

LENLIDOMIDE MAINTENANCE

INDICATION

Maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma. **Blueteq approval is required**

TREATMENT INTENT

Maintenance

GENERAL PRE-ASSESSMENT

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.
- 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

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Additional Investigations

1. 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 Celgene 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)	10 mg orally once daily on days 1 to 21. See dose modification section for dose reduction information
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CYCLE FREQUENCY:

Cycle length: 28 days – i.e. 3 weeks on lenalidomide then 1 week off. This dosing is based on NICE approval, which is different to SPC dose for maintenance

Patients can continue on maintenance lenalidomide until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS

Lenalidomide maintenance should be initiated after adequate haematological recovery following ASCT (approximately day +100) in patients without evidence of progression. Lenalidomide must not be started if the ANC is < 1.0 x 10⁹/L, and/or platelet counts are < 75 x 10⁹/L.

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Dose reduction steps:

Starting dose	10 mg days 1-21 every 28 days)
Dose level -1	5 mg (days 1-21 every 28 days)
Do not dose below 5 mg (days 1-21 every 28 days)	

This table of dose reduction steps has been modified based on current NICE TA dosing recommendation (10mg D1-21) which is different to SPC dosing

Thrombocytopenia:

When platelets	Recommended course
Falls to $< 30 \times 10^9/L$	Interrupt lenalidomide treatment
Returns to $\geq 30 \times 10^9/L$	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below $30 \times 10^9/L$	Interrupt lenalidomide treatment
Returns to $\geq 30 \times 10^9/L$	Discuss with consultant. Lenalidomide is not usually reduced below 5mg D 1-21 for this indication

Neutropenia:

When ANC	Recommended course
Falls to $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment
Returns to $\geq 0.5 \times 10^9/L$	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment
Returns to $\geq 0.5 \times 10^9/L$	Discuss with consultant. Lenalidomide is not usually reduced below 5mg D 1-21 for this indication

At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide

Renal/Hepatic Impairment:

Renal	Hepatic
$30 \leq CrCl < 50 \text{ ml/min}$ → 10mg once daily $CrCl < 30 \text{ ml/min, no dialysis}$ → 15 mg every other day* $CrCl < 30 \text{ ml/min, requiring dialysis}$ → 5 mg once daily**	No formal studies. No specific dose recommendations
* 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

- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min)
- Consider prophylactic fluconazole 50mg OD if appropriate at clinician discretion
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if counts recover post-transplant
- 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

- **Teratogenic:** The BMS 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

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- **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:** This can be managed with 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

1. Revlimid® (lenalidomide) 10mg capules. eMC UK Summary of Product Characteristics for Revlimid 10mg, BMS, November 2020
2. NICE TA. Lenalidomide maintenance treatment after an autologous stem cell transplant for newly diagnosed multiple myeloma. 2021. Available at:
<https://www.nice.org.uk/guidance/gid-tag430/documents/final-appraisal-determination-document> (last accessed: 03.02.2021)

REVIEW

Name	Revision	Date	Version	Review date
NSSG Myeloma Group	New protocol	February 2021	1.0	June 2021

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