

LENALIDOMIDE WITH DEXAMETHASONE

INDICATION

1. Newly diagnosed myeloma in patients considered ineligible for stem cell transplant. **Bluteq approval is required**
2. Relapsed myeloma after one prior therapy, which included bortezomib. **Bluteq approval is required**
3. Relapsed or refractory multiple myeloma in patients who have received two or more prior lines of therapy. [NICE TA171].

Note: lenalidomide and dexamethasone in combination with ixazomib is available through CDF in patients after 2 or 3 previous lines of therapy, this should be considered in appropriate eligible patients and started prior to patient receiving lenalidomide and dexamethasone. The CDF criteria mandate that all 3 drugs in the combination (i.e. ixazomib, lenalidomide and dexamethasone) must be commenced at the same time and ixazomib cannot be added in as an additional agent in the treatment of patients who have already previously commenced treatment with lenalidomide and dexamethasone.

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
 - FBC & film
 - Clotting screen
 - U&Es,
 - LFTs,
 - Calcium
 - Albumin
 - Uric acid
 - CRP
 - Thyroid Function.
 - Baseline random blood glucose level
 - ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
 - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
 - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
 - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
 - Serum free light chain assay (Freelite)
 - β_2 microglobulin
 - LDH
 - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below).
 - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.

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- Group and save
- Imaging as per NICE/network guidance and clinical presentation
- Bone marrow aspirate and trephine and immunophenotype if appropriate

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ

Additional Investigations

- Plasma viscosity if hyperviscosity suspected.
2. Fertility - all patients should be offered fertility advice, as appropriate.
 3. Hydration - fluid intake of at least 3 litres /day should be attempted.
 4. Document patient’s height and weight, dose on actual body weight.
 5. Treatment must be agreed at the relevant MDT.
 6. Document patient’s performance status.
 7. Counselling - all patients should receive verbal and written information on oral chemotherapy. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.
 8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent for the treatment including signing the Pregnancy Prevention Programme forms.

REGIMEN SPECIFIC PRE-ASSESSMENT

1. The conditions of the Lenalidomide Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the Pregnancy Prevention Programme.
2. Clinical Assessment of thrombo-embolic risk.

DRUG REGIMEN

Lenalidomide (Continuous therapy)	The starting dose is 25 mg orally once daily on days 1 to 21. See below for dose reductions.
WITH	
Dexamethasone	40 mg PO on days 1, 8, 15 and 22. NB: The dose may need to be reduced in the elderly or if steroid-related side effects develop.

CYCLE FREQUENCY:

Cycle length: 28 days – i.e. 3 weeks on lenalidomide then 1 week off.

Response should be assessed ideally after each cycle regularly. Suitable patients can continue on maintenance lenalidomide until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS

Myelosuppression:

Lenalidomide treatment should not normally be given if the Absolute Neutrophil Counts (ANC) < 1.0 x 10⁹/L, and/or platelet count < 30 x 10⁹/L. If the low counts are thought to be due to myeloma per se, the use of G-CSF and platelet support should be considered.

Recommended dose adjustments during treatment and to restart treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

Note: Consider re-escalating lenalidomide dose provide toxicities have completely resolved.

Starting dose = 25 mg/day.

Dose adjustments when lenalidomide is used in the newly diagnosed setting:

Dose reduction steps

Starting dose	25 mg
Dose level -1	20 mg
Dose level -2	15 mg
Dose level -3	10 mg
Dose level -4	5 mg
Dose level -5	2.5 mg

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

Neutropenia:

When neutrophils	Recommended Course
First fall to < 0.5 x 10 ⁹ /L	Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.
Return to ≥ 1 x 10 ⁹ /L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily
Return to ≥ 0.5 x 10 ⁹ /L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at the next lower dose level once daily

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For each subsequent drop below $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days
Return to $\geq 0.5 \times 10^9/L$	Resume lenalidomide at the next lower dose level once daily

Dose adjustments when lenalidomide is used in the relapsed setting:

Dose reduction steps

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

Thrombocytopenia:

When platelets	Recommended Course
First fall to $< 30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at the next lower dose level (e.g. 15 mg/day)
For each subsequent drop below $30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.

Neutropenia:

When neutrophils	Recommended Course
First fall to $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.
Return to $\geq 0.5 \times 10^9/L$ when neutropenia is the only observed toxicity	Resume lenalidomide at the starting dose (e.g. 25 mg once daily)
Return to $\geq 0.5 \times 10^9/L$ when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at the next lower dose level (at 15 mg once daily)
For each subsequent drop below $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days.
Return to $\geq 0.5 \times 10^9/L$	Resume lenalidomide at the next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.

Renal/Hepatic Impairment:

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Renal		Hepatic
30 ≤ CrCl < 50 ml/min	10mg once daily*	No formal studies. No specific dose recommendations
CrCl < 30 ml/min, no dialysis	15 mg every other day**	
CrCl < 30 ml/min, requiring dialysis	5 mg once daily***	
*Can increase to 15mg OD if no response and patient tolerating ** Can increase to 10mg OD if no response and patient tolerating *** On dialysis day, administer dose after dialysis/		

INVESTIGATIONS during treatment

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&E, Ca⁺⁺
- Ig's, paraprotein. Freelite assay if appropriate
- Urinary light chain if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl)<10ml/min)
- Consider prophylactic fluconazole 50mg OD if appropriate
- Consider prophylactic co-trimoxazole 480mg to 960mg OD on M/W/Fonly, if heavily pre-treated or previous autograft.
- Consider levofloxacin prophylaxis at 500mg od for 12 weeks (i.e. cycles 1-3) for all newly diagnosed myeloma patients. If this regimen is used in the relapsed setting, consider levofloxacin at clinician discretion, only in patients deemed at high risk of infections. Adjust dose for renal function
- Proton pump inhibitor or H2 antagonist at clinician's discretion
- Thromboprophylaxis/anticoagulation see VTE section below.
- Bone protection as per NCCN Bone Protection protocol MM.3
- Prescribe loperamide if needed for diarrhoea.
- Consider cholestyramine if suspicion of bile salt malabsorption with lenalidomide

EMETIC RISK

Minimal emetic risk.

ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

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- **Teratogenic:** The lenalidomide Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme.
- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with lenalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:
 1. Prophylactic low-molecular weight heparin OR
 2. Prophylactic. apixaban 2.5mg bd (check product specific information)

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors

If VTE occurs, lenalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

- **Rash:** Antihistamines and topical corticosteroids can often be used to treat limited, localized, treatment-related rash, but lenalidomide interruption or discontinuation should be considered for grade 2/3 rash. Re-challenge with lenalidomide is reasonable in patients who do not have a severe rash and will often allow continued treatment. Lenalidomide must be discontinued for angioedema, grade 4 rash, and exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected, and should not be resumed after discontinuation for these reactions
- **Myelosuppression:** including neutropenia and thrombocytopenia which may require dose interruptions and reductions. Monitor patients with neutropenia for signs of infection. Patients should be advised to monitor themselves for bleeding or bruising, especially if prophylactic VTE treatments are concomitantly administered. Follow dose modifications for haematological toxicity as per section above.
- **Diarrhea:** was reported in 42% of patients requiring use of antidiarrheal medication (loperamide), supportive care and adequate hydration. Bile salt malabsorption occurs in a small proportion of patients on lenalidomide, consider dietary adjustments with low fat meal intake and prescribing bile acid sequestrants (cholestyramine).
- **Drowsiness, somnolence and sedation:** Take the dose at night time. Lenalidomide may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking lenalidomide.
- **Peripheral neuropathy:** Patients should be advised to report prickling, numbness and paraesthesia. Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant neurotoxicity is uncommon.
- **Dizziness and orthostatic hypotension:** Patients should be advised that lenalidomide may

cause orthostatic hypotension and that, if affected, they should sit upright for a few minutes prior to standing up from a recumbent position.

- **There is an MHRA alert on an increased risk of secondary malignancies** in three large trials of lenalidomide treatment. The MHRA recommend vigilance in reporting such events promptly. Quoted incidence is 3 to 4% per annum.
- Hypothyroidism has been reported in patients on lenalidomide. Baseline assessment of thyroid function and ongoing monitoring is recommended.

REFERENCES

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2. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, Siegel D, Borrello I, Rajkumar SV, Chanan-Khan AA, Lonial S, Yu Z, Patin J, Olesnyckyj M, Zeldis JB, Knight RD; Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med.* 2007 Nov 22;357(21):2133-42.
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5. Revlimid® (lenalidomide) 25mg capules. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, November 2021
6. NICE. Interim treatment change options during the COVID-19 pandemic, endorsed by NHS England.. Last accessed: 20/05/2022

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, renal section, reference, pre assessment section	May 2016	4.3	May 2018
Dr Jaimal Kothari Consultant	Regimen specific pre assessment section included	May 2016	4.3	May 2018
Manuela Sultanova Service Coordinator	Formatting, Standardisation of wording in pre-assessment section, Wessex lab address and VTE	August 2017	4.4	May 2018
Network Protocol Review	Indication. VTE information. Standardise assessment, investigation, concurrent medication, adverse effects sections.	June 2018	4.5	June 2020
Myeloma Protocol Review 2019	Update of indications, dose modifications, and references	July 2019	4.6	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Update with new indications during COVID-19 pandemic	June 2020	4.7	June 2021
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	4.8	June 2021
NSSG Myeloma Group	Annual myeloma protocol review 2022	June 2022	4.9	June 2023
NSSG Myeloma Group	Updated concurrent medication section	Nov 2022	5.0	June 2023