Lenalidomide in combination with dexamethasone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant and are suitable for thalidomide-containing regimens.

**NCMAG Decision** | Routine off-patent use is **supported for the generic product.**

**Decision Rationale**

After consideration of all the available evidence regarding the benefits and risks, the Council were satisfied that the case had been made for the clinical and cost effectiveness of lenalidomide in combination with dexamethasone.
Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

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<th>Proposal Details</th>
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<tr>
<td><strong>Medicine Name</strong></td>
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<td><strong>Cancer type</strong></td>
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<td><strong>Proposed off-patent use</strong></td>
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<td><strong>Form</strong></td>
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<td><strong>Dose</strong></td>
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<th>Treatment Marketing Authorisation</th>
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<tr>
<td>Lenalidomide, as combination therapy with dexamethasone, or with bortezomib and dexamethasone, or with melphalan and prednisone, is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.</td>
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<tr>
<td>Current SMC accepted advice restricts to lenalidomide use in combination with dexamethasone and to patients unsuitable for thalidomide-containing regimen.</td>
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| Advice eligibility criteria | Not applicable |
1.0 Current Management Context

Multiple myeloma is an incurable haematological cancer caused by the proliferation of a clone of malignant plasma cells. This causes the destruction of bone and bone marrow leading to bone fractures, anaemia, low platelets, susceptibility to infections, high calcium levels in the blood and kidney dysfunction. In Europe the median age of diagnosis is 72 years and approximately 52% of patients will be alive 5 years after diagnosis.

Initial treatment for myeloma is divided into two categories – those that are eligible for high dose chemotherapy and autologous stem cell transplantation and those that are ineligible for transplantation. Eligibility for transplantation is based on patient preference, fitness and age (usually less than 70 years of age).

Within Scotland routinely available treatments for transplant ineligible patients are cyclophosphamide, thalidomide and dexamethasone attenuated (CTDa), or melphalan, prednisolone and thalidomide (MPT). CTDa has lower doses of steroid and a lower starting dose of thalidomide to the standard CTD regimen. Approximately 75% of patients are prescribed CTDa and 25% of patients are prescribed MPT. Both regimens are considered to have similar efficacy. Patients who are ineligible for thalidomide-based therapy can be routinely treated with bortezomib, melphalan, prednisolone (VMP), or lenalidomide, dexamethasone (Rd). CTDa, MPT and VMP are given for fixed durations, usually 6–8 months of treatment. Lenalidomide plus dexamethasone (Rd) is given continuously until disease progression or intolerance (Rd continuous).

Lenalidomide is an immunomodulatory drug leading to direct cytotoxic effects and changes in the tumour microenvironment and tumour cell apoptosis. Combining lenalidomide with corticosteroids has a synergistic effect and increases efficacy. Lenalidomide has serious teratogenic effects and must be prescribed via a pregnancy prevention programme. Rd is supported as a treatment option for this patient group in BSH, ESMO and National Comprehensive Cancer Network (NCCN) guidelines.

2.0 Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were lenalidomide, newly diagnosed multiple myeloma, ineligible for stem cell transplant. No filters were applied to limit the retrieval by study type. Titles and abstracts were screened by one
reviewer with decisions crossed-checked (~10% of titles) with another reviewer. The included publications were critically appraised using the following tools: The Cochrane risk of bias 2.0 tool and the International Society for Pharmacoeconomics and Outcomes Research Questionnaire to Assess the Relevance and Credibility of Network Meta-Analysis.

2.1 Evidence Review Summary | Clinical efficacy evidence

**Direct evidence comparing lenalidomide plus dexamethasone to MPT**

The key evidence to support this comparison is based on the final analysis of the phase III FIRST study. The study compared continuous cycles (until progression) of lenalidomide plus dexamethasone (Rd continuous, n=535) with 18 cycles of lenalidomide plus dexamethasone (Rd18, n=541) and with 12 cycles of the MPT regimen (n=547) in previously untreated patients with symptomatic multiple myeloma who were ≥65-year-old or, if younger than 65 years were unsuitable for transplant. The dosing was as per the licensing dosing for these regimens. Patients were randomised 1:1:1 to receive open-label treatment with Rd continuous, Rd18, or MPT and were stratified by age (≤75 vs >75 years), International Staging System disease stage (I/II vs III) and country. The primary study outcome was a comparison of progression-free survival (PFS) in Rd continuous versus MPT arms, defined as the time from randomisation to disease progression as defined by the International Myeloma Working Group uniform response criteria. The Rd18 regimen is off-label use and is not the indication proposed, therefore, the results for the Rd18 group will not be reported. The main secondary outcome was overall survival with additional secondary outcomes, which included overall response rate (ORR), time to next treatment (TTNT) and safety. Response to treatment was defined using the IMWG. Final data cut-off was January 21st 2016 and the median duration of follow-up was 67.2 months.

PFS improved with Rd continuous compared with MPT (hazard ratio [HR], 0.69; 95% confidence interval [CI] 0.59-0.79, P<0.00001). The median PFS was 26.0 months with Rd continuous and 21.9 months with MPT. Four-year PFS rate (proportions of patient who had not had a PFS event) also favoured Rd continuous compared to MPT (32.6% versus 13.6%, respectively). At the final data cut-off 56% of patients had died (286 and 337 deaths in the Rd continuous and MPT groups, respectively). There was a significant increase in median overall survival for the group treated with Rd continuous compared with the MPT regimen (HR 0.78, 95% CI 0.67-0.92). Median overall survival was 59.1 months with Rd continuous and 49.1 months with MPT. Median TTNT was longer with Rd continuous than with MPT (36.7 months versus 26.7 months, respectively).

Fifty-three percent of patients who received second-line treatment had bortezomib-based regimens (179/299 in the Rd continuous group and 170/381 in the MPT group). More patients in the Rd continuous group who received bortezomib as second-line therapy achieved a greater
response rate and a longer median length of time between the second-line and third-line treatment than patients in the MPT group (16.4 months versus 10.6 months, respectively).

**Patient-reported outcomes**

Health-related quality of life (HRQoL) data were collected during the FIRST trial using the myeloma-specific QLQ-MY20 Questionnaire, the generic oncology-related QLQ-C30 and the generic EuroQol EQ-5D questionnaires after 3, 6, 12 and 18 months of treatment and at study discontinuation. Both Rd treatment regimens and MPT improved HRQoL apart from during disease progression. The Rd group had clinically relevant improvements in HRQoL as measured by the EQ-5D at all post-baseline assessments apart from at month one while the MPT group had clinically relevant improvements only at month 3.

**Network Meta-analysis comparing Rd with CTD**

There is a lack of direct data comparing the Rd continuous regimen with cyclophosphamide, thalidomide, and dexamethasone (CTD), one of the standard of care treatment options. Indirect data are available from a network meta-analysis (NMA) comparing CTD and MPT. Studies were included in the NMA if they included newly diagnosed multiple myeloma patients who were ineligible for transplant. The NMA compared Rd continuous to CTD indirectly, based on data from the FIRST and Hungria et al trials. In addition to the full network the NMA included a simplified network for PFS and overall survival in comparators relevant for medicines licensed in Europe (Table 1). The NMA ranked treatments as the probability of being better than Rd continuous. The results of the NMA show the probability of CTD or MPT being better than Rd continuous as being 0% for both PFS and overall survival.

**Table 1: Network Meta-analysis results**

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<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>HR (95% CrI)</th>
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<tr>
<td>Overall survival</td>
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<tr>
<td>CTD versus Rd continuous</td>
<td>1.75 (1.30-2.36)</td>
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<tr>
<td>MPT versus Rd continuous</td>
<td>1.28 (1.09-1.50)</td>
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<tr>
<td>Progression free survival</td>
<td>1.98 (1.52-2.59)</td>
<td></td>
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<tr>
<td>HR (95% CrI)</td>
<td></td>
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<tr>
<td>MPT versus Rd continuous</td>
<td>1.45 (1.25-1.69)</td>
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Key: HR = hazard ratio; CrI = credible interval; Rd continuous = continuous lenalidomide and dexamethasone; CTD = cyclophosphamide, thalidomide and dexamethasone; MPT= melphalan, prednisone and thalidomide; NMA used random-effects model; Rd continuous was used as the reference comparison in the NMA with HR >1 demonstrating a benefit in favour of Rd continuous.
2.2 Evidence Review Summary | Safety evidence

Lenalidomide adverse events (AE) in this population are considered by the regulator to be generally manageable and acceptable\(^1\).

Based on data from the FIRST study, the Rd continuous regimen has a favourable AE profile compared with the MPT regimen for the following grade 3 or 4 AEs: neutropenia (30% versus 45%), febrile neutropenia (1% versus 3%) and peripheral sensory neuropathy (1% versus 9%). The reported rates of grade 3 or 4 thrombocytopenia and anaemia were similar between the groups. A higher proportion of grade 3 or 4 AE were reported in the Rd continuous group versus the MPT group for the following: infections (32% versus 17%), cataract (7% versus 1%), deep vein thrombosis (5% versus 1%) and diarrhoea (5% versus 3%). Reports of both haematologic and solid secondary primary malignancy were higher in the MPT group than the Rd continuous group\(^1\).

An NMA by Sekine et al ranked treatments from most to least tolerable for the following categories of AEs: thrombotic (MPT, Rd continuous, CTD), neurological (Rd continuous, MPT, CTD), infectious (MPT, Rd continuous, CTD) and haematological (CTD, Rd continuous, MPT)\(^1\). Despite Rd being given continuously compared to a fixed duration of treatment, Rd was comparable to MPT and CTD for haematological and thrombotic AE and was ranked as significantly more tolerable for neurological AE.

2.3 Evidence Review Summary | Clinical effectiveness considerations

Quality assessment of key clinical evidence

The FIRST study was an open-label international three group study. Overall, it was assessed as low-risk of bias. Selection bias was considered low because of the use of ‘validated interactive voice-response system’ and central randomisation. The open-label nature of the trial does pose potential for detection bias for PFS, safety and HRQoL outcomes, however, it should be noted that independent committees were used to review both the response data and safety data throughout the study.

The NMA was relevant to the proposal in terms of population, interventions and outcomes. Providing an indirect comparison with Rd continuous and CTD, the methodology was considered robust, although weaker areas of the analysis included lack of quality appraisal of the included studies, separate presentation of direct and indirect comparisons and no assessment of consistency between the direct and indirect evidence.
Lenalidomide plus dexamethasone increases survival in comparison to MPT

The final pre-specified analysis of the FIRST study, based on mature data (56% of patients had died), reported a significant increase in median overall survival for the group treated with Rd continuous compared with MPT. Differences in subsequent myeloma treatments may have confounded the overall survival results. The FIRST study results are supported by the results of the Facon NMA which included evaluation of CTD.²

Overall, results from the FIRST trial population are generalisable to the Scottish population

Reasons for patients aged under 65 being ineligible for transplant in the FIRST study included patient wishes, lack of availability of transplant and cost. This may have resulted in the study population including patients who may be transplant eligible in Scottish practice. In NHSScotland patients of suitable fitness up to aged 70 may be eligible for transplant. The median age within the FIRST trial was 73 (44-91). Data suggests patients treated in practice with MPT and CTDa are older than this.³ FIRST trial subgroup analysis between patients ≤ 75 years and > 75 years showed a consistent treatment effect for Rd continuous.

The duration of MPT in the study is longer than the duration used in practice

The intended treatment duration for MPT in the FIRST trial was 72 weeks with a median duration of 15.4 months.¹¹ Clinical practice in Scotland is for shorter courses of MPT, usually for 6-8 months. It is uncertain if the efficacy and safety outcomes for the regimen of MPT used in the study match the regimen of MPT used in practice.

Dose intensity for CTD and MPT is higher in clinical trials than those used in clinical practice.

Dose attenuation has become clinical practice since the pivotal trials supporting CTD and MPT were designed.¹⁸

Myeloma IX showed improved ORR of CTDa compared to Melphalan and Prednisolone but improvement in overall survival was hampered by adverse effects in the non-transplant eligible population.¹² Lower doses of steroids have been shown to improve tolerability and reduce mortality.²⁰

Subsequent Treatments

Rd continuous use in the proposed population setting is likely to impact on the treatment pathway as patients treated with Rd continuous in the first line setting are unlikely to receive Rd continuous in subsequent lines of therapy. Second and third line treatments within the FIRST trial are similar to those available in Scotland.
2.4 Evidence Review Summary | Benefit-risk balance

This is an on-label use which the regulator has judged to have a favourable benefit-risk balance\textsuperscript{16}. Rd continuous provides clinically meaningful benefits in PFS and overall survival and AEs are generally manageable.

Rd continuous is well tolerated within this treatment population with a manageable side effect profile and improvement in quality of life (QOL) versus MPT. The results of the NMA show the probability of CTD or MPT being better than Rd continuous as being 0\% for both PFS and overall survival.

The overall risk benefit for Rd is considered favourable.

2.5 Council Review | Benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council were satisfied that the case had been made for the clinical effectiveness for lenalidomide in combination with dexamethasone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant and are suitable for thalidomide-containing regimens.

3.0 Evidence Review Summary | Economic evidence

SMC has previously issued accepted restricted advice for the on-label use of lenalidomide (SMC 1096/15)\textsuperscript{2}. The case submitted to SMC by the manufacturing company included positioning for use in patients who were unsuitable for thalidomide-containing regimens. The key comparator for that case was the VMP (bortezomib, melphalan, prednisolone) regimen.

In order to assess the cost-effectiveness of continuous Rd in the subpopulation suitable for thalidomide-containing regimens, continuous Rd was compared to thalidomide-containing regimens (CTDa and MPT) as these treatments were considered the relevant comparators in Scottish practice. No published cost-utility analysis was identified in the literature search that compared continuous Rd to CTDa or MPT.

Following an approach from the NCMAG team, the manufacturer of the originator lenalidomide product, Bristol-Myers Squibb, kindly shared the health economic model used in their submission to NICE for this indication for the purpose of this NCMAG review. This model included a comparison of continuous Rd with MPT.
Type of economic evaluation

The model facilitated a cost-utility analysis using outcome data from the January 2016 data cut-off in the FIRST study. A hybrid model structure was used, consisting of a partitioned survival analysis using the Kaplan–Meier data for the first 92 weeks and a multi-state Markov model thereafter. The Markov model consisted of three states: progression free; progressive disease; and death. The model had a lifetime horizon of 25 years, a 28-day cycle length and applied a half-cycle correction. A UK National Health Service perspective was stated. Several adjustments were made in the model to increase generalisability to NHSScotland.

Population, intervention, comparator and outcomes

The population used in the model was adult patients with previously untreated myeloma ineligible for stem-cell transplantation. The intervention was continuous Rd. The comparator interventions were MPT and VMP. MPT was the relevant comparator in the model for the assessment of cost-effectiveness for this proposal. Utility data were derived using EQ-5D-5L data mapped to a UK value set from FIRST. Outcomes in the model were life years (LYs) and quality adjusted life years (QALYs).

Costs

Costs included were medicine acquisition, AE and monitoring. The cost of subsequent treatments was included. The model featured an annual discount rate for costs, LYs and QALYs of 3.5%.

Key results and method of uncertainty assessment

The base case incremental cost effectiveness ratio (ICER) was £1,186 per QALY gained for continuous Rd versus MPT. The incremental cost was £657. This was primarily driven by first line monitoring and subsequent treatment medicine acquisition costs. The incremental QALYs were 0.55. This was primarily driven by an increase in progression free LYs. Uncertainty was assessed using deterministic and probabilistic sensitivity analysis. The ICER remained below £6,000 per QALY gained under all these assessments.

3.1 Evidence Review Summary | Cost-effectiveness considerations

Consistency with FIRST

Clinical outcome data for both continuous Rd and MPT were from the FIRST study (January 2016 data cut-off). This facilitated the PFS, and overall survival estimates in the model for both treatments in the initial 92-week phase, and in the follow up Markov model that utilised transition probabilities derived from this data source. The proportions of patients on treatment were from patient-level data on time to treatment failure and extrapolated using parametric curves. The company used a regression model to analyse EQ-5D-5L data from FIRST to generate utility values.
Consistency with the FIRST study strengthened the internal validity of the economic model and the generalisability of results to NHSScotland.  

**Model structure**

The model structure was suitable to represent the clinical pathway for patients with multiple myeloma. The Markov states are widely used for representing patients’ transitions in oncology models. The modelled outcomes fitted the six years of observed data well, providing evidence that the modelling structure was suitable. The 25-year time horizon was sufficient to capture health benefits and costs as less than 1% of patients were alive at this point. Shortening the time horizon decreased the continuous Rd versus MPT ICER as first line monitoring costs decreased.

**Generalisability of results to NHS Scotland**

NHSScotland national framework contract prices were used for all medicines.

The dosing schedule of MPT was adjusted from that in the base model (based on FIRST) to reflect an NHSScotland regional cancer network protocol. This shortened the number of dosing cycles for the regimen. This affected cost only and not the health benefits, as the clinical data from the FIRST study could not be manipulated to reflect the shortened schedule. However, as longer schedules of MPT have marginal benefit but higher toxicity compared to shorter schedules, this is unlikely to significantly impact the continuous Rd versus MPT ICER.

Subsequent treatment proportions were from the FIRST study and may be partly reflective of practice in NHS Scotland. Those receiving first line continuous Rd mostly received subsequent bortezomib treatments. Those receiving first line MPT received an approximately even split between subsequent bortezomib and lenalidomide treatments. However, since construction of the original model additional subsequent treatments for myeloma (that include daratumumab and carfilzomib) have been accepted for use in NHSScotland. As continuous Rd delayed progression and use of subsequent treatments in the model, the inclusion of additional subsequent treatments may decrease the continuous Rd versus MPT ICER.

**Limitations of the analysis**

The cost-effectiveness of continuous Rd versus CTDa remains unknown. However, there is evidence showing similar PFS and overall survival outcomes of MPT versus CTDa. A de novo cost-minimisation analysis comparing the medicine acquisition cost of the fixed duration regimens of MPT and CTDa indicated similar costs. This provides indicative justification to suggest that continuous Rd is likely to be cost-effective versus CTDa.

The use of a full partitioned survival analysis, allowing for a selection of alternate extrapolation distributions for PFS and overall survival after 92 weeks would have provided increased confidence.
in the model’s results. However, the current model did indicate a good fit for the six years of observed data.

Summary
The economic model provided suitably robust cost-effectiveness results of high relevance to the proposal using outcome data from a suitable clinical trial. There is likely to be strong generalisability of the results in NHSScotland. The outlined limitations should be considered when interpreting the ICER results.

3.2 Council review | Cost-effectiveness evaluation

After considering all the available evidence, the Council were satisfied that the case for cost effectiveness had been made for lenalidomide in combination with dexamethasone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant and are suitable for thalidomide-containing regimens.

4.0 Evidence Review Summary | Service Impact

Rd continuous is currently a standard therapy as a result of extant COVID-19 NCMAG advice, which is due to expire in March 2023. It is an all-oral treatment regimen. No additional laboratory or radiology tests are expected. MPT and CTDa treatment duration is normally for 6-8 months, the median duration of treatment for Rd continuous was 18.4 months.

Lenalidomide must be prescribed via a pregnancy prevention programme (PPP). BMS currently operate an electronic PPP, with generic manufacturers developing either their own paper based / electronic systems or participating in the development of a generic electronic PPP, which is currently being assessed by the MHRA. Health boards will need to consider this when switching to a generic alternative and ensure a robust process is in place for the prescribing and dispensing of generic lenalidomide.

5.0 Evidence Review Summary | Budget Impact

NCMAG is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the national framework contract pricing.
Acknowledgment

NCMAG would like to acknowledge the patient group partner, Myeloma UK, for their invaluable input.

NCMAG would like to acknowledge the manufacturer of the original lenalidomide product, Bristol-Myers Squibb, for sharing their health economic model following an approach from NCMAG.
6.0 References


6. National Institute for Health and Care Excellence; Clinical Knowledge Summaries; myeloma prevalence: https://cks.nice.org.uk/topics/multiple-myeloma/background-information/prevalence/#:~:text=The%20median%20age%20at%20diagnosis%20is%2072%20years%20of%20age. page accessed 22 August 2022.


20220804 NCMAG103 Lenalidomide_Advice Document v1.0


health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

**Minor Document Amendments**

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