SMC2674

selinexor 20 mg film-coated tablets (Nexpovio®)

Menarini Stemline UK Ltd

06 September 2024

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission under the orphan equivalent medicine process

selinexor (Nexpovio®) is accepted for restricted use within NHSScotland.

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

SMC restriction: restricted for use in patients with lenalidomide-refractory multiple myeloma, and where an anti-CD38 monoclonal antibody is not appropriate.

In a randomised, open-label, phase III study, the addition of selinexor to bortezomib plus dexamethasone resulted in statistically significant improvements in progression-free survival.

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

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

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Selinexor is a first-in-class selective inhibitor of nuclear export (SINE) compound. Its action causes nuclear localisation and functional activation of tumour suppressor proteins, cell cycle arrest, reduction in several oncoproteins and apoptosis of cancerous cells. Selinexor is combined with bortezomib and dexamethasone to maximise synergistic cytotoxic effects in multiple myeloma (MM).[1, 2]

For this indication, the recommended doses (based on a 35-day cycle) are:

- Selinexor 100 mg (not exceeding 70 mg/m^2 per dose) orally once weekly on day 1 of each week.
- Bortezomib 1.3 mg/m^2 of body surface area subcutaneously on days 1, 8, 15, and 22; followed by 1 week off.
- Dexamethasone 20 mg orally on days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30.

Treatment should be continued until disease progression or unacceptable toxicity.[1]

1.2. Company proposed position

The submitting company has requested that selinexor plus bortezomib and dexamethasone is restricted for use in patients with lenalidomide-refractory multiple myeloma, and where an anti-CD38 monoclonal antibody is not appropriate.

1.3. Disease background

Multiple myeloma (MM) accounts for 2% of all new cancer cases every year in the UK, with 6,200 new cases each year.[3] The incidence of MM in Scotland is estimated to be 8.8 per 100,000 people.[4] MM predominantly affects older people and the median age at diagnosis is approximately 70 years, with more than 40% of new myeloma cases being diagnosed in those aged 75 or above.[3] Patients with multiple myeloma have a poor prognosis; based on data from 2015 to 2019, it is estimated that the 1-year and 5-year age-standardised net survival rates were 83% and 62% in Scotland, respectively.[5]

MM is an incurable haematological cancer of plasma cells. This results in the destruction of bone and bone marrow, which can cause bone fractures, anaemia, increased susceptibility to infections, elevated calcium levels in the blood, kidney dysfunction and neurological complications. Despite being incurable current treatments can delay progression and improve quality of life. However, the condition is characterised by periods of remission and relapse (due to drug resistance), with each additional line of treatment being associated with reduced remission times and worse outcomes.[2, 6] Additionally, not all patients with MM are well enough to receive subsequent lines of therapy; in Europe around 95% of those diagnosed with MM receive first-line (1L) treatment, of which 61% receive second-line (2L) treatment, and around 38% receive third-line (3L).[7]

1.4. Treatment pathway and relevant comparators

For MM, 1L treatment is decided on a patient-by-patient basis and is dependent on various factors including age, symptoms, general health, and eligibility to receive high-dose induction chemotherapy with autologous stem cell transplantation (ASCT). There may also be geographical variation in prescribing patterns in Scotland. Multi-drug resistance is common, and class-switching between treatments is recommended upon disease progression and at each relapse. Treatment options for patients with MM include: glucocorticoids (dexamethasone, prednisolone), proteasome inhibitors (bortezomib, carfilzomib), histone deacetylase inhibitors (panobinostat), immunomodulatory agents (thalidomide, lenalidomide, pomalidomide), anti-CD38 monoclonal antibodies (daratumumab, isatuximab), high-dose chemotherapy and ASCT.[2, 8, 9]

The submitting company considered carfilzomib plus dexamethasone to be the only relevant comparator for this submission and positioning (see section 1.2); this combination was accepted by SMC (SMC1242/17) for patients with MM who have received at least one prior therapy (that is 2L+). Bortezomib monotherapy was accepted by SMC for patients with MM who have received at least one prior therapy (that is 2L+) and who have already undergone or are unsuitable for bone marrow transplantation (SMC302/06, SM822/12). Experts consulted by SMC agree that bortezomib monotherapy is not a relevant comparator. Third-line and beyond (3L+) treatment options, accepted for use by SMC, for those who are lenalidomide-refractory and where anti-CD38 antibodies are inappropriate include: panobinostat plus bortezomib and dexamethasone (SMC1122/16), and pomalidomide plus dexamethasone (SMC972/14).

Clinical experts consulted by SMC agreed that carfilzomib plus dexamethasone is a relevant comparator but also listed bortezomib plus dexamethasone, and pomalidomide plus dexamethasone as comparators at the 2L+ and 3L+ stages respectively. ESMO guidelines list bortezomib plus dexamethasone as a potential treatment option in lenalidomide-refractory patients, but only in combination with another agent (for example pomalidomide, daratumumab).[8]

1.5. Category for decision-making process

Eligibility for a PACE meeting:
Selinexor meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support selinexor plus bortezomib and dexamethasone for the indication and positioning under review comes from the BOSTON study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study.

Criteria	BOSTON study.[2, 10]
Study design	An international, randomised, open-label, phase III study.
Eligible patients	• Aged ≥ 18 years, with an ECOG PS of 0 to 2. • Histologically confirmed MM as per IMWG guidelines. • Had previous treatment with 1 to 3 prior different regimens for MM, and documented evidence of disease progression on their most recent treatment regimen.

	• Patients with prior PI use (alone or as part of a combination) had to have at least a partial response to the therapy and at least a 6-month interval since their last PI therapy.
Treatments & Randomisation	Patients were randomised equally to receive selinexor plus bortezomib and dexamethasone (n=195) or bortezomib plus dexamethasone (n=207). Treatment was to continue until disease progression was confirmed by the IRC, investigator, or patient decision to discontinue study treatment, pregnancy, unacceptable adverse events (AEs) or toxicity that could not be managed by supportive care, withdrawal of consent, or death. Dose reductions and treatment interuptions for selinexor, bortezomib, and dexamethasone were permitted for the management of adverse events. Concomitant anti-emetics (for example ondansetron) were permitted during the study. ***Selinexor plus bortezomib and dexamethasone (35-day cycles)*** • Selinexor 100 mg orally on Days 1, 8, 15, 22 and 29. • Bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 8, 15 and 22. • Dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30. ***Bortezomib plus dexamethasone*** For the first 8 cycles (21-day cycles): • Bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8 and 11. • Dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 and 12. For cycles ≥ 9 (35-day cycles): • Bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 8, 15 and 22. • Dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30. Patients in the bortezomib plus dexamethasone group who had progressive disease (PD) confirmed by the Independent Review Committee (IRC) were allowed to cross over to a selinexor-containing regimen; selinexor plus dexamethasone +/- bortezomib (depending on bortezomib tolerability). Randomisation was stratified according to previous proteasome inhibitor therapies (yes versus no), number of previous lines of treatment (1 versus 2 or more) and International Staging System stage (III versus I to II).
Primary outcome	Progression-Free Survival (PFS), defined as the time between date of randomisation to the date of first progression per IMWG response criteria or death due to any cause, whichever occurred first. This was assessed by an IRC.
Secondary outcomes	• Overall response rate (ORR), defined as sCR + CR + VGPR + PR, assessed by the IRC as per IMWG criteria. • Overall survival (OS), defined as time to death or lost to follow-up, measured from the date of randomisation until death (non-key secondary outcome). • Duration of response (DOR), defined as the duration of time from first occurrence of response ≥ PR until the first date of disease progression or death, whichever occurs first.
Statistical analysis	Efficacy analyses were performed in the ITT population, which included all randomised patients. Adjustment for multiplicity testing was based on hierarchical formal testing carried out in a sequential manner in the following order: the primary outcome (PFS), followed by the secondary outcomes (ORR, then incidence of any > grade 2 peripheral neuropathy event, then response rate for responses ≥VGPR); OS and DOR were not included in the hierarchical testing strategy and results for these are descriptive only. The updated analysis (data cut-off 15 February 2021) is non-inferential and the p-values from the updated analysis were nominal.

Abbreviations: CR = complete response; ECOG PS = eastern cooperative oncology group performance status; IMWG= international myeloma working guidelines; IRC = independent review committee; ITT = intention-to-treat; MM = multiple myeloma; PI = proteasome inhibitor; PR = partial response; PS = performance status; sCR = stringent complete response; VPGR = very good partial response.

At the primary PFS analysis, selinexor plus bortezomib and dexamethasone resulted in statistically significant improvements in PFS and ORR when compared with bortezomib plus dexamethasone in the ITT population.[2, 10] PFS and ORR results at the updated analysis, used in the economic analyses, are consistent with the primary analysis.[2] The PFS results were generally consistent across multiple sensitivity analyses (including censoring rules) and across pre-specified subgroups by relevant patient and disease characteristics, including the number of prior treatments; results from the updated analysis were also consistent. Full results are in Table 2.2.

Table 2.2 Results of primary and selected secondary outcomes from BOSTON in the intention-to-treat population.[1, 2, 10]

Data cut-off date	18 February 2020 (primary analysis)		15 February 2021 (updated analysis)	
	Selinexor + bortezomib + dexamethasone (n=195)	**Bortezomib + dexamethasone (n=207)**	**Selinexor + bortezomib + dexamethasone (n=195)**	**Bortezomib + dexamethasone (n=207)**
Primary outcome: PFS as per IRC assessment (IMWG criteria).				
Median duration of follow-up (months)	13.2	16.5	13.5	24.5
Events, n	80	124	92	137
Median PFS (months)	13.9	9.5	13.2	9.5
Hazard ratio (95% CI), p-value	0.70 (0.53 to 0.93), p=0.007		0.71 (0.54 to 0.93)[a]	
Secondary outcome: ORR as per IRC assessment (IMWG criteria).				
Overall response rate, % (n)	76% (149)	62% (129)	77% (150)	63% (131)
Odds ratio (95% CI), p-value	1.96 (1.26 to 3.05), p=0.0012		1.94 (1.25 to 3.03)[a]	
sCR, % (n)	9.7% (19)	6.3% (13)	9.7% (19)	6.3% (13)
CR, % (n)	7.2% (14)	4.3% (9)	7.2% (14)	4.3% (9)
VGPR, % (n)	28% (54)	22% (45)	28% (54)	22% (45)
PR, % (n)	32% (62)	30% (62)	32% (62)	31% (64)
Secondary outcome: overall survival.				
Median duration of follow-up (months)	17.3	17.5	28.7	28.7
Deaths, n	47	62	68	80
Median OS (months)	NR	25.0	36.7	32.8
Hazard ratio (95% CI), p-value	0.84 (0.57 to 1.23)[b]		0.88 (0.63 to 1.22)[a]	
Secondary outcome: duration of response (IMWG criteria)				
Median DOR (months)	20.3	12.9	17.3	12.9

[a] the updated analysis is non-inferential; therefore the results are descriptive only.

[b] OS was not included in the hierarchical testing strategy; therefore, results are descriptive only.

CI = confidence interval; CR = complete response; DOR = duration of response; IMWG = international myeloma working guidelines; IRC = independent review committee; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; VGPR = very good partial response

The proposed positioning of the submission is for patients that are lenalidomide-refractory, and where anti-CD38 is not appropriate. The submitting company provided data from a post-hoc analysis of the lenalidomide-refractory patients in the BOSTON study (26% [106/402] of the intention-to-treat [ITT] population). At the updated analysis, in the selinexor plus bortezomib and dexamethasone group (n=53), and bortezomib and dexamethasone group (n=53), respectively reported: median PFS follow-up (10.6 months versus 26.9 months), median PFS (10.2 months versus 7.1 months) and hazard ratio 0.52 (95% confidence interval [CI]: 0.31 to 0.88) and were consistent with the results in the full ITT population.

In the lenalidomide-refractory subpopulation, results for ORR, overall survival, time to discontinuation (TTD) and time to next treatment (TTNT) at the 15 February 2021 data cut-off numerically favoured selinexor plus bortezomib and dexamethasone.

Crossover was permitted at the point of IRC-confirmed object progressive disease from the control group to a selinexor-containing regimen. It was noted that 36% (74/207) of patients randomised to the control group crossed over to receive selinexor, either in combination with bortezomib and dexamethasone (n=63) or dexamethasone (n=11). In the crossover group receiving selinexor plus bortezomib and dexamethasone (n=63), the median PFS (95% CI) was 3.9 months (3.5 to 6.9); this data was included in the cost-effectiveness analysis.[2]

Further updated OS data (data cut-off 22 March 2022) is available for the ITT population. In the selinexor plus bortezomib and dexamethasone group, and bortezomib and dexamethasone group respectively: median follow-up time (33.6 months versus 33.8 months) and the total number of deaths (74 versus 83) are reported. Since crossover was allowed in the study, a switch-adjusted HR of 0.88 (95% CI: 0.64 to 1.22) was reported. These results were consistent with the earlier data.[2]

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the: European Organisation for the Research and Treatment of Cancer (EORTC) quality of life chemotherapy-induced peripheral neuropathy questionnaire (EORTC QLQ-CIPN20) (secondary outcome), EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30), and the EuroQol five-dimensions five levels (EQ-5D-5L) questionnaire (exploratory outcome); these instruments were used at baseline and to estimate a weekly mean change. For EORTC QLQ-CIPN20, there was a reduction in the rate of worsening in the sensory scale reported in the ITT population, which favoured selinexor plus bortezomib and dexamethasone; potentially linked to a much lower exposure of bortezomib in the selinexor group. Motor and autonomic scale scores were similar in both treatment groups.[2]

For EORTC QLQ-C30, there was little difference between the two treatment groups overall.[2] For EQ-5D-5L, both treatment groups demonstrated a similar, small reduction in the EQ-5D-5L index at end of treatment, in the ITT and lenalidomide-refractory populations.

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing selinexor plus bortezomib and dexamethasone with carfilzomib plus dexamethasone, the submitting company presented a Bayesian network meta-analysis (NMA). See Table 2.3 for details.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian network meta-analysis (NMA).
Population	Adults with measurable multiple myeloma with one to three prior lines of therapy, focused on patients that are lenalidomide-refractory.
Comparators (Studies included)	Selinexor plus bortezomib and dexamethasone (BOSTON), carfilzomib plus dexamethasone (ENDEAVOR), and bortezomib plus dexamethasone (BOSTON, ENDEAVOR).
Outcomes	• PFS, measured as the time from randomisation to progression or death or last known follow-up by IRC assessment. • OS, measured as the time from randomisation to death or last follow-up.
Results	For the base case PFS results, there was no significant differences when comparing selinexor plus bortezomib and dexamethasone with: bortezomib plus dexamethasone (HR = 1.91 [95% CI: 0.83 to 4.45]) and carfilzomib plus dexamethasone (HR = 1.54 [95% CI: 0.50 to 4.76]). For the base case OS results, there was no significant differences when comparing selinexor plus bortezomib and dexamethasone with: bortezomib plus dexamethasone (HR = 1.87 [95% CI: 0.76 to 4.60]) and carfilzomib plus dexamethasone (HR = 1.62 [95% CI: 0.51 to 5.17]). Please note that the HRs are for the treatment compared with selinexor plus bortezomib and dexamethasone, meaning HR values greater than 1.0 suggest better outcomes for selinexor plus bortezomib and dexamethasone.

CI = credible interval; HR = hazard ratio; IRC = independent review committee; PFS = progression-free survival; OS = overall survival.

3. Summary of Safety Evidence

Selinexor plus bortezomib and dexamethasone results in a significant increase in toxicity compared with bortezomib and dexamethasone; with higher rates of adverse events (AEs) that are grade 3 or 4, serious, and result in treatment discontinuation. However, despite the toxicity of this combination, the medicines regulator considered the benefits of this treatment combination to outweigh the risks.[2]

Safety analyses were performed in all patients who had received at least one dose of the study medicine in the BOSTON study (n=399). As of the February 2021 data cut off, the median number of selinexor doses received was 26.0 (range: 1 to 168). 66% of patients had a selinexor dose reduction; 87% had a dose delay/interruption, and 89% had a dose modification; whilst 25% had a dose escalation of selinexor.[2]

In the selinexor plus bortezomib and dexamethasone group (n=195), and the bortezomib plus dexamethasone group (n=204) respectively: treatment-related adverse events (AEs) were reported in 96% and 82% respectively; 30% and 12% of treatment-related AEs were serious; 81% and 64% led to dose modifications; 16% and 13% led to study discontinuation; 2.1% and 0.5% had a treatment-related AE (TRAE) leading to death.[2]

In the selinexor and control groups respectively, patients reporting a treatment-related grade 3 or 4 AE were 70% and 41%. Treatment-emergent Grade 3 or 4 AEs occurring in ≥5% of patients in either treatment arm of the BOSTON study were included in the economic analyses. The most frequently reported of these were: thrombocytopenia (41% and 18%), pneumonia (12% and 10%), anaemia (16% and 9.8%), fatigue (13% and 1.0%), peripheral neuropathy (4.6% and 8.8%);

asthenia (8.2% and 4.4%), neutropenia (9.2% and 3.4%), cataract (11.3% and 2.0%), nausea (7.7% and 0.0%), diarrhoea (6.7% and 0.5%), and hypophosphataemia (5.6% and 1.5%).[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Selinexor is a first-in-class medicine, and would provide another oral option for MM patients who have had at least one prior therapy.[1, 2]
- In the BOSTON study, the addition of selinexor to bortezomib and dexamethasone resulted in statistically significant improvements in PFS and ORR for the ITT population[10]; and a numerically favourable DOR.[2]
- Evidence to support the indication and positioning under review is based on the subpopulation of BOSTON with lenalidomide-refractory patients. The results of the lenalidomide-refractory subpopulation were consistent with the ITT population for PFS, ORR, DOR.

4.2. Key uncertainties

- The supportive lenalidomide-refractory subgroup analyses were not pre-specified and the subgroup only represents 26% of the ITT population in BOSTON.
- The efficacy of selinexor plus bortezomib and dexamethasone at each individual line of therapy (that is 2L, 3L, and 4L) is uncertain.
- The subgroup analyses presented by the submitting company do not exactly match the eligible population outlined in their proposed positioning.
- There were potential generalisability issues noted within the lenalidomide-refractory subgroup (n=106). The median age was 66 years, and the majority of patients (92%) had an ECOG PS of 0 or 1; this likely represents a younger and fitter population than the population in Scottish clinical practice and the rates of AEs, and treatment discontinuations may be higher in this MM population in Scottish clinical practice than is reported in the study.
- No robust survival benefit has been demonstrated; however, OS results numerically favoured the selinexor regimen over the control group in the ITT population and the lenalidomide-refractory subgroup. Factors which may have confounded survival results include: the use and choice of subsequent treatments [7]; crossover was allowed and BOSTON's overall survival data was sensitive to adjustments for treatment crossover.
- The indirect treatment comparisons had limitations including:
    - Comparisons were only made against carfilzomib plus dexamethasone; other potential comparators outlined by clinical experts contacted by SMC, for example bortezomib plus dexamethasone, and pomalidomide plus dexamethasone, have not been provided.
    - There were issues with the generalisability of the studies relating to the age, prior cardiac issues and race of patients compared to Scottish practice, the lack of pomalidomide as a comparator and the number of patients with previous anti-CD38 use.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that the selinexor regimen fills an unmet need and is a therapeutic advancement in this area, as it provides a triplet regimen option over doublet alternatives and may provide higher response rates and progression-free survival. Some experts highlighted that it is also a useful option for patients in locations that are geographically challenging.

4.4. Service implications

No significant additional service implications are anticipated since this would be an oral medicine added onto an already available treatment combination of bortezomib plus dexamethasone.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **selinexor (Nexpovio®),** as an **orphan equivalent** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Multiple myeloma is a chronic, life-limiting blood cancer, which can have significant complications that are debilitating and painful, and drastically affect a person's quality of life.
- Despite numerous treatment options, multiple myeloma remains incurable and as the disease relapses and clinical picture deteriorates, there is a need for increased medical care and a greater dependence on family and/or carers; this has significant social and financial implications. Additionally, each additional line of treatment is associated with worse outcomes, reduced remission times, and increased side effects.
- The BOSTON study showed that the addition of selinexor to bortezomib and dexamethasone has clinical benefits in patients who received second- to fourth-line myeloma treatments; these benefits likely extend to lenalidomide-refractory patients as well.
- The addition of selinexor to bortezomib and dexamethasone resulted in increased adverse events, though grade 3 or 4 infective and neuropathic side effects did not appear to be significantly increased.
- PACE clinicians considered there may be selected patients who would benefit from this selinexor regimen based on their prior treatment and response; it would also offer another treatment option that could be used further down the treatment pathway.
- Families and carers would welcome a treatment that could keep the patient alive and well for longer; this would likely translate into substantial health benefits to their emotional and psychological wellbeing.
- Treatment with selinexor plus bortezomib and dexamethasone would require day unit attendance with subsequent resource use. Clinic visits for monitoring and blood testing would also be needed to monitor response, as with all myeloma treatments. Nausea and weight loss have been noted as problems with this medicine and dietetic support may be required for

some patients, especially those who are frailer.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 5.65% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Myeloma UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary of the economic case is presented in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (35 years)
Population	The economic evaluation considered the cost-effectiveness of selinexor in combination with bortezomib and dexamethasone for multiple myeloma patients who had 1 to 3 prior lines of therapy and were refractory to lenalidomide and unsuitable for an anti-CD38 antibody.
Comparators	Selinexor in combination with bortezomib and dexamethasone was compared with carfilzomib in combination with dexamethasone.
Model description	A partitioned survival model was adopted. The model health states were progression-free, progressed and dead. The model had a cycle length of one week with a half-cycle correction applied. The patients entered the model in the progression-free health state and moved either to the progressed health state, death or they discontinued treatment. Those who progressed were assumed to receive subsequent treatments at the same rate as that of the BOSTON study at 79.5%.[10]
Clinical data	The economic evaluation was based on the clinical evidence from the BOSTON study.[10] This was an international, randomised, open-label, phase III study. The submitting company provided data from a post-hoc subgroup analysis of the lenalidomide-refractory patients which informed the economic evaluation.
Extrapolation	OS, PFS and ToT data were extrapolated. The extrapolation was based on the Kaplan Meier estimates of the lenalidomide-refractory subgroup in BOSTON. For the extrapolation of the comparator arm the company applied the hazard ratios of carfilzomib plus dexamethasone versus bortezomib plus dexamethasone derived from the indirect treatment comparison. The hazard ratio was applied to parametric curves fitted to the bortezomib plus dexamethasone arm of BOSTON.
Quality of life	Utility values applied in the base case were derived from the BOSTON study. The values for the PFS health state was 0.710 and the progressed health state was 0.689. Adverse event decrements were applied as a one-off decrement in the first model cycle. Age-adjustment of utilities was not included in the base case.
Costs and resource use	Medicine costs included were acquisition costs, administration costs, adverse event costs and subsequent treatment costs. Other costs included in the model were health state resource use costs and terminal care cost. Health state resource use costs were assumed to be equal between the treatment arms and adverse event costs were applied as a one-off cost in the first model cycle.
PAS	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 NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for pomalidomide, panobinostat and carfilzomib and these were included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The results presented do not take account of the PAS for comparator medicines, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for comparator medicines due to commercial confidentiality and competition law issues.

Base case results are presented in Table 6.2. Selinexor plus bortezomib and dexamethasone was dominant compared to carfilzomib plus dexamethasone meaning it was estimated as resulting in lower costs and better health outcomes for patients. Disaggregated results showed most of the cost savings came from the acquisition costs of the intervention medicines and the administration costs. The greatest life years gained and quality-adjusted life years (QALYs) gained came from the progressed disease health state, though the incremental gains for these outcomes were small with the main driver of the results coming from the cost savings.

Table 6.2 Base Case Results (PAS price for selinexor only)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Selinexor plus bortezomib and dexamethasone	£153,656	1.73	-£139,232	0.23	0.15	Dominant
Carfilzomib plus dexamethasone	£292,888	1.58	-	-	-	-

Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.; Incr. = incremental; ICER = incremental cost-effectiveness ratio; LYG= life years gained; PAS = patient access scheme; QALYs =quality-adjusted life years

6.3. Sensitivity analyses

Table 6.3.1 presents a selection of scenario analyses. Two scenarios generated results in the south-west quadrant. These were generated by applying the lognormal and log-logistic OS curves.

Table 6.3.1 Scenario Analysis Results (PAS price for selinexor only)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			-£139,232	0.15	Dominant
1	Time horizon	35 years	10 years	-£135,123	0.16	Dominant
2	Referent arm	Vd	SVd	-£45,362	0.48	Dominant
3	OS curve fitted to BOSTON (SVd and Vd arms)	Weibull	Exponential	-£139,401	0.57	Dominant
4	OS curve fitted to BOSTON (SVd and Vd arms)	Weibull	Lognormal	-£146,656	-0.25	£592,717 (SW)
5	OS curve fitted to BOSTON (SVd and Vd arms)	Weibull	Log-logistic	-£146,820	-0.31	£469,903 (SW)
6	OS curve fitted to BOSTON (SVd and Vd arms)	Weibull	Gompertz	-£126,122	0.21	Dominant
7	OS curve fitted to BOSTON (SVd and Vd arms)	Weibull	Generalised gamma	-£102,676	0.45	Dominant
8	OS curve fitted to BOSTON (SVd and Vd arms)	Weibull	Gamma	-£139,825	0.23	Dominant

9	PFS curve fitted to BOSTON (SVd and Vd arms)	Lognormal	Exponential	-£105,051	0.15	Dominant
10	PFS curve fitted to BOSTON (SVd and Vd arms)	Lognormal	Weibull	-£108,026	0.15	Dominant
11	PFS curve fitted to BOSTON (SVd and Vd arms)	Lognormal	Log-logistic	-£138,757	0.15	Dominant
12	PFS curve fitted to BOSTON (SVd and Vd arms)	Lognormal	Gompertz	-£135,248	0.15	Dominant
13	PFS curve fitted to BOSTON (SVd and Vd arms)	Lognormal	Generalised gamma	-£138,701	0.16	Dominant
14	PFS curve fitted to BOSTON (SVd and Vd arms)	Lognormal	Gamma	-£105,681	0.15	Dominant
15	Comparator ToT assumption	Treated until discontinuation	Treated until progression	-£176,803	0.15	Dominant
16	Utility source	BOSTON sub-group	BOSTON ITT	-£139,232	0.14	Dominant
17	Utility source	BOSTON sub-group	Hatswell et al. (2019)	-£139,232	0.12	Dominant

Abbreviations: Incr. = Incremental; ICER =incremental cost-effectiveness ratio; ITT = intention to treat; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year; SVd = selinexor plus bortezomib and dexamethasone; ToT = time on treatment; Vd = bortezomib plus dexamethasone;
Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.
SW: The estimated result sits in the South-West (SW) quadrant of the cost-effectiveness plane meaning the assessed medicine had lower costs and lower health outcomes than the comparator.

Table 6.3.2. presents the requested scenario analyses received.

Table 6.3.2 Requested Scenario Analysis Results (PAS price for selinexor only)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			-£139,232	0.15	Dominant
1	Line of treatment	2L-4L	2L	-£150,754	CIC	Dominant
2	Line of treatment	2L-4L	2L ITT	-£295,683	-0.01	£51,705,201 (SW)
3	Line of treatment	2L-4L	3L ITT	-£341,085	-0.08	£4,305,994 (SW)
4	Extrapolation	Subgroup values	ITT values	-£277,658	-0.47	£586,624 (SW)
5	HR	Different HR between SVd and Kd	HR between SVd and Kd set to 1	-£93,500	-0.01	£6,567,072 (SW)
6	Subsequent treatment	Company estimates	SMC estimates	-£144,860	0.15	Dominant
7	Comparator	Kd	pomalidomide + dexamethasone	£32,009	0.54	£58,977

8	Combined scenario		ITT values + HR for SVd vs Kd is set to 1 + Age-adjusted utilities	-£135,228	-0.01	£134,803 (SW)

Abbreviations: CIC = commercial in confidence; Incr. = Incremental; ICER =incremental cost-effectiveness ratio; ITT = intention to treat; Kd = carfilzomib in combination with dexamethasone; QALY = quality-adjusted life year; SVd = selinexor plus bortezomib and dexamethasone; ToT = time on treatment.Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.SW: The estimated result sits in the South-West (SW) quadrant of the cost-effectiveness plane meaning the assessed medicine had lower costs and lower health outcomes than the comparator.

6.4. Key strengths

- The model type was appropriate.
- Utility values were applied treatment-independent, which is appropriate.

6.5. Key uncertainties

- Based on expert responses, pomalidomide plus dexamethasone and bortezomib plus dexamethasone were also considered relevant comparators. Scenario 7 explored the cost-effectiveness of selinexor plus bortezomib and dexamethasone versus pomalidomide plus dexamethasone. The Committee noted the impact on the ICER in this scenario but were satisfied that carfilzomib plus dexamethasone was likely to be the main comparator and the treatment most likely to be displaced.
- The patient population in the BOSTON study were likely younger and fitter than the patient population in Scottish clinical practice. The submitting company was asked to provide results based on the older cohort of the ITT and lenalidomide-refractory subgroup, but declined to provide these results on the basis that frailty, rather than age, is a more important factor in determining choice of therapy.
- Clinical data underpinning the model results are uncertain. Firstly, the lenalidomide-refractory subgroup was not pre-specified and secondly, comparative effectiveness is estimated based on results from the indirect treatment comparison, which had some limitations. Extrapolation using values for the ITT population was requested and did result in a QALY loss with an increase in cost savings. Due to these uncertainties, the Committee noted scenarios 5 and 8 in table 6.3.2 as being relevant for decision-making.
- Results based on lines of treatments were provided upon request. Due to a lack of data, third-line treatment results were only available from the ITT population and no results were available for the fourth-line.

7. Conclusion

The Committee considered the benefits of selinexor in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as selinexor is an orphan-equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted selinexor for restricted use in NHSScotland.

8. Guidelines and Protocols

The British Society for Haematology (BSH) published "Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline" in March 2021.[9]

The European Society for Medical Oncology (ESMO) and the European Haematology Association (EHA) published "Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in February 2021.[8]

The National Institute for Health and Care Excellence (NICE) published "Myeloma: diagnosis and management" (NG35) in February 2016, which was updated in October 2018.[11]

The European Myeloma Network published "European Myeloma Network guidelines for the management of multiple myeloma-related complications" in October 2015 and published "From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives" in February 2018.[12, 13]

9. Additional Information

9.1. Product availability date

08 November 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 35-day cycle (£)
Selinexor; bortezomib; dexamethasone	Selinexor orally: 100 mg on day 1, 8, 15, 22, and 29 of each 35-day cycle; Bortezomib subcutaneously: 1.3 mg/m^2 on day 1, 8, 15, and 22 of each 35-day cycle; Dexamethasone orally: 20 mg on day 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle. Treatment should be continued until disease progression or unacceptable toxicity.	**£13,698**

Costs from BNF online on 22 May 2024. Costs based on body surface area of 1.8m^2 and are calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

SMC clinical expert input stated the number of eligible patients and uptake were likely overestimated.

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

References

1. Menarini Stemline UK Ltd. Selinexor 20 mg film coated tablets (Nexpovio®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk Last updated: 07 Feb 2024.
2. European Medicines Agency (EMA). European Public Assessment Report. Selinexor (Nexpovio®). EMEA/H/C/005127/II/0001/G. Published: 19 May 2022. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio [Accessed: 16 May 2024].
3. Cancer Research UK (CRUK). Myeloma statistics: Myeloma Incidence. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Zero [Accessed: 05 September 2023].
4. Public Health Scotland. Cancer incidence and prevalence in Scotland to December 2019. Published: 2021. Available at: https://publichealthscotland.scot/publications/cancer-incidence-in-scotland/cancer-incidence-in-scotland-cancer-incidence-and-prevalence-in-scotland-to-december-2019/ [Accessed: 16 May 2024].
5. Public Health Scotland. Cancer survival in Scotland (to 2019). Published: 05 July 2022. Available at: https://www.publichealthscotland.scot/media/14024/2022-07-05-cancer-survival-report.pdf [Accessed: 16 May 2024].
6. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA*, et al.* Diagnosis and Management of Multiple Myeloma: A Review. JAMA. 2022;327(5):464-77.
7. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. Oct 2016;175(2):252-264. doi:10.1111/bjh.14213
8. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G*, et al.* Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(3):309-22.
9. Sive J, Cuthill K, Hunter H, Kazmi M, Pratt G, Smith D. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. Br J Haematol. 2021;193(2):245-68.
10. Grosicki S, Simonova M, Spicka I, Pour L, Kriachok I, Gavriatopoulou M*, et al.* Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020;396(10262):1563-73.
11. National Institute for Health and Care Excellence (NICE). Myeloma: diagnosis and management - NICE guideline 35 [NG35]. Published: 10 February 2016; Last updated: 25 October 2018. Available at: https://www.nice.org.uk/guidance/ng35 [Accessed: 28 May 2024].
12. Gay F, Engelhardt M, Terpos E, Wäsch R, Giaccone L, Auner HW*, et al.* From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives. Haematologica. 2018;103(2):197-211.
13. Terpos E, Kleber M, Engelhardt M, Zweegman S, Gay F, Kastritis E*, et al.* European Myeloma Network guidelines for the management of multiple myeloma-related complications. Haematologica. 2015;100(10):1254-66.

This assessment is based on data submitted by the applicant company up to and including 12 July 2024.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine 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 medicine 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 NHSScotland 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 NHSScotland 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.