Indication	The treatment of relapsed or refractory multiple myeloma following 2 or 3 prior lines of systemic treatment. NB: Induction chemotherapy and stem cell transplant is considered to be 1 line of therapy.
Treatment Intent	Disease Modification
Frequency and number of cycles	Every 28 days. Continue until progressive disease or unacceptable toxicity, whichever occurs first.
Monitoring parameters pre-treatment	• Virology screening should be checked prior to the start of treatment. • FBC, U&Es, clotting screen and LFT prior to each cycle. Monitor FBC every week for the first 2 cycles, then every 2 weeks during cycle 3 and then prior to each cycle. Neuts must be >/=1.0 and PLT >/=75 prior to each cycle. • <u>Renal impairment</u>: o Ixazomib: Recommended dose of 3 mg in severe renal impairment (<30ml/min) or end-stage renal disease (ESRD) requiring dialysis. o Lenalidomide: CrCl 30-49ml/min, give 10mg od (the dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment); CrCl <30ml/min, give 15mg on alternate days. End stage renal disease (CrCl <30ml/min requiring dialysis) give 5mg od. NB an alternative dosing schedule which may be considered, but is not within the licence, is: CrCl 30-49ml/min, give 25mg on alternate days; CrCl <30ml/min, give 25mg twice a week. o Allopurinol: Ensure renal function is normal before prescribing allopurinol (usual dose is 300mg od). Reduce Allopurinol dose to 100mg od if CrCl is 10-20ml/min. Reduce Allopurinol dose to 100mg on alternate days if CrCl is <10ml/min. • <u>Hepatic impairment:</u> o Ixazomib: recommend dose of 3 mg in the presence of moderate or severe hepatic impairment (bilirubin > 1.5 x ULN) o Lenalidomide: no specific dose recommendations • <u>Dose reductions (DR):</u> o Ixazomib: 1st DR to 3mg, 2nd DR to 2.3mg. If this is not tolerated discontinue o Lenalidomide: 1st DR to 15mg, 2nd DR to 10mg, 3rd DR to 5mg o Non-haematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or ≤ Grade 1 prior to restarting treatment. o See table 1 for dose modifications

	• <u>Drug interactions</u>
	  ○ Avoid concomitant administration of ixazomib with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort). Closely monitor patients for disease control if co-administration with a strong CYP3A inducer cannot be avoided.
	  ○ Monitoring of digoxin concentration is advised during lenalidomide treatment with concomitant use.
	  ○ Patients on oral hypoglycaemic agents require close monitoring of blood sugar levels.
	
	• A delayed or missed ixazomib dose should not be taken within 72 hours of the next scheduled dose.
	• A 20mg starting dose of dexamethasone may be considered in the elderly or if steroid-related side effects develop
	• Consider PCP prophylaxis/ antifungal therapy if lymphocyte count <1.0 x 10^9/L
	• Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored. Consider prescribing prophylactic anticoagulation.
	• Lenalidomide Prescription Authorisation Form must be completed at time of prescribing
	• Ensure patient is informed of requirement for strict contraception precautions during treatment with Lenalidomide. Follow Lenalidomide risk management programme. Pregnancy test every 4 weeks if patient is of child-bearing potential.
	• Male and female patients who are able to have children must use **effective contraceptive measures during and for 90 days following treatment**.
	• For oral self-administration: <u>refer to local Trust policy on oral anti-cancer medicines</u> and supply Patient Information Leaflet.

Reference(s)	SmPC (Ninlaro and Revlimid) accessed online 19/12/17 Changes made in line with 'SOP for removal of ranitidine on KMCC protocols and on aria regimens'

NB For funding information, refer to the SACT funding spreadsheet

Table 1: Dose modifications guidelines for ixazomib in combination with lenalidomide and dexamethasone	
Haematological toxicities	**Recommended actions**
Thrombocytopenia (platelet count)	
Platelet count < 30 x 10^9/L	• Withhold ixazomib and lenalidomide until platelet count ≥ 30 x 10^9/L • Following recovery, resume lenalidomide at the next dose level and resume IXAZOMIB at its most recent dose. • If platelet count falls to < 30 x 10^9/L again, withhold IXAZOMIB and lenalidomide until platelet count ≥ 30 x 10^9/L. • Following recovery, resume IXAZOMIB at the next lower dose and resume lenalidomide at its most recent dose.*
Neutropenia (absolute neutrophil count)	
Absolute neutrophil count < 0.5 x 10^9/L	• Withhold ixazomib and lenalidomide until absolute neutrophil count is ≥ 0.5 x 10^9/L. Consider adding G-CSF as per clinical guidelines. • Following recovery, resume lenalidomide at the next dose level and resume ixazomib at its most recent dose. • If absolute neutrophil count falls to < 0.5 x 10^9/L again, withhold ixazomib and lenalidomide until absolute neutrophil count is ≥ 0.5 x 10^9/L. • Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.*
Non-haematological toxicities	**Recommended actions**
Rash	
Grade[+] 2 or 3	• Withhold lenalidomide until rash recovers to ≤ Grade 1. • Following recovery, resume lenalidomide at the next lower dose level. • If Grade 2 or 3 rash occurs again, withhold ixazomib and lenalidomide until rash recovers to ≤ Grade 1. • Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose.*
Grade 4	Discontinue treatment regimen.
Peripheral neuropathy	
Grade 1 peripheral neuropathy with pain or Grade 2 peripheral neuropathy	• Withhold ixazomib until peripheral neuropathy recovers to ≤ Grade 1 without pain or patient's baseline. • Following recovery, resume ixazomib at its most recent dose.

Grade 2 peripheral neuropathy with pain or Grade 3 peripheral neuropathy	• Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or ≤ Grade 1 prior to resuming ixazomib. • Following recovery, resume ixazomib at the next lower dose.
Grade 4 peripheral neuropathy	Discontinue treatment regimen.
Other non-haematological toxicities	
Other Grade 3 or 4 non-haematological toxicities	• Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or at most Grade 1 prior to resuming ixazomib. • If attributable to ixazomib, resume ixazomib at the next lower dose following recovery.

***For additional occurrences, alternate dose modification of lenalidomide and Ixazomib**

Repeated every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	Ixazomib	4mg	po	Once a week on days 1, 8 and 15 Swallow whole with water at least one hour before or at least two hours after food. Do not crush, chew, or open capsules. (available as 2.3mg, 3mg and 4mg capsules)
	Lenalidomide	25mg	po	od on days 1-21 followed by 7 days rest (available as 2.5mg, 5mg, 10mg, 15mg capsules)
	Dexamethasone	40mg	po	Once a week on days 1, 8, 15 and 22
	Metoclopramide	10mg	po	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	po	bd
	Omeprazole	20mg	po	od
	Allopurinol	300mg	po	od for the first cycle then review
	Loperamide	2mg	po	Take 4mg (TWO capsules) initially, then 2mg (ONE capsule) after each loose stool when required. Max. 16mg (8 capsules) a day Dispense 30 capsules on cycle 1 then only if prescribed
	Consider prescribing prophylactic anticoagulation			