ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ELREXFIO 40 mg/mL solution for injection

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.

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 electroencephalogram (EEG) that resolve with intervention,	• 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. • Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.

	or raised intracranial pressure: focal/local oedema on neuroimaging[d]	• 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
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 (CMV) infection/reactivation. Progressive multifocal leukoencephalopathy (PML) 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 (44.8%), fatigue (44.3%), upper respiratory tract infection (38.8%), injection site reaction (38.3%), diarrhoea (37.7%), pneumonia (37.2%), thrombocytopenia (36.1%), lymphopenia (30.1%), decreased appetite (26.8%), pyrexia (27.3%), rash (26.2%), arthralgia (25.1%), hypokalaemia (23.0%), nausea (21.3%), and dry skin (21.3%).

Serious adverse reactions are pneumonia (30.6%), sepsis (15.3%), CRS (12.6%), anaemia (5.5%), upper respiratory tract infection (4.9%), urinary tract infection (3.3%), febrile neutropenia (2.7%), dyspnoea (2.2%), 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 20.3) 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	37.2	24.6
	Sepsis[b]	Very common	18.0	12.6
	Upper respiratory tract infection	Very common	38.8	5.5
	Urinary tract infection	Very common	12.6	4.4
	Cytomegalovirus infection (CMV)[c]	Common	9.3	2.2
Blood and lymphatic system disorders	Neutropenia	Very common	44.8	43.2
	Anaemia	Very common	54.1	42.6

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

	Thrombocytopenia	Very common	36.1	26.2
	Lymphopenia	Very common	30.1	27.9
	Leucopenia	Very common	17.5	12.6
	Febrile neutropenia	Common	2.7	2.7
Immune system disorders	Cytokine release syndrome	Very common	57.9	0.5
	Hypogammaglobulinaemia	Very common	14.2	2.7
Metabolism and nutrition disorders	Decreased appetite	Very common	26.8	1.1
	Hypokalaemia	Very common	23.0	8.7
	Hypophosphataemia	Common	6.6	0.5
Nervous system disorders	Peripheral neuropathy[d]	Very common	15.8	1.1
	Headache	Very common	19.1	0
	Immune effector cell-associated neurotoxicity syndrome (ICANS)	Common	3.3	1.1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	19.1	4.9
Gastrointestinal disorders	Diarrhoea	Very common	37.7	1.1
	Nausea	Very common	21.3	0
Skin and subcutaneous tissue disorders	Rash[e]	Very common	26.2	0
	Dry skin	Very common	21.3	0
Musculoskeletal and connective tissue disorders	Arthralgia	Very common	25.1	1.6
General disorders and administration site conditions	Injection site reaction	Very common	38.3	0
	Pyrexia	Very common	27.3	3.3
	Fatigue	Very common	44.3	6.0
Investigations	Transaminases increased	Very common	16.9	5.5

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

b. 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, campylobacter bacteraemia.

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

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

e. 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, epidermolysis.

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 (99.0%), hypotension (21.0%), and hypoxia (11.4%) and 33% 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

There has been no 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: not yet assigned

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, anti-drug antibodies (ADA) were detected in 8.3% 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 15.2 (2.4, 24.2) 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)	19 (15.4%)
Complete response (CR)	25 (20.3%)

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

Very good partial response (VGPR)	25 (20.3%)
Partial response (PR)	6 (4.9%)
Complete response rate (sCR+CR), n (%) (95% CI)	44 (35.8%) (27.3, 44.9)
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 6 months (95% CI)	89.1 (79.5, 94.4)
Rate at 9 months (95% CI)	80.7 (69.5, 88.1)
Rate at 12 months (95% CI)	74.3 (62.3, 83.0)
Rate at 15 months (95% CI)	70.8 (58.2, 80.2)
MRD-negativity rate[a] in patients achieving CR or sCR and evaluable for MRD (29 of the 44 patients who reached CR/CRs were evaluable for MRD) n (%) 95% CI (%)	 26 (89.7%) (72.7, 97.8)

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, 69% (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 $m^2 \leq$ eGFR $<$ 90 mL/min/1.73 m^2) or moderate renal impairment (30 mL/min/1.73 $m^2 \leq$ 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

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

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

2 years.

After opening

Chemical and physical in-use stability after opening the vial, including storage in prepared syringes, has been demonstrated for 7 days at 2 °C to 8 °C and 24 hours at up to 30 °C.

From a microbiological point of view, 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 and would normally not be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions.

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

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. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1770/001
EU/1/23/1770/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 December 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Wyeth BioPharma
Division of Wyeth Pharmaceuticals LLC
One Burtt Road
Andover, MA 01810
USA

Name and address of the manufacturer responsible for batch release

Pfizer Service Company BV
10 Hoge Wei
1930 Zaventem
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where ELREXFIO is marketed, all patients/carers

who are expected to use elranatamab have access to/are provided with the Patient Alert Card which will inform and explain to patients the risks of CRS and neurologic toxicities, including ICANS. The Patient Alert Card also includes a warning message for healthcare provider treating the patient that the patient is receiving elranatamab.

The Patient Alert Card will contain the following key messages:

- A description of the key signs and symptoms of CRS and ICANS
- Reminder that they should remain within proximity of a healthcare facility, and be monitored for signs and symptoms daily for 48 hours after administration of the first 2 step-up doses
- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of CRS or ICANS present themselves
- The prescribing physician's contact details

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of elranatamab 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, the MAH shall submit the results of study C1071005 a Phase 3 Randomised Study of Elranatamab Monotherapy and Elranatamab + Daratumumab Versus Daratumumab + Pomalidomide + Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma who have received at least one prior line of therapy including lenalidomide and a PI.	June 2027
In order to further characterise the duration of response and long-term safety in subjects with multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, the MAH shall submit the final study report of C1071003, a Phase 2, open-label, multicentre, non-randomised study of elranatamab monotherapy in participants with MM who are refractory to at least one PI, one IMiD, and one anti-CD38 Ab.	March 2025

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (44 mg/1.1 mL)

1. NAME OF THE MEDICINAL PRODUCT

ELREXFIO 40 mg/mL solution for injection
elranatamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: edetate disodium, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial (44 mg/1.1 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1770/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (44 mg/1.1 mL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ELREXFIO 40 mg/mL injection
elranatamab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

44 mg/1.1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (76 mg/1.9 mL)

1. NAME OF THE MEDICINAL PRODUCT

ELREXFIO 40 mg/mL solution for injection
elranatamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 1.9 mL vial contains 76 mg of elranatamab (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: edetate disodium, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial (76 mg/1.9 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1770/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (76 mg/1.9 mL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ELREXFIO 40 mg/mL injection
elranatamab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

76 mg/1.9 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ELREXFIO 40 mg/mL solution for injection
elranatamab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ELREXFIO is and what it is used for
2. What you need to know before you are given ELREXFIO
3. How ELREXFIO is given
4. Possible side effects
5. How to store ELREXFIO
6. Contents of the pack and other information

1. What ELREXFIO is and what it is used for

ELREXFIO is a cancer medicine that contains the active substance elranatamab. It is used to treat adults with a type of cancer of the bone marrow called multiple myeloma.
It is used by itself for patients whose cancer has returned (relapsed) and stopped responding to previous treatments (refractory), who have had at least three other kinds of treatment and whose cancer has worsened since receiving the last treatment.

How ELREXFIO works
ELREXFIO is an antibody, a type of protein, which has been designed to recognise and attach to specific targets in your body. ELREXFIO targets B-cell maturation antigen (BCMA), which is found on multiple myeloma cancer cells, and cluster of differentiation 3 (CD3), which is found on T lymphocytes, a particular kind of white blood cell in your immune system. This medicine works by attaching to these targets and, by doing so, bringing the cancer cells and T cells together. This helps your immune system destroy the multiple myeloma cancer cells.

2. What you need to know before you are given ELREXFIO

You must not be given ELREXFIO
If you are allergic to elranatamab or any of the other ingredients of this medicine (listed in section 6).
If you are not sure if you are allergic, talk to your doctor or nurse before you are given ELREXFIO.

Warnings and precautions
Tell your doctor or nurse about all of your medical conditions before you are given ELREXFIO, including if you have had any recent infections.

Look out for serious side effects.

Tell your doctor or nurse right away if you experience any of the following:

- Signs of a condition known as 'cytokine release syndrome' (CRS). CRS is a serious immune reaction with symptoms such as fever, difficulty breathing, chills, headache, low blood pressure, fast heartbeat, feeling dizzy, and increased levels of liver enzymes in the blood.
- Effects on your nervous system. Symptoms include feeling confused, feeling less alert, or having difficulty speaking or writing. Some of these may be signs of a serious immune reaction called 'immune effector cell-associated neurotoxicity syndrome' (ICANS).
- Signs and symptoms of an infection such as fever, chills, fatigue, or difficulty breathing.

Tell your doctor or nurse if you notice any signs of the above.

ELREXFIO and vaccines
Talk to your doctor or nurse before you are given ELREXFIO if you have had a recent vaccination or are going to have a vaccination.

You should not receive live vaccines within the four weeks before your first dose of ELREXFIO, while you are treated with ELREXFIO, and at least four weeks after stopping treatment with ELREXFIO.

Tests and checks
Before you are given ELREXFIO, your doctor will check your blood counts for signs of infection. If you have any infection, it will be treated before you start ELREXFIO. Your doctor will also check if you are pregnant or breast-feeding.

During treatment with ELREXFIO, your doctor will monitor you for side effects. Your doctor will monitor you for signs and symptoms of CRS and ICANS for 48 hours after each of your first two doses of ELREXFIO. Your doctor will also regularly check your blood counts, as the number of blood cells and other blood components may decrease.

Children and adolescents
ELREXFIO is not intended for children or adolescents below 18 years of age. This is because it is not known how the medicine will affect them.

Other medicines and ELREXFIO
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines (e.g., cyclosporine, phenytoin, sirolimus, and warfarin). This includes medicines you can get without a prescription, and herbal medicines.

Pregnancy and breast-feeding
It is not known if ELREXFIO affects an unborn baby or if it passes into breast milk.

<u>Pregnancy-information for women</u>

ELREXFIO is not recommended during pregnancy.

Tell your doctor or nurse before receiving ELREXFIO if you are pregnant, think you might be pregnant or are planning to have a baby.

If you are able to become pregnant, your doctor should do a pregnancy test before you start treatment.

If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away.

<u>Contraception</u>

If you could become pregnant, you must use effective contraception during treatment and for 6 months after stopping treatment with ELREXFIO.

Breast-feeding

You should not breast-feed during treatment and for 6 months after stopping treatment with ELREXFIO.

Driving and using machines
Some people may feel tired, dizzy, or confused while receiving ELREXFIO. Do not drive, use tools, or operate machines until at least 48 hours after each of your 2 step-up doses, and until your symptoms improve, or as instructed by your healthcare professional.

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

3. How ELREXFIO is given

How much is given
You will receive ELREXFIO under the supervision of a healthcare professional experienced in cancer treatment. The recommended dose of ELREXFIO is 76 mg, but the first two doses will be lower.

ELREXFIO is given as follows:
- You will receive a first step-up dose of 12 mg on Day 1 of Week 1.
- You will then receive a second step-up dose of 32 mg on Day 4 of Week 1.
- From Week 2 to Week 24 (Day 1), you will receive a full treatment dose of 76 mg once a week, as long as you are getting benefit from ELREXFIO.
- From Week 25 onwards, your doctor may change your treatment from once a week to once every two weeks, as long as your cancer has responded to ELREXFIO treatment.

You should stay close to a healthcare facility for 48 hours after each of the first two step-up doses in case you have side effects. Your doctor will monitor you for side effects for 48 hours after each of your first two doses.

How the medicine is given
ELREXFIO will always be given to you by your doctor or nurse as an injection under your skin (subcutaneous). It is given in the stomach area or thigh.

You may get a reaction at the injection site including, redness of the skin, pain, swelling, bruising, rash, itching, or bleeding. These effects are usually mild and clear up by themselves without the need for any additional treatment.

Other medicines given during treatment with ELREXFIO
You will be given medicines one hour before each of your first three doses of ELREXFIO. These help to lower the chance of side effects, such as cytokine release syndrome (see section 4). These medicines may include:
- Medicines to reduce the risk of fever (such as paracetamol)
- Medicines to reduce the risk of inflammation (corticosteroids)
- Medicines to reduce the risk of an allergic reaction (antihistamines, such as diphenhydramine)

You may also be given these medicines for later doses of ELREXFIO based on any symptoms you have after taking ELREXFIO.

You may also be given additional medicines based on any symptoms you experience or your medical history.

If you are given more ELREXFIO than you should
This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you for side effects.

If you miss your appointment to have ELREXFIO
It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Get medical help straight away if you get any of the following serious side effects, which may be severe and can be fatal.

Very common (may affect more than 1 in 10 people):
- Cytokine release syndrome, a serious immune reaction that may cause fever, difficulty breathing, chills, dizziness or light-headedness, fast heartbeat, increased liver enzymes in your blood;
- Low levels of neutrophils (a type of white blood cell that fights infection; neutropenia);
- Low levels of antibodies called 'immunoglobulins' in the blood (hypogammaglobulinaemia), which may make infections more likely;
- Infection, which may include fever, chills, fatigue, or shortness of breath.

Common (may affect up to 1 in 10 people):
- Immune effector cell-associated neurotoxicity syndrome (ICANS), a serious immune reaction that may cause effects on your nervous system. Some of the symptoms are:
    - Feeling confused
    - Feeling less alert
    - Having difficulty speaking or writing

Tell your doctor right away if you notice any of the above-listed serious side effects.

Other side effects
Other side effects are listed below. Tell your doctor or nurse if you get any of these side effects.

Very common (may affect more than 1 in 10 people):
- Low levels of red blood cells (anaemia)
- Feeling tired or weak
- Nose and throat infection (upper respiratory tract infection)
- Reactions at or near the injection site, including redness of the skin, itching, swelling, pain, bruising, rash, or bleeding
- Diarrhoea
- Lung infection (pneumonia)
- Low levels of blood platelets (cells that help blood to clot; thrombocytopenia)
- Low levels of a type of lymphocytes, a type of white blood cell (lymphopenia)
- Fever (pyrexia)
- Decreased appetite
- Skin rash
- Dry skin
- Pain in your joints (arthralgia)
- Low levels of potassium in the blood (hypokalaemia)

- Feeling sick (nausea)
- Headache
- Difficulty breathing (dyspnoea)
- Blood poisoning (sepsis)
- Low number of white blood cells (leucopenia)
- Increased level of liver enzymes in the blood (transaminases increased)
- Nerve damage in legs and/or arms that may cause tingling, numbness, pain, or loss of sensation (peripheral neuropathy)
- Infection of the parts of the body that collect and pass out urine (urinary tract infection)

Common (may affect up to 1 in 10 people):
- Low level of phosphates in the blood (hypophosphataemia)
- Low number neutrophils in the blood, combined with a fever (febrile neutropenia)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store ELREXFIO

ELREXFIO will be stored at the hospital or clinic by your doctor.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C). Do not freeze.

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

Chemical and physical in-use stability after opening the vial, including storage in prepared syringes, has been demonstrated for 7 days at 2 °C to 8 °C and 24 hours at up to 30 °C.

From a microbiological point of view, 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 and would normally not be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions.

Do not use this medicine if you notice discolouration or other visible signs of deterioration.

6. Contents of the pack and other information

What ELREXFIO contains
- The active substance is elranatamab. ELREXFIO comes in two different package sizes:
    - One 1.1 mL vial contains 44 mg of elranatamab (40 mg/mL).
    - One 1.9 mL vial contains 76 mg of elranatamab (40 mg/mL).

The other ingredients are edetate disodium, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, water for injections (see "ELREXFIO contains sodium" in section 2).

What ELREXFIO looks like and contents of the pack
ELREXFIO 40 mg/mL solution for injection (injection) is a colourless to pale brown liquid.

ELREXFIO is supplied in two strengths. Each carton pack contains 1 glass vial.

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This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

ELREXFIO 40 mg/mL solution for injection is supplied as 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 1) 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 1. 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

After opening, the vial and dosing 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, unless preparation has taken place in controlled and validated aseptic conditions. After opening, including storage in syringes prepared in an aseptic environment, ELREXFIO is stable for 7 days at 2 °C to 8 °C and 24 hours at up to 30 °C.

Administration instructions

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

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 of the thigh.

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

Traceability

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

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.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for elranatamab, the scientific conclusions of PRAC are as follows:

In view of available data on cytomegalovirus infection from clinical trial and spontaneous reports, including in 21 cases a close temporal relationship, and in 4 cases a positive re-challenge, considers a causal relationship between elranatamab and cytomegalovirus infection is at least a reasonable possibility. The PRAC concluded that the product information of products containing elranatamab should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for elranatamab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing elranatamab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.