaptive Biotechnologies).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ELREXFIO in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters are presented as geometric mean (coefficient of variation [CV]%) for unbound elranatamab unless otherwise specified. The C_{max} and AUC_{tau} of elranatamab after the first subcutaneous dose increased in a dose proportional manner over the evaluated dose range via subcutaneous administration (~ 6 to 76 mg). The median accumulation ratio after 24 weeks of weekly dosing 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 predicted C_{avg}, C_{max}, and C_{trough} of elranatamab are presented in Table 8.

Table 8. Predicted pharmacokinetic parameters of elranatamab following the recommended dose

Timepoint	**Parameters**

	C_{avg} (mcg/mL)	C_{max} (mcg/mL)	C_{trough} (mcg/mL)
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.

Distribution

Based on the population pharmacokinetic model, the predicted mean volume of distribution of unbound elranatamab was 4.78 L, 69% (CV) for the central compartment, and 2.83 L for the peripheral compartment.

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, 100% (CV).

Special populations

No clinically relevant differences in the pharmacokinetics of elranatamab were observed based on 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 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 ≤ 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 renal impairment (eGFR less than 30 mL/min/1.73 m^2).

Hepatic impairment
No 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 × ULN and any 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 × ULN and any AST) or severe (total bilirubin > 3.0 × ULN and any AST) hepatic impairment.

5.3 Preclinical safety data

Carcinogenicity and mutagenicity

No animal studies have been performed to assess the carcinogenic or 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 notable 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

Prepared syringe

Chemical and physical in-use stability has been demonstrated for 24 hours at 30 °C.

From a microbiological point of view, unless the method of opening precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
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 40 mg/mL solution for injection

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

ELREXFIO 40 mg/mL solution for injection

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

6.6 Special precautions for disposal and other handling

ELREXFIO 40 mg/mL solution for injection is supplied as a ready-to-use solution that does not need dilution prior to administration. Do not shake.

ELREXFIO is a clear to slightly opalescent, and colourless to pale brown solution. 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 40 mg/mL solution for injection vials are for single use only.

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 each one of the step-up doses.

Table 9. Preparation instructions for ELREXFIO

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

Once punctured, the vial and dosing syringe should be used immediately. If the prepared dosing syringe is not used immediately, store syringe between 2 °C to 30 °C for a maximum of 24 hours.

Disposal

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

7. LICENSE HOLDER

Pfizer Pharmaceuticals Ltd., 9 Shenkar St. Herzliya Pituach 46725.

8. LICENSE NUMBER

177-77-37990

Revised in 02/2026