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 immune-modulatory agent and at least one anti-CD38 antibody. NB Patients with amyloidosis or POEMS syndrome are not eligible for teclistamab treatment. NB patients previously treated with any bispecific antibody targeting BCMA and CD3 (e.g. elranatamab) are not eligible for teclistamab.
Treatment Intent	Disease Modification
Frequency and number of cycles	Cycle 1 step up regime Cycle 2 onwards repeat every 7 days to commence 7 days after day 5 of cycle 1. In patients who have a complete response or better for a minimum of 6 months consider reducing dose frequency to 1.5mg/kg 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 1). If blood parameters not met, withhold treatment until blood counts resolve. • Immunoglobulin levels should be monitored during treatment. • **Hepatic impairment:** No dose adjustment is recommended for patients with mild hepatic impairment. • **Renal impairment:** No dose adjustment is recommended for patients with mild or moderate renal impairment. • **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 3 step up doses in cycle 1. The patient should be monitored daily and instructed to remain within easy access to the hospital for these 48-hour periods cycle 1 day 1, day 3 and day 5. 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. A dose of tocilizumab should be immediately available if required. Access to an additional tocilizumab dose should be ensured within 8 hours of the first. o 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, treatment should be withheld, and the patient should be immediately evaluated for hospitalisation. ○ See **table 2** 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 teclistamab. 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 or first occurrence of Grade 3 with the previous dose of teclistamab 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 3** 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 from initiation of the step-up schedule, up to 7 days after the first maintenance dose or during a CRS event. During this time period, toxicity or medicinal product concentrations should be monitored in patients who are receiving concomitant sensitive CYP450 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 TECVAYLI ® (teclistamab) patient alert card at all times.
References	CDF list V1.333 accessed online KMCC protocol HAEM-MYEL-053 V1

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

Table 1: Recommended actions for adverse reactions following administration of teclistamab

Adverse reactions	**Grade**	**Actions**
Cytokine release syndrome[a]	Grade 1 • Temperature ≥ 38° C[b]	• Withhold until adverse reaction resolves. • See Table 2 for management of cytokine release syndrome. • Administer pre-treatment medicinal products prior to next dose.
	Grade 2 • Temperature ≥ 38° C[b] with either: • Hypotension responsive to fluids and not requiring vasopressors, or • Oxygen requirement of low-flow nasal cannula[c] or blow-by Grade 3 (Duration: less than 48 hours) • Temperature ≥ 38° C[b] with either: • Hypotension requiring one vasopressor with or without vasopressin, or • Oxygen requirement of high-flow nasal cannula[c], facemask, non-rebreather mask, or Venturi mask	• Withhold until adverse reaction resolves. • See Table 2 for management of cytokine release syndrome. • Administer pre-treatment medicinal products prior to next dose • Monitor patient daily for 48 hours following the next dose. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent or duration: more than 48 hours) • Temperature ≥ 38° C[b] with either: • Hypotension requiring one vasopressor with or without vasopressin, or • Oxygen requirement of high-flow nasal cannula[c], facemask, non-rebreather mask, or Venturi mask. Grade 4 • Temperature ≥ 38° C[b] with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), 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. • See Table 2 for management of cytokine release syndrome.

Table 1 continued: Recommended actions for adverse reactions following administration of teclistamab

Adverse reactions	**Grade**	**Actions**
Immune effector cell-associated neurotoxicity syndrome (ICANS)[d]	Grade 1	• Withhold until adverse reaction resolves. • See Table 3 for management of immune effector cell-associated neurotoxicity syndrome.
	Grade 2 Grade 3 (First occurrence)	• Withhold until adverse reaction resolves. • See Table 3 for management of immune effector cell-associated neurotoxicity syndrome. • Monitor patient daily for 48 hours following the next dose. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue therapy • See Table3 for management of immune effector cell-associated neurotoxicity syndrome.
Haematologic toxicities	Absolute neutrophil count less than 0.5× 10^9/L	• Withhold until absolute neutrophil count is 0.5× 10^9/L or higher.
	Febrile neutropenia	• Withhold until absolute neutrophil count is 1.0× 10^9/L or higher, and fever resolves.
	Haemoglobin less than 8 g/dL	• Withhold until haemoglobin is 8 g/dL or higher.
	Platelet count less than 25 000/µ L Platelet count between 25 000/µ L and 50 000/µ L with bleeding	• Withhold until platelet count is 25 000/µ L or higher and no evidence of bleeding.
Other adverse	Grade 3 Grade 4	• Withhold until adverse reaction improves to Grade 2 or better.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) grading for CRS (Lee et al 2019).
[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 anticytokine therapy (e.g., tocilizumab or corticosteroids).
[c] Low-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is >6 L/min.
[d] Based on ASTCT grading for ICANS.
[e] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

Table 2: Recommendations for management of cytokine release syndrome with tocilizumab and corticosteroids

Grade[e]	Presenting symptoms	Tocilizumab[a]	Corticosteroids[b]
Grade 1	Temperature ≥ 38° C[c]	May be considered	Not applicable
Grade 2	Temperature ≥ 38° C[c] with either: • Hypotension responsive to fluids and not requiring vasopressors, or • Oxygen requirement of low-flow nasal cannula[d] or blow-by	Administer tocilizumab[b] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement within 24 hours of starting tocilizumab, administer methylprednisolone 1 mg/kg intravenously twice daily, or dexamethasone 10 mg intravenously every 6 hours. Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.
Grade 3	Temperature ≥ 38° C[c] with either: • Hypotension requiring one vasopressor with or without vasopressin, or • Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily, or dexamethasone 10 mg intravenously every 6 hours. Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.
Grade 4	Temperature ≥ 38° C[c] with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), or • Oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above, or administer methylprednisolone 1 000 mg intravenously per day for 3 days, per physician discretion. If no improvement or if condition worsens, consider alternate immunosuppressants [b].

[a] Refer to tocilizumab prescribing information for details.
[b] Treat unresponsive CRS per institutional guidelines.
[c] 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 anticytokine therapy (e.g., tocilizumab or corticosteroids).
[d] Low-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is >6 L/min.
[e] Based on ASTCT grading for CRS (Lee et al 2019).

Table 3 Guidelines for management of immune effector cell-associated neurotoxicity syndrome (ICANS)

Grade	Presenting symptoms[a]	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score 7-9[b] Or, depressed level of consciousness[c]: awakens spontaneously.	Management of CRS per Table 2. Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.
		Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.	
Grade 2	ICE score 3-6[b] Or, depressed level of consciousness[c]: awakens to voice.	Administer tocilizumab per Table 2 for management of CRS. If no improvement after starting tocilizumab, administer dexamethasone[d] 10mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.	
Grade 3	ICE score 0-2[b] Or, depressed level of consciousness[c]: awakens only to tactile stimulus, or seizures[c], 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[c].	Administer tocilizumab per Table 2 for management of CRS. In addition, administer dexamethasone[d] 10mg intravenously with the first dose of tocilizumab, and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.	
Grade 4	ICE score 0[b] Or, depressed level of consciousness[c] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[c], either: • life-threatening prolonged seizure (>5 minutes), or	Administer tocilizumab per Table 2 for management of CRS. As above, or consider administration of methylprednisolone 1000 mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1000 mg per day intravenously for 2 or more days.	As above, or consider administration of methylprednisolone 1000 mg per day intravenously for 3 days; if improves, then manage as above.
		Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed. In case of raised intracranial pressure/cerebral oedema, refer to institutional guidelines for management.	

	• repetitive clinical or electrical seizures without return to baseline in between, or motor findings[c]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure / cerebral oedema[c], 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	

[a] Management is determined by the most severe event, not attributable to any other cause.
[b] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., " show me 2 fingers" or " close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point; and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.
[c] Attributable to no other cause.
[d] All references to dexamethasone administration are dexamethasone or equivalent.

Table 4 Recommendations for restarting therapy after dose delay

Last dose administered	**Duration of delay from the last dose administered**	**Action**
Step-up dose 1	More than 7 days	Restart step-up dosing schedule at Step-up dose 1 (0.06 mg/kg)[a]
Step-up dose 2	8 days to 28 days	Repeat Step-up dose 2 (0.3 mg/kg)[a] and continue step-up dosing schedule.
	More than 28 days	Restart step-up dosing schedule at Step-up dose 1 (0.06 mg/kg)[a]
Any maintenance doses	8 days to 28 days	Continue at last maintenance dose and schedule.
	More than 28 days	Restart step-up dosing schedule at Step-up dose 1 (0.06 mg/kg)[a]
[a] Pre-treatment medicinal products should be administered prior to dose and patients monitored accordingly.		

Cycle 1 only: Step up dosing schedule

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Paracetamol	1000mg	PO		Give 60 to 180 minutes prior to the teclistamab injection.
	Chlorphenamine	4mg	PO		
	Dexamethasone	16mg	PO		
	TECLISTAMAB	**0.06mg/kg**	SC		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, injections should be at least 2 cm apart. Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.
3	Paracetamol	1000mg	PO		Give 60 to 180 minutes prior to the teclistamab injection.
	Chlorphenamine	4mg	PO		
	Dexamethasone	16mg	PO		
	TECLISTAMAB**	**0.3mg/kg**	SC		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, injections should be at least 2 cm apart. Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.
5	Paracetamol	1000mg	PO		Give 60 to 180 minutes prior to the teclistamab injection.
	Chlorphenamine	4mg	PO		
	Dexamethasone	16mg	PO		
	TECLISTAMAB***	**1.5mg/kg**	SC		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, injections should be at least 2 cm apart. Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.

**Step-up dose 2 may be given between two to seven days after Step-up dose 1.
***First maintenance dose may be given between two to seven days after Step-up dose 2. This is the first full maintenance dose (1.5 mg/kg).

Cycle 2 onwards: Repeat every 7 days
NB Cycle 2 Day 1 must be 7 days after day 5 of cycle 1.
(A minimum of 5 days should be maintained between doses of teclistamab.)

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Paracetamol*	1000mg	PO		Give 60 to 180 minutes prior to the teclistamab injection.
	Chlorphenamine*	4mg	PO		
	Dexamethasone*	16mg	PO		
	TECLISTAMAB	**1.5mg/kg**	SC		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, injections should be at least 2 cm apart. Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.

*Pre-meds can be withdrawn from cycle 2 unless previous reactions, or if a dose delay was required see table 4 for guidance on pre-med administration.

TTO dispense on cycle 1 and then every 4th cycle onwards.

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 teclistamab treatment dose).
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last teclistamab treatment dose).
	Allopurinol	300mg	PO	OD, starting 24hrs before first cycle and reviewed after 4 weeks. Prescribe continuing supply if required.
	Consider antifungal prophylaxis			

Alternative dose schedule for patients who have a complete response or better for a minimum of 6 months Repeat every 14 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Paracetamol*	1000mg	PO		Give 60 to 180 minutes prior to the teclistamab injection.
	Chlorphenamine*	4mg	PO		
	Dexamethasone*	16mg	PO		
	TECLISTAMAB	**1.5mg/kg**	SC		Inject into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, it may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, injections should be at least 2 cm apart. Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.
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 teclistamab treatment dose).	
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last teclistamab treatment dose).	
	Consider antifungal prophylaxis				

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