Indication	For previously treated (at least 1 prior treatment) follicular lymphoma (grades 1-3a); patients can be anti-CD20 antibody resistant or sensitive. NB The patient must not have had previous therapy with lenalidomide.
Treatment Intent	Disease modification.
Frequency and number of cycles	Repeat every 28 days. Rituximab should be stopped after 5 cycles. From cycle 2 rituximab may be given SC Maximum of 12 cycles of Lenalidomide. A formal medical review **MUST** occur by the end of the first 8 weeks of treatment to establish if treatment should continue.
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. • Cases of viral reactivation have been reported. • The conditions of the Pregnancy Prevention Programme must be fulfilled and the Lenalidomide Prescription Authorisation Form must be completed at time of prescribing. • FBC, U&Es and LFTs weekly for the first cycle, every 2 weeks for cycles 2 to 4 and then at the start of each cycle thereafter or more frequently if clinically indicated. • BP baseline and as clinically indicated. • **<u>Dose modification and adverse effects:</u>** • Patients with a large tumour burden or with lymphocytes >25 x 10^^{9}/l who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. These patients should be very closely monitored and consideration given to the use of a reduced infusion rate for the first infusion or a split dosing over two days during the first cycle. • Careful monitoring and evaluation for Tumour flare reaction (TFR) is recommended. Lenalidomide may continue in patients with Grade 1 or 2 reactions without dose interruption or modification. The decision to initiate symptomatic treatment e.g. NSAID or steroids for Grade 1 or 2 reactions is at the clinician's discretion. In the event of grade 3 or 4 reactions lenalidomide should be withheld and appropriate medical management started. When TFR resolves to </= Grade 1 restart lenalidomide at the same dose. • Tumour lysis syndrome (TLS): All patients should be well hydrated and receive TLS prophylaxis and carefully monitored for signs/symptoms of TLS. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), starting prior to cycle 1. The patient should be well hydrated until at least the end of the first week of the first cycle (For further information see SPC). Consider the use of rasburicase for patients with bulky disease; withhold allopurinol during treatment with rasburicase. Rasburicase should be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

	• Lenalidomide starting dose 20mg once daily on days 1-21, first dose reduction to 15mg once daily on days 1-21, second dose reduction to 10mg once daily on days 1-21, third and final dose reduction to 5mg once daily on days 1-21. • Dose adjustments of lenalidomide, during treatment and restart of treatment, are recommended to manage Grade 3 or 4 thrombocytopenia, neutropenia, or other Grade 3 or 4 toxicity judged to be related to lenalidomide. • For patients on a starting dose of 10 mg, in case of dose reduction to manage Grade 3 or 4 neutropenia or thrombocytopenia, or other Grade 3 or 4 toxicity judged to be related to lenalidomide do not dose below 5 mg every other day or 2.5 mg once daily. • **Haematological:** Treat when neutrophils >/= 1.0 x 10^9/L and/or platelets >/= 50x 10^9/L, unless secondary to lymphoma infiltration of bone marrow. • If neutrophils fall to < 1.0 x 10^9/L for a period of at least 7 days or if neutrophils fall to < 1.0 x 10^9/L and the patient has a temperature >/=38.5◦c or neutrophils fall to <0.5 x 10^9/L, interrupt lenalidomide treatment; once resolved resume treatment at the next lower dose. For each subsequent episode of neutropenia as previously defined, withhold until recovery and then decrease the dose of Lenalidomide to the next dose level. Do not dose < 5mg daily on days 1-21 every 28 days. • Thrombocytopenia: If platelets fall below 50 x 10^9/L interrupt lenalidomide treatment, once resolved resume treatment at the next lower dose. For each subsequent episode of thrombocytopenia (PLT <50), interrupt treatment and when resolved decrease the dose of Lenalidomide to the next dose level. Do not dose < 5mg daily on days 1-21 every 28 days. • **Non-haematological adverse effects:** • For other Grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ Grade 2 depending on the physician's discretion. • Lenalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, and should not be resumed following discontinuation from these reactions. • If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, lenalidomide must be permanently discontinued. • Treatment with lenalidomide has been associated with an increased risk of venous thromboembolism. All patients should be risk assessed and prophylactic anticoagulation considered. Patients with risk factors for myocardial infarction should be closely monitored. • Monitor patients for diarrhoea associated with lenalidomide and manage accordingly. Bile acid malabsorption should be considered and where appropriate a trial of colestyramine given. • **Hepatic Impairment:** • Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations. • **Renal Impairment:** Lenalidomide: if CrCl 30-59ml/min give 10mg OD; if the patient tolerates this dose for 2 cycles the dose may be escalated to 15mg OD. If CrCl <30ml/min and not on dialysis give 5mg OD, if CrCl <30ml/min and the patient is on dialysis give 5mg OD following dialysis. After initiation of lenalidomide therapy, subsequent

	lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance. Allopurinol: reduce dose in renal impairment. • **Infusion rates:** ○ Rituximab: First infusion – Initiate at 50 mg/hr. Increase at 50mg/hr increments every 30mins to 400mg/hr max. Subsequent infusions – Initiate infusion at 100mg/hr. Increase rate at 100mg/hr increments every 30mins to 400mg/hr max. From cycle 2 onwards rapid infusion may be used if requested by prescriber (patient must not have had a grade 3 or 4 reaction to previous rituximab treatment). In this case infuse first 100ml over 20 minutes, and if no reaction, infuse remaining 400ml over 60 minutes. Use rapid rituximab infusion chart. From cycle 2 onwards rituximab can be administered by subcutaneous injection. • **<u>Rituximab Infusion/Sub-cutaneous injection (SC) related reaction:</u>** • Consider withdrawing any anti-hypertensives 12 hours before treatment with Rituximab. • Ensure pre-medication of rituximab with chlorphenamine, hydrocortisone or prednisolone (if using SC rituximab) & paracetamol. Monitor rituximab infusion closely (complete monitoring form), watch for signs of dyspnoea, fever, rigors. If such symptoms occur stop infusion and seek medical advice. Infusion may be recommenced at half the previous rate, once symptoms have subsided. • Patients should be observed for at least 15 minutes following SC administration. A longer period may be appropriate in patients with increased risk of hypersensitivity reactions. • Anaphylaxis drugs must be available when treating with Rituximab. • **<u>Common drug interactions: (for comprehensive list refer to BNF/SPC)</u>** Lenalidomide may increase digoxin concentration, monitor digoxin levels during treatment. Increased risk of rhabdomyolysis when administered with statins Clinicians should be aware that combined oral contraceptives may increase the risk of venous thromboembolism when given with Lenalidomide. • **Missed dose:** If less than 12 hours after the usual administration time the patient should take the dose and continue as normal the following day. If more than 12 hours after the usual administration time the dose should be omitted and continue with the schedule the following day. • Pregnancy test – if patient is of child-bearing age (at least every 4 weeks). • In the event rituximab has to be discontinued for toxicity, lenalidomide can be continued up to the maximum of 12 cycles. • Patients should be advised that lenalidomide can have an effect on their ability to drive and use machines. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	SPC lenalidomide and rituximab accessed online 20.04.2023. KMCC protocol HAEM-NHL-087 V1

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

Cycle 1 only: cycle length 28 days

Days	Drug	Dose	Route	Infusion Duration	Administration
1, 8,15,22	Paracetamol	1gm	PO		Stat
	Chlorphenamine	10mg	IV	1 min	By slow injection
	Hydrocortisone	100mg	IV		Stat
	Commence Rituximab at least 30 mins – 1 hour after pre-medication.				
	RITUXIMAB	**375mg/m²**	IV	See notes above	Sodium chloride 0.9% 500ml
TTO	Drug	Dose	Route	Directions	
Day 1	**LENALIDOMIDE**	**20mg**	PO	OD for 21 days only. Followed by a 7 days' rest. The capsules should not be opened, broken or chewed. Take with water, either with or without food.	
	Metoclopramide	10mg	PO	10mg up to three times a day PRN. Do not take for more than 5 days continuously.	
	Allopurinol	300mg	PO	OD NB should be started at least 2 days prior to cycle 1. **CYCLE 1 only then review.**	
	Co-trimoxazole	480mg	PO	BD Monday, Wednesday and Friday.	
	Aciclovir	400mg	PO	BD	
	Chlorhexidine Mouthwash	10ml	mouthwash	Use topically as a mouthwash, rinsing mouth for at least 1 minute four times a day.	
	Consider prophylactic anticoagulation and prophylactic antifungals				

Cycles 2-5: IV administration repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Paracetamol	1gm	PO		Stat
	Chlorphenamine	10mg	IV	1 min	By slow injection
	Hydrocortisone	100mg	IV		Stat
	Commence Rituximab at least 30 mins – 1 hour after pre-medication.				
	RITUXIMAB	**375mg/m²**	IV	See notes above	Sodium chloride 0.9% 500ml
TTO	Drug	Dose	Route	Directions	
Day 1	**LENALIDOMIDE**	**20mg**	PO	OD for 21 days only. Followed by a 7 days' rest. The capsules should not be opened, broken or chewed. Take with water, either with or without food.	
	Metoclopramide	10mg	PO	10mg up to three times a day PRN. Do not take for more than 5 days continuously.	
	Co-trimoxazole	480mg	PO	BD Monday, Wednesday and Friday.	
	Aciclovir	400mg	PO	BD	
	Chlorhexidine Mouthwash	10ml	mouthwash	Use topically as a mouthwash, rinsing mouth for at least 1 minute four times a day. Dispense only if required.	
	Consider prophylactic anticoagulation and prophylactic antifungals				

Cycles 2-5: S/C administration repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Paracetamol	1gm	PO		Stat
	Chlorphenamine	4mg	PO		Stat
	Prednisolone	30mg	PO		Stat
	Commence Rituximab at least 30 mins – 1 hour after pre-medication.				
	RITUXIMAB	**1400mg**	SC	5 mins	Should only be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender or hard or areas where there are moles or scars.
	Observe for at least 15 minutes following administration of SC rituximab				
TTO	Drug	Dose	Route	Directions	
Day 1	**LENALIDOMIDE**	**20mg**	PO	OD for 21 days only. Followed by a 7 days' rest. The capsules should not be opened, broken or chewed. Take with water, either with or without food.	
	Metoclopramide	10mg	PO	10mg up to three times a day PRN. Do not take for more than 5 days continuously.	
	Co-trimoxazole	480mg	PO	BD Monday, Wednesday and Friday.	
	Aciclovir	400mg	PO	BD	
	Chlorhexidine Mouthwash	10ml	mouthwash	Use topically as a mouthwash, rinsing mouth for at least 1 minute four times a day. Dispense only if required.	
	Consider prophylactic anticoagulation and prophylactic antifungals				

Cycles 6-12: repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**LENALIDOMIDE**	**20mg**	PO	OD for 21 days only. Followed by a 7 days' rest. The capsules should not be opened, broken or chewed. Take with water, either with or without food.
	Metoclopramide	10mg	PO	10mg up to three times a day PRN. Do not take for more than 5 days continuously.
	Co-trimoxazole	480mg	PO	BD Monday, Wednesday and Friday.
	Aciclovir	400mg	PO	BD
	Chlorhexidine Mouthwash	10ml	mouthwash	Use topically as a mouthwash, rinsing mouth for at least 1 minute four times a day. Dispense only if required.
	Consider prophylactic anticoagulation and prophylactic antifungals			