National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG104 Carfilzomib | Advice Document v1.0 | January 2023

Carfilzomib once-weekly regimen in combination with dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. [A]

NCMAG Decision | off-label once-weekly carfilzomib in combination with dexamethasone is **supported** as an alternative option to the on-label twice-weekly regimen

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement, or the national framework contract price, delivering the cost-effectiveness results upon which the decision was based, or a PAS/ national framework contract/ list price that is equivalent or lower.

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

Decision rationale

After consideration of all the available evidence regarding the benefits and risks, the Council were satisfied that the clinical- and cost-effectiveness of off-label once-weekly carfilzomib in combination with dexamethasone and supports offering it as an option for patients.

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	Consultant haematologists from across NHSScotland regional cancer networks who treat myeloma patients, supported by specialist cancer pharmacists
Medicine Name	Carfilzomib
Cancer type	Multiple myeloma
Proposed off-label use [B]	Carfilzomib once-weekly regimen in combination with dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
Medicine Details	Form Intravenous infusion Dose 70mg/mg^2 of body surface area (BSA) on days 1, 8, and 15 of each 28-day cycle, with the exception of day 1 cycle 1 when the dose is 20mg/m^2. In patients with a BSA greater than 2.2 m^2, the dose is based upon a BSA of 2.2m^2. All doses should be administered by intravenous infusion over 30 minutes. Patient should receive concomitant dexamethasone on days 1, 8, 15 of all cycles; and day 22 of cycles 1 to 9 only. Treatment cycles are repeated every 28 days until disease progression or unacceptable toxicity[1].
Advice eligibility criteria	Patients who would otherwise be considered suitable candidates for on-label carfilzomib 56mg/m^2 BSA twice weekly.

[B] The dose and frequency of the proposed use are off-label, however this regimen has been approved by the US FDA for the proposed indication[2]. SMC has accepted the use of on-label carfilzomib, at a dose of 56mg/m^2 BSA twice weekly, in combination with dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (SMC1242/17)[3].

1. 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. Relapsed myeloma can have significant symptom burden including pain. Improvements in quality of life in the relapsed setting are less than those achieved with first line treatment[4].

There are an increasing number of regimens available in the relapsed and refractory setting with specifications on combinations and line of therapy for use. Carfilzomib and dexamethasone alone has a marketing authorisation for the treatment of adult patients with multiple myeloma who have received at least one prior treatment and is routinely accessible for this use in NHSScotland.

Carfilzomib is a second-generation proteasome inhibitor that causes cancer cell death and has shown efficacy in bortezomib resistant myeloma. Once weekly carfilzomib dosing at 70mg/m^2 of BSA is licensed by the US Food and Drug Administration (FDA)[2] the Canadian Health Products and Food Branch[5], the Australian Therapeutics Goods Authority[6] and the New Zealand Medicines and Medical Devices Safety Authority[7].

2. 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 carfilzomib, once versus twice weekly and relapsed, refractory, multiple myeloma. 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 Cochrane risk of bias 2.0 tool.

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

Evidence comparing once-weekly versus twice-weekly carfilzomib regimens

The key evidence to support this comparison is based on a prespecified interim analysis of the phase III ARROW study[8]. The study compares carfilzomib 70mg/m^2 BSA intravenous (IV) once-weekly plus dexamethasone (once-weekly regimen n=240) with carfilzomib 27mg/m^2 BSA IV twice-weekly plus dexamethasone (twice-weekly regimen n=238), in patients with relapsing and remitting multiple myeloma (RRMM). The study included patients with two or three prior treatments for myeloma including a proteasome inhibitor and immunomodulatory agent, who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were randomised 1:1 to receive open-label once- or twice-weekly carfilzomib regimens and were stratified according to age (<65 years and ≥65 years); international staging system at study entry (stage 1 versus 2 or 3) and whether patients were refractory to bortezomib (yes or no). The primary outcome was progression free survival (PFS), defined as time from randomisation until

disease progression or death from any cause. Secondary outcomes include overall response, overall survival and safety. Response to treatment was defined using the international myeloma working group uniform response criteria[8].

At the time of the interim cutoff analysis, data-cut 15 June 2017, 274 events of disease progression or death had occurred (126 and 148 events in the once-weekly and twice-weekly regimens respectively). After a median follow-up of approximately 12 months, the once-weekly regimen significantly prolonged PFS compared to the twice-weekly regimen, median PFS 11.2 months versus 7.6 months respectively, (hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.54-0.88, p=0.003). Overall response rates were 63% versus 41% in the once- and twice-weekly regimens respectively (odds ratio [OR] 2.49, 95% CI 1.72-3.60). Overall survival data are immature at the time of analysis, however the 12 month survival rates were 76.6% versus 71.9% in the once-weekly and twice-weekly regimens respectively[8].

Pooled analysis comparing off-label carfilzomib 70g/m^2 BSA once-weekly with the on-label 56mg/m^2 BSA twice-weekly regimen

There is a lack of direct evidence comparing the off-label once weekly regimen with the on-label twice-weekly 56mg/m^2 BSA carfilzomib in combination with dexamethasone regimen (56mg/m^2 BIW regimen). A post-hoc side-by-side analysis pools data from three studies: ARROW (described above); CHAMPION-1, a phase 1/2 single arm dose finding study which aimed to identify the maximum tolerated dose of carfilzomib administered once-weekly in patients with RRMM with 1-3 prior lines of therapy (n=116); and ENDEAVOR, a randomised, phase 3 study comparing carfilzomib 56mg/m^2 BIW regimen (n=464) with bortezomib in patients with RRMM with 1-3 prior lines of therapy[9]. The post-hoc analysis provides a side-by-side comparison of the once-weekly regimen (n=146) with the on-label 56mg/m^2 BIW regimen (n=217) in a subgroup of patients with RRMM who had received 2 to 3 prior lines of therapy and were not refractory to bortezomib. The outcomes of interest in this analysis were objective response rate (ORR), PFS and safety[9].

The results suggested a similar ORR and PFS for the once-weekly and 56mg/m^2 BIW regimens respectively. The ORR was 70% compared to 72% in the once-weekly and 56mg/m^2 BIW regimens. Median PFS was 12 months for the once-weekly regimen compared to 14 months for the 56mg/m2 BIW regimen. Following adjustment for prognostic covariates there was no evidence of a difference between the regimens for ORR (OR 1.12, 95% CI 0.74-1.69) and PFS (HR 0.91; 95% CI 0.69-1.19)[9].

Patient reported Outcomes

Health-related quality of life (HRQoL) data were collected during the ARROW study using the myeloma-specific QLQ-MY20 Questionnaire, the generic oncology-related QLQ-C30 and the generic EuroQoL EQ-5D questionnaires prior to study treatment on day one of cycle one, then repeated at the beginning of each subsequent cycle. Patient satisfaction and convenience was examined at day one of cycle two and at the end of treatment. Greater HRQoL was noted in the once-weekly compared to the twice-weekly regimen for the physical functioning, role functioning

and fatigue. No other differences were noted between the regimens. There was a trend towards greater satisfaction and convenience for patients who received the once-weekly regimen compared with the twice-weekly regimen[10]. There is no HRQoL data for the comparison with the licensed 56mg/m^2 BIW regimen.

Safety evidence

In the ARROW study, the once weekly carfilzomib regimen was reported to have a comparable adverse event (AE) profile to the twice-weekly carfilzomib 27mg/m^2 BSA regimen[8]. In the carfilzomib once-weekly and twice weekly regimens respectively, the following were reported: 68% and 62% treatment emergent AEs with grade 3 or higher, 13% and 12% discontinued treatment, 9% and 8% treatment-emergent deaths, of which 2% and 1% were considered treatment-related. In the carfilzomib once-weekly and twice-weekly regimens, the following grade 3 or higher AEs were reported: anaemia (18% in each group), pneumonia (10% versus 7%), thrombocytopenia (7% in each group) and cardiac failure (3% versus 4%)[8].

In the pooled analysis, the carfilozmib 56mg/m^2 BIW regimen had a less favorable adverse event profile than the once weekly regimen[9]. In the once-weekly regimen and 56mg/m^2 BIW regimen respectively, the following were reported: 68% and 85% grade 3 AE or higher, 39% and 65% serious adverse events, and 10% and 14% discontinued treatment. In the once-weekly regimen and 56mg/m^2 BIW regimen, the following grade 3 or higher AEs were reported: cardiac failure (1.4% versus 5.1%), acute renal failure (3.4% versus 6.0%), embolic and thrombotic events (2.1% versus 2.3%) and hypertension (5.5% versus 15.7%)[9].

Quality assessment of the key clinical evidence

The ARROW study was a phase III randomised multicentre open label study[8]. Overall, it was assessed as low risk of bias. Randomisation was completed using validated randomisation software and via interactive response technology, therefore limiting the possibility of selection bias. Due to the open-label nature of the trial there was a risk of outcome detection bias, the study utilised central laboratories for measurable disease assessment, therefore limiting overall risk.

To compare the efficacy and safety of the once-weekly regimen with the licensed 56mg/m^2 BIW regimen a pooled side-by-side comparison was conducted with data being drawn from subpopulations of three trials (CHAMPION-1; ENDEAVOR and ARROW)[9]. Such naïve or unadjusted indirect comparisons are subject to bias with a risk of inaccurate estimates and, therefore, findings should be interpreted with caution. An attempt was made to adjust for the between trial differences, with the following prognostic covariates accounted for in their regression analysis: age (<65, 65 to <75, and ≥75 years), International Staging System (ISS) stage (1 versus 2 and 3), bortezomib-refractory status (yes versus no), lenalidomide-refractory status (yes versus no), and number of prior lines of therapy (1-2 versus 3). There is limited detail on the development and performance of the model, including rationale for selection of the prognostic covariates, which

increases uncertainty when interpreting the results. Additionally, it is uncertain if the analysis had sufficient power to detect a difference between the two treatments.

Clinical effectiveness considerations

There is uncertainty in the robustness of the pooled side-by-side post-hoc analysis

There is a lack of evidence directly comparing the proposed carfilzomib regimen with the on-label regimen and the key supporting evidence comes from a post-hoc pooled side-by-side analysis. There are important clinical and methodological differences between the three studies included in the pooled analysis. It is unclear if the methods applied in the pooled analysis account for these differences and there is a significant risk of confounding when carrying out side-by-side analysis as randomisation is broken and treatments are not anchored on a common control arm. Prognostic factors were examined using multiple Cox proportional hazards of the entire population in the three trials. After adjusting for selected prognostic co-variates, no evidence of a difference was found in PFS between once-weekly and 56mg/m^2 twice-weekly carfilzomib regimen, however it is unclear if this method had the power to show a difference between treatments. Additionally, there are wide confidence intervals around the ORR comparison, indicating increased uncertainty around the estimate. Cytogenetics were not available as part of the statistical analysis.

There is a lack of data comparing the proposed carfilzomib once-weekly 70mg/m^2 regimen with the on-label 56mg/m^2 twice-weekly regimen in the second line setting

To ensure consistency in patient populations the post-hoc analysis only included patients who had 2-3 prior lines of therapy, carfilzomib is also available to patients who have only received one prior line of therapy[9]. The CHAMPION-1 study (phase I/II dose-finding study) demonstrated once-weekly 70mg/m^2 carfilzomib was associated with an overall response rate of 77% (104 patients) and median progression-free survival was 12.6 months in a cohort of patients who had 1-3 prior lines of therapy with a median of one prior line of therapy[1]. ORR and PFS for patients with 1 prior line of therapy were not described. There may be some uncertainty around the comparative efficacy of once-weekly dosing versus 56mg/m^2 twice-weekly dosing in patients who have only had one prior therapy.

There is uncertainty on the generalisability of the post-hoc analysis to the Scottish population

No median age was provided in the post hoc analysis, 50.4% of patients were over 65 years of age[9]. The median age of diagnosis of myeloma in Scotland is 72 years of age, which suggests that the patient population in the post-hoc analysis of carfilzomib use in the relapsed setting may be younger than those treated in clinical practice. Real world data suggests that carfilzomib tends to be used in a younger population, this may be due to carfilzomib's toxicity profile[11, 12]. The CHAMPION, ARROW and ENDEAVOR studies had similar eligibility criteria. In the post-hoc analysis 50% of patients were ECOG performance status 0 and 50% were 1-2, which may reflect the population treated in NHSScotland[12].

There are a lack of overall survival data

Overall survival data were not available from the post-hoc analysis study[9]. Median follow-up time was 12.9 months for once-weekly carfilzomib and 11.2 months for 56mg/m^2 twice-weekly carfilzomib. The ARROW trial reported 12-month survival rates were 76.6% versus 71.9% in the once-weekly (70mg/m^2) and twice-weekly (27 mg/m^2) regimens respectively[8]. Multiple myeloma patients may receive multiple lines of treatment, therefore any overall survival data would likely be confounded by subsequent lines of treatment.

4. Patient group summary

A patient group partner statement from Myeloma UK was received and used to inform Council review and decision-making. The key points from the statement are:

- The complications of myeloma can be significant, debilitating and painful and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system which can lead to increased infections.
- Carfilzomib has been a very beneficial step in the myeloma treatment pathway, adding to the range of treatments available and it is well tolerated, with reduced rates of peripheral neuropathy compared to some other treatment options.
- The option to move from a twice-weekly to a once-weekly regimen would be beneficial for patients, ranging from those still in employment to more frail patients with mobility challenges, as they value a treatment schedule with reduced impact on their day-to-day lives.

In summary |Myeloma is complex and heterogeneous cancer, it is important to have a range of highly effective treatments available for patients. Once-weekly carfilzomib is less burdensome and reduces the impact of treatment on patients' day-to-day lives.

5. Benefit-risk balance

The once-weekly 70mg/m^2 BSA carfilzomib regimen appears to have comparable efficacy to the twice-weekly on-label regimen. The off-label once-weekly regimen is reported to have lower rates of grade 3 or higher toxicities and serious adverse events in comparison to the on-label twice-weekly regimen. Once-weekly dosing is likely to have practical benefits for patient experience with one less visit per week to a clinical setting.

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 has been made for the clinical effectiveness of the proposed off-label once-weekly carfilzomib regimen in combination with dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. The off-

label once-weekly regimen may be discussed with patients as an alternative option to the on-label once-weekly regimen.

7. Economic Evidence Review Summary

Economic Overview

Type of Economic Evaluation

A de-novo cost-minimisation analysis (CMA), which requires evidence of comparable efficacy between the relevant treatments, was performed. Clinical data to support the CMA was based on the post-hoc side-by-side analysis pooling data from three studies where similar efficacy was demonstrated for the once-weekly 70mg/m^2 carfilzomib regimen with the on-label twice-weekly 56mg/m^2 regimen, both in combination with dexamethasone[9]. No relevant published cost-utility analysis was identified in the literature search.

Population, intervention, comparator and outcomes

The population was patients with relapsed or refractory multiple myeloma who have been treated with at least one prior therapy. The intervention was once-weekly 70mg/m^2 carfilzomib. The comparator was twice-weekly 56mg/m^2. Both were in combination with dexamethasone. As a CMA was performed, quality-adjusted life-years (QALYS) were not required in the analysis as equal efficacy was assumed.

Costs

Only carfilzomib and dexamethasone acquisition costs were included. Both treatment regimens are given in 28-day cycles, until disease progression or unacceptable toxicity. As incremental costs differed between cycle 1 and cycle 2 onwards, incremental cost results are reported separately for cycle 1 and cycle 2 onwards. A 1.8m^2 BSA was assumed. Costs were not discounted.

Key results

Cycle 1: Compared with the twice-weekly 56mg/m^2, the once-weekly 70mg/m^2 regimen was estimated to produce a saving of £3,168 per patient (BNF medicine list prices). When including PAS discounts and national framework contract prices, the once-weekly 70mg/m^2 regimen was estimated to produce per-patient cost-savings.

Cycle 2 onwards: Compared with the twice-weekly 56mg/m^2, the once-weekly 70mg/m^2 regimen was estimated to produce a saving of £3,696 per patient (BNF medicine list prices). When including PAS discounts and national framework contract prices, the once-weekly 70mg/m^2 regimen was estimated to produce per-patient cost-savings.

Cost-effectiveness considerations

Generalisability of results

The dosing schedules of the two carfilzomib regimens reflect the supporting studies, and the Summary of Product Characteristics for the on-label use and practice in NHSScotland.

NHSScotland PAS and national framework contract prices were used in the analysis to obtain results of greater relevance.

Limitations

The CMA assumes similar health benefit of the two carfilzomib regimens. If the once-weekly 70mg/m^2 regimen does not provide similar health benefit, the cost-savings would require consideration of any health benefit reduction of using this regimen.

Only carfilzomib and dexamethasone acquisition costs were included. However, it can also be expected that the once-weekly treatment would reduce the administration frequency and associated service delivery cost. Given the favourable adverse event profiles of the 70mg/m^2 once-weekly regimen it can be reasonable to assume the costs of managing adverse events would be also reduced. The inclusion of these other costs is therefore likely to strengthen the cost-saving conclusions[9].

Summary

The cost-minimisation analysis provided suitably robust results of high relevance to the proposal. These are likely to be generalisable to NHSScotland. The outlined limitations should be considered when interpreting the cost-saving results.

8. Council review | Cost-effectiveness evaluation

After consideration of all the available evidence, the Council were satisfied that the case for cost effectiveness had been made for the additional option of once-weekly carfilzomib in combination with dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

9. Service Impact

The proposed once-weekly carfilzomib regimen would be associated with a 50% reduction in day-case unit chair time for chemotherapy IV administration, nursing time, as well as pharmacy aseptic service compounding.

10. 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 impact with appropriate confidential pricing information.

11. Acknowledgements

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

12.References

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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