

carfilzomib 10mg, 30mg, 60mg powder for solution for infusion (Kyprolis®). SMC No. (1242/17)

Amgen Ltd.

07 July 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan process

carfilzomib (Kyprolis®) is accepted for use within NHS Scotland.

Indication under review: In combination with dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Carfilzomib in combination with dexamethasone, compared with another proteasome inhibitor in combination with dexamethasone, increased progression free survival in adults with relapsed or refractory multiple myeloma who had received between one and three previous lines of treatment.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost effectiveness of carfilzomib and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

In combination with dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.¹

Dosing Information

Carfilzomib 20mg/m² (maximum dose 44mg) by intravenous (IV) infusion over 30 minutes in cycle 1 on days 1 and 2. If tolerated, the dose should be increased to 56mg/m² (maximum dose 123mg) from day 8 of cycle 1. Carfilzomib is given on days 1, 2, 8, 9, 15, and 16 of 28-day cycles.

Treatment may be continued until disease progression or until unacceptable toxicity occurs.

In combination with carfilzomib, dexamethasone alone is administered as 20 mg orally or IV on days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle. Dexamethasone should be administered 30 minutes to 4 hours before carfilzomib.

Dose adjustments of carfilzomib do not need to be made for weight changes of less than or equal to 20%. Dose adjustments to manage toxicity are detailed in the summary of product characteristics (SPC).

Treatment should be supervised by a physician experienced in the use of anti-cancer therapy.¹

Product availability date

29 June 2016

Carfilzomib has been designated as an orphan medicine by the European Medicines Agency and meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Carfilzomib is the second proteasome inhibitor licensed for treatment of multiple myeloma (MM). It irreversibly binds to 20S proteasome, the proteolytic core particle within the 26S proteasome and has been shown to delay tumour growth.¹ This submission relates to its use in combination with dexamethasone alone for adult patients who have received at least one prior therapy. SMC issued advice in January 2017 (No.1171/16) that carfilzomib is not accepted for use in combination with lenalidomide plus dexamethasone for this patient group.

An open-label phase III study (ENDEAVOR) recruited adults with relapsed or refractory MM (R/RMM) who had one to three prior therapies and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Randomisation was stratified by previous proteasome inhibitor therapy (yes versus no), previous lines of treatment (1 versus 2 or 3), International Staging System (ISS) stage (I versus II to III) and planned route of bortezomib administration (IV versus subcutaneous [SC]). Patients were equally assigned to carfilzomib (56mg/m² [except on days 1 and 2 of cycle 1, 20mg/m²] IV on days 1, 2, 8, 9, 15 and 16 of 28-day cycle) plus dexamethasone (20mg IV or oral on days 1, 2, 8, 9, 15, 16, 22 and 23 of 28-day cycle) or

bortezomib (1.3mg/m² IV or SC on days 1, 4, 8 and 11 of 21-day cycle) plus dexamethasone (20mg IV or oral on days 1, 2, 4, 5, 8, 9, 11 and 12 of 21-day cycle). Cycles were repeated until disease progression, unacceptable toxicity or withdrawal of consent. The primary outcome, progression-free survival (PFS), was defined as time from randomisation until death from any cause or progressive disease, assessed on International Myeloma Working Group – Uniform Response Criteria (IMWG-URC) by an independent review committee (IRC). It was compared between groups in the intention-to-treat population, which comprised all randomised patients.^{2,3}

At the first interim analysis (cut-off 10th November 2014) the primary endpoint was achieved; after a median follow-up for PFS in the carfilzomib and bortezomib groups of 11.9 and 11.1 months respectively, 37% (171/464) and 52% (243/465) of patients had an event (progression or death). PFS was significantly increased in the carfilzomib group, compared with bortezomib, with a hazard ratio (HR) of 0.53 (95% confidence interval [CI]: 0.44 to 0.65), p<0.0001, and median PFS of 18.7 versus 9.4 months. Overall response rate (defined as a partial response or better on IMWG-URC) was significantly greater in the carfilzomib group, compared with the bortezomib group: 77% (357/464) versus 63% (291/465), odds ratio of 2.03 (95% CI: 1.52 to 2.72), p<0.0001. Median duration of overall response was significantly longer with carfilzomib than bortezomib, 21.3 versus 10.4 months. The proportions of patients achieving at least a very good partial response (i.e. very good partial, complete or stringent complete response) were 54% (252/464) versus 29% (133/465) in the respective groups.^{2,3}

At the first interim analysis and an updated analysis (cut-off 3rd March 2016) overall survival data were immature. In the latest updated analysis (cut-off 3rd January 2017) median follow-up for overall survival was 37.5 and 36.9 months in the respective carfilzomib and bortezomib groups and 41% (189/464) and 45% (209/465) of patients had died. The HR for overall survival was 0.79 (95% CI: 0.648 to 0.964), p=0.010. Median overall survival was 47.6 and 40.0 months in the respective groups.^{4,3}

Some subscales of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core module (QLQ-C30) and quality of life questionnaire for MM (QLQ-MY20) assessed up to week 72 were statistically significantly different between carfilzomib and bortezomib indicating better quality of life with carfilzomib. However, these differences of 3.51, -1.89, -2.35 and -2.33 for QLQ-C30 global health status, fatigue and pain and QLQ-MY20 side-effects of treatment subscales, respectively, did not exceed the minimum clinically important difference (MID) of 5 units on the 100 unit scales. This was also observed in similar analyses of functional assessment of cancer therapy/gynaecologic oncology group neurotoxicity (FACT/GOG-Ntx) “additional concerns” subscale, where there was a statistically significant difference between carfilzomib and bortezomib of 0.84 (on a score range of 0 to 44).³ The clinical study report notes that the MID is unknown, but it has been suggested that it may be 3.3 to 4.4.⁵

Summary of evidence on comparative safety

The European Medicines Agency review of carfilzomib in this indication concluded that safety data were generally consistent with its known safety profile. New adverse events added to the summary of product characteristics (SPC) included rhinitis and lung infection.³

At the 10th November 2014 cut-off almost all patients in both treatment groups reported at least one adverse event. Adverse events reported by at least 5% more patients in carfilzomib group, than in with bortezomib group included: anaemia, 39% versus 27%; pyrexia, 28% versus 14%,

dyspnoea, 28% versus 13%; hypertension, 25% versus 8.8%; cough, 25% versus 14%; upper respiratory tract infection, 20% versus 15%; bronchitis, 16% versus 9.0%, muscle spasms, 19% versus 5.9%; headache, 17% versus 10%; and vomiting, 14% versus 8.8%, respectively. Adverse events reported by at least 5% fewer patients in the carfilzomib group than in the bortezomib group included: diarrhoea, 31% versus 38%; constipation, 15% versus 27%; peripheral neuropathy, 9.3% versus 26%; parasthaesia, 7.8% versus 16%; dizziness, 8.0% versus 15%; and peripheral sensory neuropathy, 5.8% versus 15%, respectively.³

In the carfilzomib group, compared with the bortezomib group, there was a higher incidence of adverse events within the group “venous thromboembolic events”, 10.6% versus 3.1%; and a lower incidence of \geq grade 2 within the group “peripheral neuropathy”, 6.0% versus 32%. This was observed in subgroups with and without peripheral neuropathy at baseline, as detailed in table 1.³

Table 1: Analysis of peripheral neuropathy \geq grade 2 by baseline peripheral neuropathy

Reported adverse event of PN \geq grade 2	Carfilzomib (N=463)		Bortezomib (N=456)	
	Baseline PN (N=214)	No baseline PN (N=249)	Baseline PN (N=238)	No baseline PN (N=218)
Yes	16 (7.5%)	12 (4.8%)	90 (38%)	56 (26%)
No	198 (92%)	237 (95%)	148 (62%)	162 (74%)

PN = peripheral neuropathy (group term, comprising 31 preferred terms, with seven of these reported during the study); CI = confidence interval.

In the carfilzomib group, compared with bortezomib group, adverse events of at least grade 3 were reported by 73% versus 67%, with 54% versus 50% of these treatment-related. There was also a higher incidence of serious adverse events in the carfilzomib group, 48% versus 36%, respectively, with 24% versus 15% treatment-related. Serious adverse events occurring in at least 1% more patients in the carfilzomib group included dyspnoea, 3.0% versus 0.2%; pyrexia, 3.2% versus 0.7%; pulmonary embolism, 2.2% versus 0.7%; cardiac failure, 1.7% versus 0.7%; bronchopneumonia, 1.3% versus 0; and plasmacytoma, 1.1% versus 0, respectively.³

Rates of discontinuations of any investigational product due to adverse events were similar across the carfilzomib and bortezomib groups, 20% versus 21% respectively, with 13% versus 17% treatment-related. There was a lower incidence of dose reductions due to adverse events in the carfilzomib group, 23% (106/463) versus 48% (218/456). The majority of dose reductions due to adverse events in the bortezomib group, 62% (135/218), were due to neuropathy-related adverse events (compared with 7% (7/106) in the carfilzomib group).^{2,3}

Summary of clinical effectiveness issues

Carfilzomib is the second proteasome inhibitor, after bortezomib, licensed for treatment of MM.^{1,6} This submission relates to its use in combination with dexamethasone alone for adult patients who have received at least one prior therapy. It has been designated as an orphan medicinal product for treatment of MM.

MM is a malignant plasma cell proliferation, with diagnosis based on detection of monoclonal component (M protein) in the serum or urine, plasma cell infiltration of the bone marrow and evidence of end organ damage (CRAB criteria: hypercalcaemia, renal insufficiency, anaemia or bone lesions). It can also be associated with recurrent infections and the hyperviscosity

syndrome. MM usually has a chronic phase lasting several years and an aggressive terminal phase. It is incurable and with each successive relapse response rates decrease.⁷

Clinical experts consulted by SMC advised that second- and third-line treatment of MM is dependent upon therapy in the first-line setting. Patients (generally younger and fitter) who had bortezomib, thalidomide plus dexamethasone (VTD) in the first-line setting may be treated in the second-line setting with lenalidomide plus dexamethasone. For patients (generally older and less fit) who had a thalidomide regimen without a proteasome inhibitor in the first-line setting (e.g. cyclophosphamide, thalidomide plus dexamethasone [CTda] or melphalan, prednisolone plus thalidomide [MPT]) later lines of therapy include bortezomib plus dexamethasone or lenalidomide plus dexamethasone, with the bortezomib regimen generally used second-line and the lenalidomide regimen third-line.

Clinical experts consulted by SMC note that there is an unmet need for effective therapies for some groups of patients, e.g. those unsuitable for current second line treatments or those who progress during induction with VTD.

In the pivotal study, at the first interim analysis (cut-off 10th November 2014), there was a significant increase in PFS of approximately 9 months with carfilzomib compared with bortezomib, which was considered by the EMA to be clinically relevant. Carfilzomib was also associated with an increased incidence, duration and depth of response. At the latest analysis (cut-off 3rd January 2017) there was a significant increase in overall survival of approximately 8 months with carfilzomib compared to bortezomib.^{4,3} There are no comparative data relative to other treatment options, such as lenalidomide plus dexamethasone.

The open-label design of the study may have contributed to a patient disposition difference, of about 7.5%, that was due to patient or clinician decision to discontinue treatment and may have influenced the assessment of subjective outcomes, such as quality of life and adverse events.

Patients recruited to the pivotal study had a median age of 65 years and 47% (433/929) of the study population were aged less than 65 years.³ They were generally younger than the majority of patients in Scotland with MM. In 2014 within Scotland 435 people were diagnosed with MM, with 70% (306/435) aged at least 65 years and 43% (189/435) aged at least 75 years. The median age at diagnosis was between 70 and 74 years.⁸ However, subgroup analyses of the pivotal study by age provide reassurance, although the number of patients aged at least 75 years was limited, 15% (143/929).³

Clinical experts consulted by SMC advise that in practice bortezomib is given by the subcutaneous route, with the majority of patients (who tend to be older than those in the study) receiving it in off-label weekly regimens, e.g. 1.3mg/m² once weekly for four weeks then one week off; or 1.5 to 1.6mg/m² once weekly for two weeks then one week off and the course continued for longer to give a total dose of about 80% of that which would be given in the twice weekly regimen. Treatment is usually continued for six cycles, with a small number of patients receiving the licensed maximum dose of eight cycles.

The pivotal study aimed to give all patients (irrespective of age or frailty that may influence dose selection in practice) the licensed bortezomib dose of 1.3mg/m² twice weekly for two weeks then one week off in 21-day cycles. During the study 48% (218/456) of the bortezomib-treated group had a dose reduction due to adverse events (with most, 62% [135/218], due to neuropathy-related events). This resulted in a median dose intensity of proteasome inhibitor of 86% in the bortezomib group (compared with 93% in the carfilzomib group).^{2,3} By starting with the licensed dose and

reducing when necessary, patients were likely to be on the optimal dose they could tolerate and this may have been continued for longer than they would have received in practice, as the study permitted patients to continue on bortezomib (after the licensed maximum of eight cycles) until disease progression or unacceptable toxicity. However, this study design may have contributed to a greater incidence of adverse events associated with bortezomib treatment, compared to practice where patient factors (such as age and frailty) may influence dose selection prior to commencing treatment and where all patients are given bortezomib SC (to minimise toxicity), in contrast to the study where 77% (360/465) received bortezomib SC.²

To address concerns about differences in bortezomib regimen in the ENDEAVOR study versus Scottish practice a matching adjusted indirect comparison (MAIC) was presented. It compared PFS and overall survival within the bortezomib plus dexamethasone group of the ENDEAVOR study with a treatment group in an open-label phase III study (CASTOR) where bortezomib plus dexamethasone was given in the licensed regimen up to a maximum of eight cycles to patients with R/RMM who had received at least one prior treatment. The outcomes of the MAIC were applied to an economic scenario analysis.⁴ The limitations of the MAIC include no assessment of safety or quality of life data and a lack of information on search strategy and inclusion/exclusion criteria that supported the selection of the CASTOR study as representative of the bortezomib plus dexamethasone eight cycle regimen. The cut-off dates for data included in the MAIC are unclear and there is a possibility that there may be a difference in maturity of data across the studies.

More than 90% of patients in the pivotal study had ECOG performance status of 0 or 1.² This may limit application of results to patients with poorer performance status. Patients were excluded from the study if they did not achieve at least a partial response with at least one previous therapy; were refractory to bortezomib or carfilzomib; or had more than three prior lines of therapy. Patients were also excluded if they had significant neuropathy (i.e. grade 2 with pain or grade 3 or 4).³ This may limit application of results to these patient groups, especially safety data to the latter group.

Pre-specified subgroup analysis by the number of prior therapies and by previous bortezomib use were generally consistent with the primary analysis as indicated in the table below.³

Table 2: Subgroup analysis of PFS survival.³

Prior therapies	Carfilzomib		Bortezomib		Hazard Ratio (95% CI)	p-value
	N	Median PFS	N	Median PFS		
One	232	22.2	232	10.1	0.45 (0.33; 0.61)	<0.0001
Two	157	14.9	145	8.4	0.60 (0.43; 0.83)	0.0008
≥Three	75	13.9	88	7.4	0.61 (0.39; 0.95)	0.0136
Prior Bortezomib						
Yes	250	15.6	252	8.1	0.56 (0.44; 0.73)	<0.001
No	214	-	213	11.2	0.48 (0.36; 0.66)	<0.001

PFS = progression free survival in months; CI = confidence interval

Clinical experts consulted by SMC consider that carfilzomib is a therapeutic advance due to its effects on PFS and overall response. They suggest that it would be used as second-line therapy and that it may have a significant service impact due to requirement for IV administration versus bortezomib given SC and the orally administered lenalidomide regimen.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of carfilzomib, as an orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Although there have been advances in the treatment of multiple myeloma, it remains incurable and mortality rates are high. Over time the condition becomes resistant to treatment and patients report an increasing sense of despair and resignation as they experience repeated relapses
- Carfilzomib plus dexamethasone provides an opportunity to increase overall and progression free survival compared with bortezomib plus dexamethasone, a current second-line treatment option. Of particular significance, carfilzomib is associated with a reduced rate of peripheral neuropathy compared with bortezomib.
- By providing a prolonged period of disease control and reducing peripheral neuropathy carfilzomib substantially improves patients' quality of life and physical symptoms. This can improve the emotional wellbeing of patients and carers and allow patients to be more involved in and enjoy family life and society.
- The differing adverse event profile of carfilzomib expands the range of treatment options available for patients who require individualised treatment pathways. By providing an additional treatment option it gives hope and reassurance to reduce the psychological impact of this incurable disease.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 12% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Myeloma UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing carfilzomib plus dexamethasone to bortezomib plus dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy. Results were also presented for patients who had only one prior therapy.

A partitioned survival model with 3 health states (PFS, progressed disease [PD] and death), over a lifetime horizon of 30 years was used. Clinical data were obtained by fitting survival curves to the ENDEAVOUR study data for PFS and overall survival (OS) using data from the updated analysis (cut-off 3rd March 2016).^{2,3} Patients in the model were assumed to be 65 years old, the same age as those in the clinical study.

The efficacy of carfilzomib was modelled relative to the efficacy of bortezomib. For PFS in the bortezomib arm, a Weibull curve was fitted to the ENDEAVOUR study data. A piecewise Cox

model was used with a cut-off point at 12 months and hazard ratios of 0.56 and 0.32 applied for up to 12 months and from 12 months onwards.

Similarly, for OS in the bortezomib arm, a Weibull curve was fitted for the first 48 months. Beyond this, OS for bortezomib was modelled by fitting a second Weibull curve to long-term follow-up data (median follow-up 8.6 years) from the bortezomib arm of a published study.⁹ A piecewise approach was also used to model OS with a cut-off point at 12 months and hazard ratios of 0.98 and 0.68 applied for up to 12 months and from 12 months onwards.

Disease-specific quality of life measures reported in the pivotal study were mapped to generic, preference-based utility data using a published algorithm.¹⁰ It was assumed that patients receiving second line treatment had a baseline utility equal to the mapped study utilities (0.727 for both arms). This was applied for 2 cycles. Then treatment-specific utilities for later cycles in the PFS health state were modelled (0.735 for carfilzomib and 0.708 for bortezomib). Post progression utilities were modelled using a value of 0.659 for both arms obtained from the mapping exercise. Best supportive care (BSC) when all treatment lines had ceased, was modelled at 0.640, being a published post-progression utility which has been used in previous economic evaluations of treatments for MM.¹¹ Utility decrements were applied to selective adverse events.

Medicine costs included acquisition costs for carfilzomib and comparator treatment, administration costs, treatment of adverse events and monitoring costs. Resource use came from a case review study conducted by the submitting company and palliative care costs from a recognised publication.¹²

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. A PAS is in place for bortezomib and this was included in the analysis by using an estimate of the relevant price of bortezomib through publicly available information.

The base case incremental cost effectiveness ratio (ICER), with the PAS discount for carfilzomib was estimated as £33,522. Results for a subgroup of patients who have received only one prior therapy reported an ICER of £24,820 with the PAS for carfilzomib.

Selected ICERs for sensitivity analyses with the PAS discount for carfilzomib are provided in Table 3.

Table 3: Results of sensitivity analysis with PAS for carfilzomib plus dexamethasone for ITT population

Scenario description	Incremental ICER
Base case	£33,522
Time horizon 25 years	£34,901
Time horizon 20 years	£37,827
Time horizon 15 years	£43,719
Administration costs of bortezomib 50% (£100) those of carfilzomib (£199) [base case both £199]	£37,686
Vd treatment per SmPC (max. 8 cycles); HR from a matching-adjusted indirect comparison of 1.36 and 1.35 respectively applied to baseline PFS and OS curve for Vd	£30,848
Vd treatment weekly for 32 doses; HR of 1.36 and 1.35 applied to baseline PFS and OS curve for Vd	£31,483
Waning treatment effect	£50,152
Discount bortezomib 36%	£35,425

Vd = bortezomib plus dexamethasone

- The main weaknesses included: The model assumed it was the younger fitter Scottish patients who would receive carfilzomib second line (and thus have a similar age and fitness profile to those in the pivotal study) but clinical experts suggested this group now receive a bortezomib regimen first line and a lenalidomide regimen second line. Hence it is the older less fit patients who receive bortezomib second line in practice. However pre-specified subgroup analyses from the pivotal study suggested hazard rates for PFS and overall survival were consistently observed irrespective of the age and performance status.
- The complexity of the approach to modelling OS, particularly the assumption that the relative risk reduction is constant over time, including in the progressed disease state. This resulted in a predicted OS gain of 2.25 years (27 months) in favour of carfilzomib. However the company provided sensitivity analyses which explored treatment waning effects in terms of OS and reduced the time horizon and the results are reported in Table 3 above.
- The use of bortezomib/dexamethasone in clinical practice differs from the study design. However, sensitivity analyses provided reassurance that adjusting for this factor may not increase the ICER although there remains uncertainty on the accuracy of the adjustment to the efficacy of bortezomib.
- The analysis used the same administration cost for subcutaneous and intravenous administration which was considered inappropriate. However additional sensitivity has subsequently been provided by the company testing assumptions regarding treatment administration in the economic model (see Table 5 above)

The Committee also considered the benefits of carfilzomib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy was satisfied. In addition, as carfilzomib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted carfilzomib for use in NHS Scotland.

Other data were also assessed but remain commercially confidential.*

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published guidelines “Myeloma: diagnosis and management” in 2016.¹³

The British Council on Standards in Haematology published “Guidelines for the diagnosis and management of multiple myeloma 2014” in February 2014.¹⁴ These were archived in 2016.

The European Society for Medical Oncology (ESMO) published “Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up” in August 2013. These guidelines note that the choice of therapy for relapsed disease depends on several factors including age, performance status, co-morbidities, the type, efficacy and tolerance of previous treatment, the number of prior lines of treatment, the available remaining treatment options and the time since the last treatment. These guidelines note that the EMA has approved lenalidomide plus dexamethasone and bortezomib alone or plus pegylated doxorubicin but that bortezomib is mostly used in combination with dexamethasone in relapsed disease. Thalidomide and bendamustine are effective drugs, often used, [but not approved at the time of publication]. A second stem-cell transplant may be considered in young patients who responded well to previous transplant and is associated with a PFS >24 months. Patients should be offered participation in clinical trials when possible.¹⁵

Additional information: comparators

The choice of therapy for R/RMM depends on previous treatment(s) and the response to these. For patients who have received one prior therapy (i.e. second-line treatment) the bortezomib plus dexamethasone and lenalidomide plus dexamethasone regimens are licensed and SMC advice restricts use of lenalidomide to those patients who have received prior bortezomib and are unsuitable for thalidomide. For patients at later relapses (i.e. for third-line or later treatment) several regimens could be used, for example: bortezomib plus dexamethasone, lenalidomide plus dexamethasone, pomalidomide plus dexamethasone or panobinostat plus bortezomib and dexamethasone.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)
Carfilzomib Dexamethasone	56mg/m² IV on days 1, 2, 8, 9, 15 and 16 of 28-day cycle* 20mg orally on day 1, 2, 8, 9, 15,16, 22, 23 of 28-day cycle	10,560
Lenalidomide Dexamethasone	25mg orally daily on days 1-21 of 28-day cycle 40mg orally on days 1-4, 9-12, 17-20 for first 4 cycles, then on days 1-4 of 28-day cycle	4,416 (4,512 in first four)
Bortezomib Dexamethasone	1.3mg/m ² IV or SC on day 1, 4, 8, 11 of 21-day cycle 20mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 of 21-day cycle	3,098
Panobinostat Bortezomib Dexamethasone	Cycle 1 to 8 20mg orally on day 1, 3, 5, 8, 10, 12 of 21-day cycle 1.3mg/m ² IV or SC on day 1, 4, 8, 11 of 21-day cycle 20mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 of 21-day cycle	7,754

Panobinostat	Cycle 9 to 16 20mg orally on day 1, 3, 5, 8, 10, 12 of 21-day cycle	6,205
Bortezomib		
Dexamethasone		
Pomalidomide	4mg orally on days 1-21 of 28-day cycle	8,932
Dexamethasone		

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 03 March 2017 for dexamethasone; from new product assessment form (NPAF) for carfilzomib; and from Electronic Medicines Compendium Dictionary of Medicines and Devices (eMC DM&D) on 06 March 2017 for all other medicines. Costs are based on based on 1.8m² body surface area. * 20mg/m² on days 1 and 2 of cycle 1, corresponding to cost of £8,496 for cycle one. In the ENDEAVOR study the median duration of treatment was 12 cycles for the carfilzomib regimen and 8 cycles for the bortezomib regimen. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 1,371 patients eligible for treatment with carfilzomib in year 1 rising to 1,772 patients in year 5.

SMC is unable to publish the with PAS 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 PAS.

*Other data were also assessed but remain commercially confidential.**

References

1. Amgen Ltd. Summary of product characteristics for carfilzomib (Kyprolis[®]), last updated 20 December 2016.
2. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; 17: 27-38
3. European Medicines Agency. European public assessment report, Committee for Medicinal Products for Human Use (CHMP) group of variations including an extension of indication assessment report EMA/517040/2016, 26 May 2016.
4. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016;375:754-66.
5. Commercial in Confidence*
6. Janssen Cilag. Summary of product characteristics for bortezomib, last updated 1 March 2017.
7. European Medicines Agency. European public assessment report, Committee for Medicinal Products for Human Use (CHMP) assessment for Kyprolis, EMA/670306/2015, 24 September 2015.
8. National Services Scotland. Cancer statistics: multiple myeloma. www.isdscotland.org.
9. Orlowski RZ, Nagler A, Sonneveld P et al. Final overall survival results of a randomized trial comparing bortezomib plus pegylated liposomal doxorubicin with bortezomib alone in patients with relapsed or refractory multiple myeloma. *Cancer* 2016;122:2050-6.
10. Proskorovsky I, Lewis P, Williams CD et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual Life Outcomes* 2014;12:35.
11. Van Agthoven M, Segeren CM, Buijt I *et al.* A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. *Eur J Cancer* 2004;40:1159-69.
12. Georghiou T, Bardsley M. Exploring the cost of care at the end of life. 2014. Available from: <http://www.nuffieldtrust.org.uk/publications/exploring-cost-care-end-life>.
13. National Institute for Health and Care Excellence. Myeloma: diagnosis and management, 2016.
14. British Council for Standards in Haematology (BCSH). Guidelines for the diagnosis and management of multiple myeloma 2014, February 2014.
15. European Society of Medical Oncology (ESMO). Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, in August 2013.

This assessment is based on data submitted by the applicant company up to and including 19 April 2017.

[*Agreement between the Association of the British Pharmaceutical Industry \(ABPI\) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:](#)

http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium 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.