National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG119 Pomalidomide in combination with dexamethasone|

Advice Document v1.0 | February 2025

Pomalidomide in combination with dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior treatment regimen including lenalidomide, and where more effective alternatives are not suitable.[A]

NCMAG Decision | this off-label use is **supported**

This advice applies only in the context of National framework confidential pricing agreements in NHSScotland for generic pomalidomide, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith Scottish Medicines Consortium remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness case for pomalidomide in combination with dexamethasone in the proposed population. After consideration of all relevant information under the Decision-making framework for value judgements, the Council made a decision to support this use.

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.

Proposal Details	
Proposers	NHSScotland Haematologists
Medicine Name	Pomalidomide plus dexamethasone
Cancer type	Multiple myeloma
Proposed off-label[B] use	Pomalidomide in combination with dexamethasone for the treatment of adult patients with multiple myeloma who have

	received one prior line of therapy that has included lenalidomide
Medicine Details	**Pomalidomide**[1] Form: oral dosage form Dose: 4mg orally once daily on days 1 to 21 of each 28-day cycle. **Dexamethasone** [2] Form: oral dosage form Dose: 40mg orally once daily on days 1, 8, 15, 22 of each 28-day cycle. For patients > 75 years of age, the starting dose of dexamethasone is: 20mg orally once daily 1, 8, 15, 22 of each 28-day cycle Treatment should continue until disease progression or unacceptable toxicity occurs.
Advice eligibility criteria	**Inclusion Criteria:** • 18 years of age or older • Prior treatment with lenalidomide • Eastern Cooperative Oncology Group Performance Status 0 to 2 • Patients who are not suitable for more effective alternatives due to: ○ Co-morbidities • Unacceptable treatment burden associated with regular subcutaneous or intravenous therapy **Exclusion Criteria:** • Patients who are suitable for more effective alternatives

[B] Pomalidomide has a marketing authorisation for the following indications:

- Pomalidomide in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide
- Pomalidomide in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy

1. Current Management Context

Multiple myeloma symptoms, incidence and prognosis

Multiple myeloma (MM) is an incurable haematological cancer caused by the proliferation of malignant plasma cells. This leads to the destruction of bone and bone marrow, resulting in bone fractures, anaemia, low platelet counts, susceptibility to infections, high calcium levels, kidney dysfunction, and neurological complications[3]. Approximately 500 new cases of myeloma are diagnosed each year in Scotland with approximately 75% of patients being 65 years or older[4].

Multiple myeloma is characterised by periods of remission and relapse due to drug resistance, with each additional line of treatment associated with shorter remission times and worse outcomes[3].Survival rates for MM have improved in recent years. For example, one-year survival improved by approximately 5% between 2010-2014 compared to 2015-2019, reaching 83%. The estimated five-year age-standardised net survival is 62%[5].

Multiple Myeloma Treatment Pathway in Scotland

There are an increasing number of treatments available for MM, with the choice of treatment decided on a patient-by-patient basis. Factors such as age, symptoms, disease burden, fitness, co-morbidities, and patient preference (eg, preference for an all-oral treatment) are considered.

First line treatment is determined by eligibility for autologous stem cell transplant (ASCT). Patients eligible for ASCT usually receive induction therapy followed by high-dose chemotherapy, ASCT, consolidation treatment, and maintenance with lenalidomide. For patients who do not receive a stem cell transplant due to fitness or preference, first line treatment typically involves a lenalidomide-containing regimen.

In the second line setting for patients refractory to lenalidomide, currently accepted treatment options in NHSScotland include carfilzomib-dexamethasone, daratumumab-bortezomib-dexamethasone, selinexor-bortezomib-dexamethasone, or bortezomib-dexamethasone. These regimens require either subcutaneous or intravenous administration. Weekly oral cyclophosphamide and dexamethasone may be an alternative treatment option, however there is a limited evidence base for this. Pomalidomide and dexamethasone (Pomd) is accepted for use in the third line and beyond setting. The proposal is to use pomalidomide plus dexamethasone earlier in the treatment pathway, at second line, for patients who are not suitable for currently accepted second line treatment options either due to frailty, co-morbidities or challenges with the burden of treatment, including travel to cancer services due to geographical remoteness, the need for carer support or mobility.

International Context for proposed off-label use

The European Society for Medical Oncology and National Comprehensive Cancer Network support various triplet regimens or carfilzomib and dexamethasone in the second line setting, depending on patient fitness and prior treatments. Pomd is considered an option in the third line and beyond

setting, depending on prior treatments and patient characteristics[6]. Pomd is not stated as a second line option in the guidelines although it is recognised that patients may not tolerate a triplet regimen.

Pharmacology of pomalidomide

Pomalidomide is an immunomodulatory drug that has a direct anti-myeloma effect by killing tumour cells, inhibiting angiogenesis, and stimulating the immune system to target myeloma cells [1]. Standard practice is for patients to receive concurrent thromboprophylaxis.

2. Evidence Review Approach

A literature search was conducted to identify clinical and economic evidence 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 pomalidomide, dexamethasone, multiple myeloma and recurrent. Titles and abstracts were screened with a second opinion sought from another reviewer when required. The included studies were critically appraised using the Cochrane risk of bias version 2.0 or the risk of bias in non-randomised studies - of interventions tools[7, 8].

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

The APOLLO study was identified as supporting the use of pomalidomide and dexamethasone in the treatment of refractory multiple myeloma[9]. The APOLLO study was a phase III randomised, open label, multicentre study which compared daratumumab plus pomalidomide and dexamethasone (DaraPomd) with a control arm of pomalidomide and dexamethasone (Pomd)[9]. Included patients were diagnosed with relapsed or lenalidomide-refractory multiple myeloma with measurable progressive disease; had received at least one previous line of therapy and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2.

Patients were randomised equally (1:1) to receive DaraPomd (n=151) or Pomd (n=153). Randomisation was stratified by the number of previous lines of therapy (1 versus 2 and 3 versus ≥4) and the International Staging System disease range (I versus II versus III)[9].

The first group received daratumumab 1,800mg subcutaneous or intravenous 16mg/kg weekly during cycles one and two and then every two weeks during cycles three to six and every four weeks thereafter. Additionally, patients in both treatment arms received pomalidomide 4mg orally daily (starting dose; could be modified) on days one to 21 and dexamethasone 40mg orally (20mg for patients aged ≥75 years) on days 1, 8, 15 and 22 of each 28-day cycle. Treatment continued until disease progression or unacceptable toxicity[9]. The dosing schedule used in the study for the comparator medicine, Pomd, is the relevant treatment of interest for this proposal.

The primary outcome was progression-free survival (PFS), defined as the time from randomisation to date of disease progression or death, in the intention-to-treat population. Secondary outcomes included overall survival, overall response rate (ORR); and safety[9].

Results

At the primary data cut off, July 2020, 89 (60%) of 149 patients in the DaraPomd and 117 (78%) of 150 patients in the Pomd group had discontinued treatment: mainly due to disease progression[9].

The median duration of follow-up was 16·9 months (interquartile range [IQR] 14.4–20.6). The median age was 67 years. Across both treatment groups 45% of patients had an ECOG score of 1 or 2; 54% of patients had an International Staging System disease stage of 2 or 3; 22% of patients had only one previous line of therapy; median number of previous lines of therapy was 2 (IQR 2 to 3). The median duration of treatment was 11.5 months (IQR 4.6 to 17.1) in the DaraPomd group and 6.6 months (IQR 3.2 to 14.3) in the Pomd group.

The daratumumab regimen prolonged median PFS compared with Pomd alone. The Pomd regimen was associated with a median PFS of 6.9 months, which was consistent in the lenalidomide refractory subgroup (6.5 months). In the full study population Pomd was associated with an overall response rate of 46%. The complete results of primary and secondary outcomes of the APOLLO study as well as the extended follow up from the APOLLO study are presented in Table 1[9, 10].

Table 1| The results of key outcomes from the APOLLO study

	Daratumumab plus pomalidomide and dexamethasone (n=151)	**Pomalidomide plus dexamethasone (n=153)**
Primary Outcome: PFS		
Median follow up, months (IQR)	16.9 months (14.4 to 20.6)	
PFS events, %	84 (56%)	106 (69%)
Median PFS, months (95% CI)	12.4 (8.3 to 19.3)	6.9 (5.5 to 9.3)
Hazard ratio (95% CI)	0.6 (0.5 to 0.8) p=0.0018	
Subgroup analysis: PFS in patients with lenalidomide refractory multiple myeloma		
(Events/patients in subgroup)	**n = 76/120**	**n = 89/122**
Median PFS, months (95% CI)	9.9 (6.5 to 13.1)	6.5 (4.7 to 8.9)
Hazard ratio (95% CI)	0.66 (0.49 to 0.90)	
Subgroup analysis: PFS in patients with one prior line of therapy		
(Events/patients in subgroup)	**n= 9/16**	**n= 12/18**

	Daratumumab plus pomalidomide and dexamethasone (n=151)	Pomalidomide plus dexamethasone (n=153)
Median PFS, months (95% CI)	14.1 (6.5 to NE)	12.6 (3.7 to 19.6)
Hazard ratio (95% CI)	0.7 (0.3 to 1.7)	
Secondary Outcomes		
Overall response, %	104 (69%)	71 (46%)
Odds ratio (95% CI)	2.7 (1.7 to 4.4)	
Overall survival (Final analysis)		
Deaths, %	55%	59%
Median follow-up, months (95% CI)	39.6 (0.1 to 57.0)	
Median OS, months	34.4 (23.7 to 40.3)	23.7 (19.6 to 29.4)
Hazard ratio (95% CI)	0.8 (0.6 to 1.1)	

Key: PFS: progression-free survival; IQR: interquartile range: CI confidence interval; OS: overall survival

Supportive evidence

Evidence for Pomd in patients with one prior line of treatment is limited. The MM-003 study was a multicentre, open-label, randomised phase III trial comparing pomalidomide and dexamethasone (PomD) with a regimen containing high dose dexamethasone alone (HiDex)[11]. MM-003 was the licensing study for Pomd, used to treat patients with relapsed or relapsed and refractory multiple myeloma who have received at least two prior regimens including bortezomib and lenalidomide and have demonstrated disease progression on the last therapy. The patients were randomised (2:1) to 28-day cycles of pomalidomide (4 mg/day on days 1 to 21) plus dexamethasone (40 mg/day on days 1, 8, 15, and 22) (PomD), or high-dose dexamethasone (40 mg/day on days 1 to 4, 9 to 12, and 17 to 20) (HiDex) and treatment continued in both treatment arms until disease progression or unacceptable toxicity. Randomisation was stratified by age (≤75 years versus >75 years), disease population (refractory versus relapsed and refractory versus bortezomib intolerant), and number of previous treatments (two versus more than two). The primary outcome was PFS and secondary outcomes were overall survival, ORR, time to progression, duration of response, safety, and quality of life.

The median follow-up was 10.0 months (IQR 7.2 to 13.2), median PFS with PomD was 4.0 months (95% confidence interval [CI] 3.6 to 4.7; 77%, 233/302) versus 1.9 months (95% CI, 1.9 to 2.2; 87%, 133/153) with HiDex (hazard ratio [HR] 0.48 [95% CI 0.39 to 0.60]; p<0.0001). Overall survival was 12.7 months (95% CI, 10.4 to 15.5) in the PomD group which was significantly longer than the HiDex group at 8.1 months (95% CI, 6.9 to 10.8) (HR 0.74 [0.56-0.97]). Subgroup analyses in patients with two previous treatments or disease refractory to lenalidomide were all consistent with the PFS analysis in the full study population favouring treatment with PomD. PomD was numerically favourable to HiDex for PFS (HR 0.47 [0.18 to 1.25]). Additionally, PomD was

favourable to HiDex in patients that were refractory to lenalidomide (HR 95% CI 0.50 [0.40 to 0.62]), or where the last previous treatment was lenalidomide (HR 95% CI 0.38 [0.26 to 0.58]).

Patient reported outcomes

Patient reported outcomes from the APOLLO study are reported by Terpos *et al* [12]. There were no changes from baseline as observed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) global health status scores in either group. However, physical and emotional functioning, disease symptoms, and adverse effects of treatment were maintained at baseline levels in the DaraPomd group but declined in the Pomd group.

The patient reported outcomes from MM-003 were reported by Weisel *et al*[13]. Clinically meaningful improvements in health-related quality of life were observed more frequently in patients that received PomD than those receiving HiDex. Treatment with PomD significantly lengthened median time to clinically meaningful worsening in HRQoL in comparison to HiDex in four HRQoL domains; Physical Functioning, Emotional Functioning, Side Effects of Treatment and Health Utility.

Safety evidence

Grade 3 to 4 adverse events (AE) from the APOLLO and MM-003 are reported in Table 2.

The APOLLO study had 149 patients that received DaraPomd and 150 patients receiving Pomd. Only the results from the Pomd group are reported in this section. Serious AEs were reported in 39% of patients. The most common serious AEs were pneumonia (8%) and lower respiratory tract infection (9%). Serious treatment-related AEs occurred in 10% of patients and the most common serious AEs were pneumonia (1%), lower respiratory tract infection (1%) and febrile neutropenia (1%). Discontinuation of treatment due to an AE occurred in 3% of patients. No adverse event leading to death, deemed related to Pomd, occurred in the Pomd arm.

Study MM-003 had 300 patients receiving PomD and 150 patients receiving HiDex in the safety population[11]. Only the results from the PomD group are reported in this section. Serious AEs (defined as death, or requiring hospitalisation or resulting in disability or incapacity) occurred in 61% of the Pomd group. Discontinuation of treatment due to an AE was not reported. The most common cause of death was progression from multiple myeloma (68%) followed by infection (10%). Treatment related deaths accounted for 4% of deaths in the PomD group which included eight cases of infections, two cases of multiorgan failure or sudden death and one nervous system disorder.

Table 2 | Adverse events on pomalidomide plus dexamethasone in the APOLLO and MM-003 studies

	APOLLO	MM-003
Treatment	**Pomalidomide plus dexamethasone**	**Pomalidomide plus dexamethasone**
Grade 3 or higher of interest		
Neutropenia	51%	48%
Anaemia	22%	33%
Thrombocytopenia	18%	22%
Leukopenia	5%	9%
Lymphopenia	3%	Not reported
Febrile neutropenia	3%	10%
Infections/infestations	20%	34%
Bone pain	Not reported	7%
Fatigue	5%	5%
Hyperglycaemia	5%	Not reported

Quality assessment of clinical evidence

The APOLLO study and MM-003 were both phase III open label randomised multicentre studies[9, 11]. Overall, the studies were judged to have low risk of bias though there were some concerns noted based on assessment with the Cochrane Risk of Bias version 2 tool[8]. Randomisation was completed using a validated interactive response technology system thus limiting the risk of selection bias. The studies used an open label design meaning treatment assignments were not masked for patients or investigator staff, which could introduce bias on subjective outcomes. However, steps were taken to reduce outcome bias such as masking the personnel involved in analysing the results until the primary analysis.

Clinical effectiveness considerations

Pomalidomide plus dexamethasone has efficacy in multiple myeloma, however there is a lack of direct evidence against the relevant comparator in the proposed population.

The licensed indication for Pomd is in patients who have received at least two prior treatments, including both lenalidomide and bortezomib. In the MM-003 registration study Pomd was superior to high dose dexamethasone for key efficacy outcomes PFS, ORR and OS. In the APOLLO study Pomd was inferior to DaraPomd, a triplet regimen, for key efficacy outcomes, however this is not a relevant comparator for this proposal. The ORR was 46% in the full population in the Pomd arm. The median PFS in the Pomd arm was 6.9 months in the full population, 12.6 months for those

with one prior line of therapy, 6.5 months for those with 2-3 prior lines of therapy, and 6.6 months for those with ≥4 lines of therapy[9]. However, the sample size for the one prior therapy group of patients is small (n=18), with wide confidence intervals, making the efficacy estimate highly uncertain. For patients who were lenalidomide refractory, the median PFS was 6.5 months.

Reduced intensity on-label regimens and oral cyclophosphamide are the current options for the proposed population, but these have significant challenges and limitations, and there is an unmet need for an effective oral regimen

The proposal is to use Pomd earlier than its current, accepted, on-label use as third line treatment, and instead use it as a second line treatment after first line lenalidomide when alternative second line treatments are unsuitable (carfilzomib-dexamethasone, daratumumab-bortezomib-dexamethasone, selinexor-bortezomib-dexamethasone, or bortezomib-dexamethasone). These regimens require subcutaneous or intravenous administration or have adverse event profiles that make them unsuitable for patents with comorbidities, such as impaired cardiac function or peripheral neuropathy. They are also unsuitable for frailer patients at risk of complications from gastrointestinal toxicity, infusion reactions or increased toxicity of triplet regimens. To access pomalidomide in the third line, patients may be treated with one of these regimens, at reduced doses, with a low threshold for early discontinuation. However, this approach presents a challenging clinical situation for clinicians and patients.

Other less frequently used regimens for frailer patients may include oral weekly cyclophosphamide with or without steroids. However, the efficacy of these regimens is low, with reported PFS ranging from 3 to 4 months, often in heavily pre-treated populations. The quality of the evidence is also weak, consisting mainly of retrospective analyses or the control arm with different dosing to that used in clinical practice[14, 15].

Evidence supporting on-label third and later line use of Pomd is consistent with second line efficacy

The licensed indication for Pomd is in patients who have received at least two prior treatments, including both lenalidomide and bortezomib. The MM-003 registration study compared Pomd (n=302) to high dose dexamethasone (HiDex) (n=153) and included heavily pre-treated myeloma patients (median of 5 prior lines of therapy). An exploratory analysis found no difference in relative effectiveness compared to HiDex for patients with ≤3 or >3 prior lines of therapy, or type of prior therapy, and this lack of dependency on position of treatment is supported by other trial data[16, 17].

Real world data suggests the proposed NHSScotland population may be older and have poorer performance status than the APOLLO and MM-003 study populations

An NHSScotland real world data report on the use of Pomd as a second line treatment after lenalidomide, an indication supported for 2.5 years under interim COVID-19 NCMAG advice, supported consideration of the generalisability of the randomised controlled studies. Twenty patients were included in the analysis, with a median age of 78 years. No patients were PS 0; 40%

were PS 1, and 60% were PS 2 or worse. The median overall survival was 12 months (95% CI 10.1 - 41.7), and the median treatment duration was 5.6 months (IQR 1.9 - 10.4). The confidence intervals and the IQR were wide for overall survival and treatment duration, respectively. Treatment duration is used as a proxy for PFS, but it may be an underestimate if patients stop treatment before actual progression (for example, a treatment holiday) or an overestimate if patients continue treatment beyond progression according to IMWG criteria. Seventy percent of patients did not receive a subsequent regimen. There were no early deaths (within 30 days) in the patient group analysed, which may give some reassurance on the safety profile of Pomd. The NHSScotland real world data is likely more reflective of the proposed patient population who will receive Pomd[18].

In the APOLLO study the median age in the full population was 68 years and 87% of patients were PS 0 or 1. In the MM-003 study the median age was 64 years and 82% had an ECOG performance status of 0. The NHSScotland real world data suggests that the patient population treated with pomalidomide and dexamethasone in the second line is older and frailer than those in the APOLLO and MM-003, which limits the generalisability of the studies to the proposed patient population. However, given the older age and worse PS of the proposed patient population, the generalisability of supporting evidence for other second line regimens in the proposed population are uncertain.

Other supporting non-comparative evidence

A prospective non-interventional study (n=144) in Germany evaluated the effectiveness and safety of Pomd in an older multiple myeloma patient population with a median age of 73 years. All patients had been treated with lenalidomide with a median of three prior treatments, and 61% had a performance status of 0-1. The median PFS and OS were 6.3 months (95% CI 5.2-8.6) and 12.9 months (95% CI 10.6-15.1), respectively[19]. This may provide reassurance that Pomd is effective in older patients.

Other supporting evidence includes a non-comparative observational study of multiple myeloma patients treated with Pomd in routine clinical practice in France (n=2,099), in which 97% of patients had prior lenalidomide. In the subgroups of patients with 1 or 2 prior lines of treatment (n=914), 3 prior lines of treatment (n=644), and ≥4 prior lines of treatment, median PFS was 7.8 months, 6.0 months, and 5.3 months respectively[19].

There is no direct evidence for the safety of pomalidomide and dexamethasone relative to cyclophosphamide in the second line setting, although the safety profile is well-characterised in the on-label indication.

In the Pomd arms of APOLLO and MM-003 studies respectively, grade 3 or worse adverse events included neutropenia, anaemia, thrombocytopenia, febrile neutropenia, infections and fatigue. However, the number of patients treated with Pomd in the second line setting was small in the APOLLO study, which may limit the generalisability to the proposed patient population. These adverse event rates are consistent with another Phase 3b safety study in the third line and beyond setting[17]. The on-label safety data may provide reassurance on the safety of Pomd in the second

line setting, although adverse events may be higher in the proposed patient population of older and frailer patients.

The safety evidence for cyclophosphamide is not well characterised in multiple myeloma due to a lack of robust evidence and use as part of combination regimens. Common adverse effects associated with cyclophosphamide include haematological toxicity, mucositis, urinary and kidney toxicity[20].

4. Patient group summary

We received a statement from Myeloma U.K. who are a registered charity. Myeloma U.K. reported that pharmaceutical industry funding accounted for 5.6% of total funding received in 2023. A representative from Myeloma U.K. attended the NCMAG council meeting. The key points from the submission are documented below:

- Multiple myeloma is an incurable and complex cancer. It causes significant, debilitating and painful complications such as bone pain and destruction, kidney damage and fatigue, which impacts the day-to-day life of patients, families and carers. Treatment requires hospital visits and therapies have side effects, furthermore, the condition has a social, practical and financial impact on lives.
- Myeloma patients are often older (50% are more than 70 years), frailer and with comorbidities. Due to the variation in patient clinical pictures, treatment pathways are complex and there is not always a suitable second line treatment available. Currently, there is an unmet need for an effective second line all-oral treatment regimen.
- Patients value treatments that induce remission, prolong life and allow for a normal independent day-to-day living. Pomalidomide and dexamethasone is an oral regimen that can be taken at home or in the community setting, which will interfere less with normal life, holidays, and seeing friends.

5. Benefit-risk balance

Pomalidomide in combination with dexamethasone is on-label for use in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. The efficacy and safety of Pomd are well-characterised in the on-label indication. The proposed off-label use of Pomd is in the second line setting, rather than the third line or later setting and there is some evidence that comparative efficacy is maintained irrespective of line of therapy. The treatment effect estimate for Pomd in the second line setting relative to other treatment options in NHSScotland is highly uncertain. While there is no data or clinical reason to expect a worse safety profile in the second line setting compared to third line or beyond, the proposed patient population will likely be older and frailer.

The proposed regimen is for use in older, more frail patients who have limited routinely available evidence-based treatment options. There is an unmet need for an effective oral regimen as second line treatment after lenalidomide.

6. Council Review |Clinical 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 of the pomalidomide plus dexamethasone regimen in the proposed population. Under the decision-making framework for value judgements, Council considered the clinical case to be compelling.

7. Economic Evidence Review Summary

Economic Overview

The literature search for economic evidence on this topic returned no cost-effectiveness analysis which evaluated Pomd for the treatment of adult patients with multiple myeloma who have received one prior line of therapy that had included lenalidomide.

Scottish Medicines Consortium (SMC) has previously accepted pomalidomide in combination with dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy (SMC No. (972/14)[21].

Type of economic evaluation

No relevant published cost-utility analysis was identified in the literature search. Therefore, a de-novo cost-comparison was performed.

Population, intervention, comparator and outcomes

The patient population was adult patients with multiple myeloma who have received one prior line of therapy that had included lenalidomide, and where more effective alternatives are not suitable. The intervention was pomalidomide (4mg orally daily on days 1 to 21) with dexamethasone (40mg orally once daily for patients 75 years of age or less, or 20mg orally once daily for patients greater than 75 years of age, on days 1, 8, 15, 22 of each 28-day cycle). A simplified assumption was made to include equal proportion of patients in both age categories for costing dexamethasone use. The most relevant comparator, based on clinical expert opinion, was cyclophosphamide (300 to 500mg weekly, an average dose of 400mg was used in calculation) with dexamethasone (20mg weekly) (Cyd). As a cost-comparison analysis was performed, quality-adjusted life-years (QALYs) were not included in the analysis.

Costs

The cost comparison included acquisition costs and thromboprophylaxis costs for Pomd regimen. The confidential NHSScotland national framework prices (excluding VAT) of the 21-pack of 4mg tablets of pomalidomide and 100-pack of 50mg tablets of cyclophosphamide were used.

Following the patent expiry, NHSScotland National Procurement team undertook a tendering process for generic pomalidomide, however this was not finalised before the NCMAG Council consideration of this proposal in December 2024. The results corresponding to an upper estimate of the NHSScotland national framework contract price were used in confidence for decision-making. In January 2025, NHSScotland national framework contract prices for all generic pomalidomide products were confirmed to be lower than the estimate used for decision-making.

The duration of treatment was assumed to be 7 cycles of Pomd, based on PFS of 6.5 months from APOLLO study (lenalidomide refractory patient subgroup). The duration of Cyd was assumed to be 4 cycles of 28 days, based on PFS of 3 to 4 months observed in published studies[14, 15].

Given the absence of comparative safety data for Pomd versus Cyd, the incremental costs associated with adverse events were uncertain. The costs associated with implementing thromboprophylaxis to reduce the incidence of thromboembolic events in patients treated with pomalidomide were included. Based on clinical expert opinion, it was assumed that 90% of patients would be prescribed apixaban 2.5mg twice daily and the rest would receive prophylactic low molecular weight heparin, for example enoxaparin 40mg subcutaneous once daily, for the duration of pomalidomide treatment.

Results

All figures in the cost-comparison exclude VAT.

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence pricing contracts. Base case cost-comparison results suggested that treatment with Pomd would result in higher total costs than the comparator treatment. The main source of these increased costs was the higher treatment acquisition cost with pomalidomide compared to cyclophosphamide.

Cost-effectiveness considerations

Generalisability of the cost comparison

The NHSScotland national framework prices for medicines were considered in confidence to increase the generalisability of the net costs.

Limitations of the cost comparison

There was no published cost-effectiveness analysis for the proposed use and cost-effectiveness is not known.

Due to an absence of cost-utility analysis, the analysis only compared costs. Given the lack of treatment options in this patient population, Pomd may offer clinical benefit. An estimate of cost-effectiveness can be made by modelling the benefits over a longer period and comparing with costs. However, due to absence of a QALY estimate, an incremental cost-effectiveness ratio (ICER) is not available, and the cost-effectiveness remains unknown.

There are uncertainties in the comparator and treatment pathways in NHSScotland.

The proposed regimen is for use in older, more frail patients who have a lack of evidence-based treatment options. It was challenging to identify relevant comparators in this patient population. In consultation with the clinical experts, treatment with Cyd was identified as the only relevant comparator in NHSScotland. Whilst sometimes trialled in attenuated doses for this population, as a bridge to accessing Pomd, the DaraBd regimen was not considered suitable as a comparator in this population due to frailty, co-morbidities and potential challenges with travel to cancer services due to geographical remoteness or mobility issues. As daratumumab is administered parenterally and is currently on patent, its inclusion would increase the overall cost of the comparator arm.

There is uncertainty around subsequent treatments following Pomd and Cyd. The cost-comparison analysis does not include potential costs, or cost avoidance, of these treatments. The direction of impact remains unknown.

The cost-comparison excluded dosing adjustments and adverse event monitoring costs.

Duration and dose may vary in real-world setting due to multiple factors. Due to issues of data paucity, adjusting for these factors would likely increase the uncertainty of estimated medicine acquisition costs and were therefore not considered in the calculation. The dosing was not adjusted to account for dose reductions or treatment interruptions.

The costs of implementing thromboprophylaxis was included for Pomd regimen only. The cost of other supportive medicines prescribed alongside Cyd were not included; however, these are expected to have a minimal impact on overall costs. Due to the lack of robust comparative safety data of Pomd against Cyd, cost associated with adverse event management were not included in the cost-comparison.

Summary

The NHSScotland national framework contract price was not finalised ahead of the NCMAG Council consideration of this proposal in December 2024. Provisional decision-making was based on an upper estimate for generic pomalidomide products. Based on this estimate, Pomd was cost-increasing compared to Cyd. In January 2025, NHSScotland national framework contract prices for all included generic pomalidomide products were lower than the estimate used for provisional decision-making. With the lower price, the analysis indicates that the overall conclusion remains cost-increasing, however to a lesser extent.

8. Council review | Cost-effectiveness evaluation

After consideration of the available evidence, the Council accepted that in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider additional relevant information including service impact and estimated net medicines budget impact under the Decision-making framework for value judgements.

9. Service Impact

Pomd is not expected to have a significant service impact. It is an all-oral regimen that does not require any specific monitoring. It may increase the total number of patients who receive treatment and require management of treatment-related toxicities, if it is used in preference to best supportive care. As an all-oral therapy, it may be service sparing if it replaces subcutaneous or intravenous treatments, although there is significant uncertainty if it will replace any subcutaneous or intravenous regimens.

The estimated patient numbers are expected to range from 4 to 10 patients per year.

10. Budget Impact

In the absence of a cost-effectiveness analysis, a detailed budget impact analysis was conducted.

Patient uptake

The number of patients expected to be treated with Pomd was estimated to be around 7 patients per year in Scotland. The figure was based on regional cancer network data and extrapolated to provide a national estimate. Discontinuation and mortality rates were not included. Additional scenarios to explore uptake of 4 to 10 patients per year were considered.

Per patient medicine cost and treatment duration

These prices include VAT.

The budget impact analysis included medicine acquisition costs. The confidential NHSScotland national framework prices (including VAT) of the 21-pack of 4mg tablets of pomalidomide and 100-pack of 50mg tablets of cyclophosphamide were used.

Following patent expiry, NHSScotland National Procurement team undertook a tendering process for generic pomalidomide, however this was not finalised before the NCMAG Council consideration of this proposal in December 2024. The results corresponding to an upper estimate of the NHSScotland national framework contract price were used in confidence for decision-making. In January 2025, NHSScotland national framework contract prices for all generic pomalidomide products were confirmed to be lower than the estimate used for decision-making.

The duration of treatment was assumed to be 7 cycles of Pomd, based on median PFS of 6.5 months from APOLLO study (lenalidomide-refractory patient subgroup). The duration of Cyd was assumed to be 4 cycles of 28 days, based on PFS of 3 to 4 months observed in published studies[14, 15].

Comparator displacement

Based on feedback from clinical experts, the introduction of Pomd was assumed to displace 100% of Cyd in the proposed patient population.

Results

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence pricing contracts. Based on the confidential upper estimate of the national framework price of pomalidomide generic product (including VAT) used for provisional decision making, the use of Pomd would increase the net medicines budget for this patient group when compared to Cyd.

Scenario considerations

Additional scenarios exploring the impact of changes in annual patient uptake and duration of treatment were conducted to aid decision-making. Exploratory scenarios with annual patient uptake of 4 and 10 patients and duration of Pomd treatment based on longer PFS of 12.6 months, observed in the APOLLO study subgroup with one prior line of therapy, were considered. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence pricing contracts. Based on the confidential upper estimate of the national framework price of pomalidomide generic product (including VAT) used for provisional decision making, in all exploratory scenarios the results indicated that the use of Pomd would increase the net medicines budget for this patient group when compared to Cyd.

Limitations

In addition to previously discussed limitations (Section 7) of the cost-comparison, the annual uptake in this patient population is uncertain. Additional scenarios exploring the impact of changes in annual patient uptake and duration of treatment were considered in confidence.

Summary

The Council considered the net medicines budget impact using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the budget impact using confidential pricing due to commercial in confidence issues.

Based on the confidential upper estimate of the national framework price of pomalidomide generic product (including VAT) used for provisional decision making, the use of Pomd will increase the net medicines budget for this patient group when compared to Cyd. In January 2025, NHSScotland national framework contract prices for all generic pomalidomide products were confirmed to be lower than the estimate used for decision-making. With the lower price, the analysis indicates that the impact on net medicines budget remains cost-increasing, however to a lesser degree.

Separate information will be supplied to the boards to facilitate local budget impact assessment.

11. Council review | Overall proposal evaluation

After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use.

12. Acknowledgements

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This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of 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

Date	Previous version	Amendment	Updated version	Approved by