Indication	For the treatment of relapsed or refractory myeloma in patients who have relapsed or are refractory to their last anti-myeloma regimen AND have received at least 3 prior systemic therapies which must have included at least one proteasome inhibitor, at least one immunomodulatory agent and at least one anti-CD38 antibody. NB Patients with amyloidosis or POEMS syndrome are not eligible for elranatamab treatment. NB patients previously treated with any bispecific antibody targeting BCMA and CD3 (e.g. teclistamab) are not eligible for elranatamab.
Treatment Intent	Disease Modification
Frequency and number of cycles	Cycle 1 step up regime. Cycle 2 repeat every 7 days for 23 cycles. Cycle 25 onwards (patients who have received at least 24 weeks of treatment and have achieved a response) Repeat every 14 days. Continue until disease progression or unacceptable toxicity or patient choice to stop treatment. A formal medical review as to whether treatment should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, U&Es and LFTs prior to each dose, proceed with treatment if neuts >/= 0.5 without febrile neutropenia, Hb >/= 80g/L, PLT >/= 25 (if PLT 25-50 with bleeding, see table 3). If blood parameters not met, withhold treatment until blood counts resolve. • **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 policy. • **Hepatic impairment:** No dose adjustment is recommended in mild hepatic impairment (total bilirubin > 1 to 1.5 × ULN and any AST, or total bilirubin </= ULN and AST > ULN). No data in moderate or severe impairment. • **Renal impairment**: No dose adjustment is recommended in patients with mild to moderate renal impairment (CrCl >30ml/min). Limited data in severe impairment, consultant decision. • **Management of adverse reactions and dose adjustments:** o Clear arrangements must be in place for the patient to be monitored for signs and symptoms of toxicities including **CRS and ICANS** for 48 hours after administration of the 2 step up doses in cycle 1 of elranatamab treatment and the patient should be instructed to remain within easy access to the hospital for these 48-hour periods following cycle 1, day 1 and cycle 1, day 4. o Healthcare professionals must be familiar with the grading of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, the required monitoring and management and the indications for use of tocilizumab, and have all undergone training in these clinical issues Tocilizumab should be immediately available if required for the

	treatment of CRS, clinicians should ensure there is access to an additional dose (in case it is required) which is given >/= 8 hours after the first dose. ○ No recommended dose modification. Dose delay may be required to manage toxicity. See **tables 1, 2 and 3** for guidance on dose management. ○ If a dose interruption is required follow the guidance in **table 4** for restarting treatment. ○ **Cytokine release syndrome:** At the first sign of CRS, elranatamab should be withheld, and the patient should be immediately evaluated for hospitalisation. ○ See **table 1** for CRS dose modification and management guidance. ○ All patients must be counselled on the risk, signs and symptoms of CRS and advised to contact their healthcare team immediately if they experience signs and symptoms of CRS. ○ **Neurologic toxicities, including ICANS** have occurred in patients receiving elranatamab. ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema. ○ Patients who experience Grade 2 or higher ICANS with the previous dose of elranatamab should be instructed to remain within easy access to the hospital and be monitored for signs and symptoms daily for 48 hours following the next dose. ○ See **table 2** for ICANS dose modification and management guidance. • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** no formal drug interaction studies have been performed. The initial release of cytokines associated with the start of treatment 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. • **Driving:** Due to the potential for ICANS, patients should be advised not to drive or operate heavy or 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. • Patients should carry the elranatamab patient alert card at all times.
References	CDF V1.333 accessed online KMCC protocol HAEM-MYEL-052 V1

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1. 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 elranatamab. 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 elranatamab. • Monitor patients daily for 48 hours following the next dose of elranatamab. 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 4 for recommendations on restarting elranatamab after dose delays.
d. Low-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is > 6 L/min.

Table 2. 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 elranatamab. 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 elranatamab. Instruct patients to remain within proximity of a healthcare facility.
Grade 3 (Recurrent)	ICE score 0-2[c] or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local oedema on neuroimaging[d]	• Permanently discontinue 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. • Provide supportive therapy, which may include intensive care.

Table 2 continued

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 4 for recommendations on restarting elranatamab after dose delays. f. All references to dexamethasone administration are dexamethasone or equivalent medicinal products.		

Table 3. Recommended actions for other adverse reactions

Adverse reactions	Severity	Actions
Haematologic adverse reactions	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]	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 4 for recommendations on restarting elranatamab after dose delays
* Other than CRS and ICANS.

Table 4. Recommendations for restarting treatment 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 elranatamab dose.

Cycle 1 only (7 days): step up dosing schedule

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Paracetamol	1000mg	PO		Give 60 minutes prior to the elranatamab injection.
	Chlorphenamine	4mg	PO		
	Dexamethasone	20mg	PO		
	Omeprazole	20mg	PO		
	ELRANATAMAB	**12mg**	**SC**		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue of the thigh. Do not inject into areas where the skin is red, bruised, tender, hard, or areas where there are scars.
Day 4	Paracetamol	1000mg	PO		Give 60 minutes prior to the elranatamab injection.
	Chlorphenamine	4mg	PO		
	Dexamethasone	20mg	PO		
	Omeprazole	20mg	PO		
	ELRANATAMAB	**32mg**	**SC**		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue of the thigh. Do not inject into areas where the skin is red, bruised, tender, hard, or areas where there are scars.

Cycle 2 to cycle 24 repeat every 7 days
(A minimum of 6 days should be maintained between doses of elranatamab.)

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Paracetamol*	1000mg	PO		Give 60 minutes prior to the elranatamab injection.
	Chlorphenamine*	4mg	PO		
	Dexamethasone*	20mg	PO		
	Omeprazole*	20mg	PO		
	ELRANATAMAB	**76mg**	**SC**		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue of the thigh. Do not inject into areas where the skin is red, bruised, tender, hard, or areas where there are scars.

*Pre-meds can be withdrawn from cycle 3 unless previous reactions, or if a dose delay was required see table 4 for guidance on pre-med administration.

Cycle 25 onwards: repeat every 14 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Paracetamol*	1000mg	PO		Give 60 minutes prior to the elranatamab injection.
	Chlorphenamine*	4mg	PO		
	Dexamethasone*	20mg	PO		
	Omeprazole*	20mg	PO		
	ELRANATAMAB	**76mg**	**SC**		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue of the thigh. Do not inject into areas where the skin is red, bruised, tender, hard, or areas where there are scars.

*Pre-meds can be withdrawn from cycle 3 unless previous reactions, or if a dose delay was required see table 4 for guidance on pre-med administration.

TTO-dispense 28 days' supply on cycle 1 and then every 4 weeks.

TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	Take 10mg up to TDS when required. Do not take for more than 5 days continuously.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last elranatamab treatment dose).
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last elranatamab treatment dose).
	Allopurinol	300mg	PO	OD, starting 24hrs before first cycle and reviewed after 4 weeks. Prescribe continuing supply only if required from cycle 5 onwards.
	Consider antifungal prophylaxis			