SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

LENALIDOMIDE & DEXAMETHASONE Multiple Myeloma

PROTOCOL REF: MPHALEDEHA
(Version No. 1.2)

Approved for use in:

- Patients with previously untreated multiple myeloma ***(1st line treatment)*** who are ineligible for stem cell transplant and in whom thalidomide is contraindicated or cannot be tolerated ***(NICE TA587)***
- Patients who have received one previous line of treatment **only** for multiple myeloma, which included bortezomib, and are ineligible for stem cell transplant ***(i.e. 2nd line treatment) (NICE TA586).*** They must not have had prior lenalidomide treatment.
- Patients who have received two or more lines of prior therapies ***(i.e. 3rd line treatment) (NICE TA171)***

Blueteq registration required (NB separate forms depending on line of therapy)

Dosage:

For patients with previously untreated multiple myeloma (1st Line)

Drug	Dose	Route	Frequency
Lenalidomide	**25mg once daily**	PO	Day 1 to 21
Dexamethasone	**40mg once WEEKLY***	PO	Days 1, 8, 15 and 22

*Reduce dose to 20mg in patients >75 years

Cycle length: every 28 days. Continue until disease progressions or intolerance.

For patients with previously treated with at least one prior therapy

Drug	Dose	Route	Frequency
Lenalidomide	**25mg once daily**	PO	Day 1 to 21
Dexamethasone	**40mg once daily**	PO	**CYCLE 1 TO 4:** Days 1 to 4, 9 to 12 and 17 and 20 **CYCLE 5 ONWARDS:** Days 1 to 4

*Differing doses and frequencies of dexamethasone may be used at the discretion of the prescriber. Prescribers should carefully evaluate which dose of dexamethasone to use, considering the condition and disease status of the patient.

Cycle length: every 28 days. Continue until disease progressions or intolerance.

Administration:

- Lenalidomide capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.
- If a lenalidomide dose is missed and <12hours late the missed dose should be taken. Missed doses >12hours should be omitted and the next dose taken as scheduled.
- Dexamethasone tablets should be taken in the morning after food.
- The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the pregnancy prevention programme and provide patients with appropriate patient educational brochure and patient card.

Pregnancy Prevention Programme:

Due to the increased risk of birth defects associated fetal exposure to lenalidomide the following should be adhered to:

- A Treatment Initiation Form (TIF) must be completed prior to treatment initiation with lenalidomide
- A Prescription Authorisation Form (PAF) must be completed by the prescriber for each supply of lenalidomide. This must be approved by a pharmacist when verifying each

prescription and confirmation of dispensing completed by the relevant dispensing pharmacy. Supply must be completed within 7 days of the prescription generation.

- A maximum of 3 months can be supplied for men or women of non-child bearing potential
- A maximum of 1 month can be supplied for women of child bearing potential. A negative pregnancy test must be confirmed within 3 days of prescription generation.

Emetogenic risk:

Low risk

Supportive treatments:

- Allopurinol 300mg daily for 28 days (cycle one only)
- Aciclovir 400mg twice daily
- Co-trimoxazole 480mg once daily
- Nystatin 1mL four times daily **OR** Fluconazole 50mg once daily for antifungal prophylaxis (if higher doses of steroids being used - review each cycle)
- Omeprazole 20mg once daily - review each cycle
- Ondansetron 4-8mg TDS PRN for 5-7 days, usually prescribed for cycle 1 only
- VTE prophylaxis:
    - Dalteparin 5,000 units subcutaneous injection daily (or alternative prophylactic LMWH)
    - Therapeutic dose LMWH in high risk patients. Patients may continue previously established DOAC treatment or be switched to a LMWH.
    - Aspirin 75mg daily (for those patients who decline LMWHs or for those deemed to be low risk on long term treatment)
- Consider adding clarithromycin 500mg twice daily if poor response to initial treatment to augment effect of lenalidomide. Be mindful of drug-drug interactions. Dose can be reduced to 250mg twice daily if tolerability an issue. Avoid in patients with a history of *C. Difficile.*

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
	Creatinine Clearance (mL/min)	**Dose Adjustment**
Lenalidomide	30 – 50	10mg once daily*
	<30 not requiring dialysis	15mg alternate days
	End stage renal disease (<30)	5mg once daily

*The dose may be escalated to 15mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment

Hepatic Dose Modifications	
Lenalidomide	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Interactions:

Lenalidomide:

- Agents that may increase the risk of thrombosis, such as HRT should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone.
- **Digoxin** – concomitant administration with lenalidomide increased plasma exposure of digoxin, monitoring of the digoxin concentration is advised during lenalidomide treatment.
- **Statins** – there is an increased risk of rhabdomyolysis when statins are administered with lenalidomide. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Please refer to the SPC for full list of interactions and further information.

Main toxicities:

Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with low dose dexamethasone.
The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were: • Pneumonia (9.8%) • Renal failure (including acute) (6.3%) The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Multiple Myeloma: patients with at least one prior therapy
In two phase 3 placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination. The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were: • Venous thromboembolism (deep vein thrombosis, pulmonary embolism) • Grade 4 neutropenia The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment + PS recorded	X	X	X	X	Prior to every cycle
SACT Assessment	X	X	X	X	Prior to every cycle
FBC	X	X	X	X	(Weekly for the first month and then monthly thereafter unless clinically indicated). Prior to every cycle
Celgene Pregnancy Prevention Program Consent	X				
Celgene prescription authorization form		X	X	X	
U&E & LFTs, CrCl (Cockcroft and Gault)	X	X	X	X	Prior to every cycle
Bone profile	X				As clinically indicated
Virology screen Hep B and C/HIV	X				
Dental assessment	X				As clinically indicated
HbA1C	X				As clinically indicated
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X	X	X	Prior to every cycle
Neurological assessment (for neuropathy)	X	X	X	X	Prior to every cycle
Respiratory Rate					If clinically indicated
Blood glucose	X				Repeat if clinically indicated
Imaging as per NICE/network guidance and clinical indication	X				To restage as indicated
Pregnancy test	X				If clinically indicated
Thyroid function test	X				If clinically indicated
Height	X				
Weight	X	X	X	X	Prior to every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity:

Untreated / First line use of lenalidomide:

Cycle should proceed if:

ANC is ≥ 1.0 x 10^9/L	Platelets ≥ 50 x 10^9/L

Dose step reductions:

Dose Level	Lenalidomide	Dexamethasone
Starting dose	25mg	40mg
Dose level 1	20mg	20mg
Dose level 2	15mg	12mg
Dose level 3	10mg	8mg
Dose level 4	5mg	4mg
Dose level 5	5mg on alternate days	Not applicable

Dose reduction for both products can be managed independently

Thrombocytopenia:

When platelets	Recommended course
Fall to < 25 x 10^9/L	Stop lenalidomide dosing for remainder of cycle*
Return to ≥ 50 x 10^9/L	Decrease by one dose level when dosing resumed at next cycle

*If dose limiting toxicity occurs on > day 15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28 day cycle.

Neutropenia:

If neutropenia is the only toxicity at any dose level, consider adding G-CSF and maintain the dose level of lenalidomide.

When neutrophils	Recommended course
First fall to <0.5 x 10^9/L	Interrupt lenalidomide treatment
	If neutropenia is the only observed toxicity: Resume lenalidomide at starting dose once daily when returns to ≥ 1.0 x 10^9/L

	If dose-dependent haematological toxicities other than neutropenia are observed: Resume lenalidomide at dose level 1 – once daily when returns to ≥ 0.5 x 10^9/L
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
	Resume lenalidomide at next lower dose level once daily when returns to ≥ 0.5 x 10^9/L

For haematological toxicity the dose of lenalidomide may be re-introduced to the next higher dose level upon improvement in bone marrow function (no haematological toxicity for at least 2 consecutive cycles, ANC ≥ 1.5 x 10^9/L, with a platelet count ≥ 100 x 10^9/L at the beginning of a new cycle).

Previously treated myeloma (2nd Line and onwards):

Lenalidomide treatment must not be started if:

ANC < 1.0 x 10^9/L	Platelets < 75 x 10^9/L*

*Dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.

Dose step reductions

Dose Level	Lenalidomide
Starting dose	25mg
Dose level 1	15mg
Dose level 2	10mg
Dose level 3	5mg

Thrombocytopenia:

When platelets	Recommended course
Fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
	Resume lenalidomide at dose level 1 when returns to ≥ 30 x 10^9/L
	Interrupt lenalidomide treatment

For each subsequent drop below 30 x 10^9/L	When returns to ≥ 30 x 10^9/L - Resume lenalidomide at next lower dose level (dose level 2 or 3) once daily. Do not dose below 5mg once daily

Neutropenia:

If neutropenia is the only toxicity at any dose level, consider adding G-CSF and maintain the dose level of lenalidomide.

When neutrophils	Recommended course
First fall to <0.5 x 10^9/L	Interrupt lenalidomide treatment
	If neutropenia is the only observed toxicity: Resume lenalidomide at starting dose once daily when returns to ≥ 0.5 x 10^9/L
	If dose-dependent haematological toxicities other than neutropenia are observed: Resume lenalidomide at dose level 1 – once daily when returns to ≥ 0.5 x 10^9/L
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
	When returns to ≥ 0.5 x 10^9/L - Resume lenalidomide at next lower dose level (dose level 2, 3 or 3) once daily. Do not dose below 5mg once daily.

Non- Haematological toxicity:

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.

References:

1. Summary of Product Characteristics, Revlimid®, Lenalidomide, Celgene, last updated 23rd May 2019 [accessed on 10th May 2023] https://www.medicines.org.uk/emc
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3. NICE TA 171 – Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. Published: 18 June 2009 www.nice.org.uk [accessed on 10th May 2023]
4. NICE TA586. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib – Issue date: June 2019 www.nice.org.uk [accessed on 10th May 2023]
5. NICE TA587. Lenalidomide plus dexamethasone for previously untreated multiple myeloma. – Issue date: June 2019 www.nice.org.uk [accessed on 10th May 2023]

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
			To be completed by author
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June 2023	1.2	**Jennifer Gibson (Principal Pharmacist Haematology)**	**Transferred to new template. Added pregnancy prevention program section.**