SMC2673

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 end of life and orphan equivalent medicine process

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

Indication Under Review: in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

In a single-arm, open-label, phase IIb study, selinexor plus dexamethasone resulted in an overall response rate of 25%, in patients with multiple myeloma that was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab.

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, reversible covalent, selective inhibitor of nuclear export (SINE) compound that inhibits XPO1 causing 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 dexamethasone to maximise synergistic cytotoxic effects in multiple myeloma.[1, 2]

For this indication, the recommended dose (based on a 28-day cycle) is selinexor 80 mg plus dexamethasone 20mg orally on days 1 and 3 every week. Treatment should be continued until disease progression or unacceptable toxicity. Refer to the summary of product characteristics for dose reduction steps for adverse reactions.[1]

1.2. Disease background

Multiple myeloma 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, and kidney dysfunction.[2, 3] Multiple myeloma accounts for 2% of all new cancer cases every year in the UK, with 6,200 new cases each year.[4] The incidence of multiple myeloma in Scotland is estimated to be 8.8 per 100,000 people.[5] Multiple myeloma predominantly affects older people and the median age at diagnosis is approximately 70 years, with more than 40% of new cases being diagnosed in those aged 75 or above.[2, 4] 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.[6] There is a paucity of overall survival (OS) data in penta-refractory multiple myeloma (that is, refractory to one anti-CD38 monoclonal antibody, two proteasome inhibitors and two immunomodulatory drugs). However, median OS has been estimated at 5.6 to 7.1 months.[7-12]

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 response rates and duration of response; likely due to continuous changes in the disease biology, in which a higher proportion of malignant cells express a more aggressive, highly proliferative phenotype over time.[2, 3] Furthermore, not all patients are well enough to receive subsequent lines of therapy; in Europe (including the UK) it is estimated that around 95% of those diagnosed with multiple myeloma receive first-line (1L) treatment, of which 61% receive second-line (2L) treatment, and around 38% receive third-line (3L).[2, 13] Additionally, only 1% reached the fifth-line stage, though this was reported in 2016.[13]

1.3. Treatment pathway and relevant comparators

Treatment options for patients with multiple myeloma include: glucocorticoids (dexamethasone and prednisolone), proteasome inhibitors (bortezomib and carfilzomib), histone deacetylase inhibitors (panobinostat), immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), anti-CD38 monoclonal antibodies (daratumumab and isatuximab), high-dose chemotherapy and autologous stem cell transplantation.[2, 14, 15]

The approval of daratumumab and its increased usage in earlier lines of treatment has resulted in a new group of patients with multiple myeloma that is classified as 'triple-class refractory', that is with disease that is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent, and an anti-CD38 monoclonal antibody.[2] At the fifth-line stage and beyond (5L+), patients have generally been exposed to all medicines that have demonstrated efficacy as monotherapy (with or without glucocorticoids), including bortezomib (PI), carfilzomib (PI), lenalidomide (immunomodulatory agent), pomalidomide (immunomodulatory agent), daratumumab (anti-CD38 monoclonal antibody), and isatuximab (anti-CD38 monoclonal antibody).[2, 7, 16]

Experts contacted by SMC highlighted that there is currently no standard of care fifth-line treatment option for refractory multiple myeloma. Potential treatment options include: cyclophosphamide +/- dexamethasone; bendamustine; panobinostat plus bortezomib and dexamethasone; bortezomib plus dexamethasone; pomalidomide plus dexamethasone; and best supportive care. European guidelines recommend selinexor plus dexamethasone as a treatment option for triple-class refractory patients.[14]

1.4. Category for decision-making process

Eligibility for a PACE meeting:
Selinexor meets SMC orphan equivalent and end of life criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support selinexor plus dexamethasone for the indication under review comes from the STORM study (part 2). Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	STORM study (part 2)[2, 17-19]
Study Design	An international, single-arm, two-part, open-label, phase IIb study. Part 2 of STORM included patients with penta-exposed, triple-class refractory multiple myeloma, defined as quad-refractory plus prior treatment with daratumumab. Therefore, only part 2 of this study is relevant to this submission.
Eligible Patients	• Age ≥ 18 years. • Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2. • Measurable disease as per International Myeloma Working Group (IMWG) guidelines. • Had previous treatment with ≥3 antimyeloma regimens including: an alkylating agent, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab and a glucocorticoid. • Had refractory multiple myeloma[a] to at least: one immunomodulatory drug (that is, lenalidomide and/or pomalidomide), one proteasome inhibitor (that is, bortezomib and/or carfilzomib), glucocorticoids and daratumumab. • Refractory to the most recent antimyeloma regimen.
Treatments	All patients enrolled into STORM part 2 received: • Oral selinexor 80 mg (or 45 mg/m^2) on days 1 and 3 every week (as part of a 28-day cycle). • Oral dexamethasone 20 mg on days 1 and 3 every week (as part of a 28-day cycle). Treatment continued until disease progression, death, or unacceptable toxicity. Concomitant antiemetics (for example ondansetron) were permitted during the study.

Primary outcome	Overall response rate (ORR), defined as stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR), assessed by an independent review committee (IRC) based on the 2016 IMWG response criteria.
Secondary outcomes	These included but were not limited to: duration of response (DOR), progression-free survival (PFS), overall survival (OS), time to progression (TTP) and time to next treatment (TTNT).
Statistical analysis	The primary efficacy analysis was performed in the modified intention-to-treat (mITT) population, which included all patients with penta-exposed, triple-class refractory multiple myeloma who met all eligibility criteria and received at least one dose of selinexor plus dexamethasone. No formal statistical analysis was conducted; results are descriptive only.

[a]Refractory multiple myeloma was defined as: progression during treatment or within 60 days after completing therapy, or ≤25% response to therapy.

Among the 123 patients enrolled in STORM part 2, 68% (83/123) of patients had multiple myeloma that was refractory to two proteasome inhibitors (bortezomib and carfilzomib), two immunomodulators (lenalidomide and pomalidomide) and an anti-CD38 monoclonal antibody (daratumumab); that is, they were penta-refractory. This subpopulation, termed the BCLPD (bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab)-refractory subpopulation, was pre-specified and was the primary population that supported the licence for this indication.[1] The results from the final updated analysis (data cut-off September 2019) are presented in Table 2.2.

Table 2.2. Results of primary and selected secondary outcomes of the STORM study (part 2) in the BCLPD-refractory subpopulation (data cut-off September 2019)[1, 2]

	Selinexor plus dexamethasone (n=83)
Primary outcome: ORR as per IRC assessment	
Overall response rate, % (n)	25% (21)
Stringent Complete Response, % (n)	1.2% (1)
Complete Response, % (n)	0% (0)
Very Good Partial Response, % (n)	4.8% (4)
Partial Response, % (n)	19% (16)
Secondary outcome: DOR as per IRC assessment	
Median DOR (95% CI)	3.8 months (2.3 to 10.8)
Secondary outcome: PFS as per IRC assessment	
Median PFS (95% CI)	2.8 months (1.9 to 4.3)
Secondary outcome: OS	
Median OS (95% CI)	8.4 months (5.9 to 11.2)

BCLPD = bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab; CI = confidence interval; DOR = duration of response; IRC = independent review committee; ORR = overall response rate; OS = overall survival; PFS = progression-free survival

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the Functional Assessment of Cancer Therapy–Multiple Myeloma (FACT-MM) questionnaire. This questionnaire combines the General version of the FACT (FACT-G; 27 items) with a myeloma-specific subscale (MM domain; 14 items). The total FACT-MM score is obtained by adding individual subscale scores for physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items) and functional well-being domains (7 items) of the FACT-G and the MM domain. The FACT-MM Trial Outcomes Index (TOI) is comprised of the physical and functional subscales and the MM domain. Overall, most

patients in the BCLPD-refractory population maintained HRQoL, based on validated patient-reported FACT-G, FACT-MM and FACT-MM TOI scores.[20] The FACT-G HRQoL data were used in a mapping procedure to generate EQ-5D-3L data for use in the economic model.

2.3. Supportive studies

Supportive results come from part 1 of the STORM study; the results from this part of the study as well as the changing multiple myeloma treatment landscape contributed to the part 2 study design. Part 1 included patients with both quad-exposed (lenalidomide, pomalidomide, bortezomib and carfilzomib), double-class-refractory (at least one proteasome inhibitor and one immunomodulatory agent) and penta-exposed, triple-class-refractory multiple myeloma (quad + refractory and either daratumumab or isatuximab) patients. Part 1 recruited 79 patients, with 19 patients (24%) being penta-refractory. Two dosing schedules were assessed in part 1: selinexor 80 mg twice-weekly for 3 weeks of each 4-week cycle and selinexor 80 mg twice-weekly continuously in 4-week cycles; dexamethasone 20 mg twice-weekly was given with each dose of selinexor. All outcomes assessed in part 1 were exploratory efficacy analyses. ORR by IRC assessment was 20% (16/79), including four (5.1%) patients with a VGPR (5.1%) and 12 (15%) patients with a PR; these values were slightly lower than those in part 2 but were consistent. For patients with a response, the median DOR was 6.2 months (95% confidence interval [CI]: 3.6 to 9.8). The median PFS was 4.7 months (95% CI: 3.3 to 7.6) and the median OS was 7.3 months (95% CI: 5.8 to 10.9).[2]

The BOSTON study is an international, randomised, open-label, phase III study, in patients with multiple myeloma who had received one to three prior antimyeloma regimens, and had disease progression on or after their most recent regimen. Patients were randomised equally to receive selinexor plus bortezomib and dexamethasone (n=195) or bortezomib plus dexamethasone (n=207). At the final analysis (data cut-off February 2021), in the selinexor plus bortezomib and dexamethasone group and the bortezomib plus dexamethasone groups respectively: the median PFS by IRC assessment was 13.2 months versus 9.5 months; the median OS was 36.7 months versus 32.8 months; the ORR was 77% versus 63%. While this study was completed as a confirmatory study, mainly for safety data, it provided less support from an efficacy perspective since the treatments were given in prior lines of treatment. Additionally, very small proportions of patients in the intention-to-treat (ITT) population had prior daratumumab exposure (4.2% [17/402]) or refractoriness to daratumumab (4.0% [16/402]), lenalidomide exposure (38% [154/402]) and refractoriness to lenalidomide (26% [106/402]).[2]

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

A simulated treatment comparison (STC) and unanchored matching adjusted indirect comparison (MAIC) were conducted comparing the efficacy of selinexor plus dexamethasone (using data from STORM part 2) versus standard of care (using data from the MAMMOTH study) in adult patients with penta-refractory multiple myeloma. Only overall survival was assessed, as progression-free survival was not reported in the MAMMOTH penta-refractory subgroup. The STC was used in the economic base case and the MAIC was used in economic scenario analysis.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Simulated treatment comparison (STC) and unanchored matching adjusted indirect comparison (MAIC).
Population	Adult patients with penta-refractory multiple myeloma (that is, refractory to one anti-CD38 monoclonal antibody, two proteasome inhibitors and two immunomodulatory agents).
Comparators	Standard of care (n=63 in the MAMMOTH study), which was used as a proxy for best supportive care (BSC).
Studies included	STORM part 2 BCLPD-refractory population (n=83)[1, 2] and MAMMOTH penta-refractory subgroup (n=70).[7]
Outcomes	Overall survival only (progression-free survival was not reported in the MAMMOTH subgroup).
Results	In the STC analysis, selinexor plus dexamethasone was associated with significantly longer overall survival compared with standard of care. In the MAIC analyses, there was no significant difference in overall survival after adjustment. **STC results - hazard ratio (HR) (95% confidence interval [CI])** Lognormal model: HR 0.43 (95% CI: 0.23 to 0.80) **MAIC results – HR (95% CI)** Naïve analysis (unweighted): HR 0.63 (95% CI: 0.44 to 0.90) Fully adjusted: HR 0.68 (95% CI: 0.33 to 2.10)

3. Summary of Safety Evidence

The European regulator deemed the tolerability of selinexor to be low and the observed toxicity to be significant. However, this was considered manageable with appropriate monitoring and dose adjustments or discontinuation.[2] Comparative safety data from the phase III BOSTON study provided further data to characterise the safety profile of selinexor.[2, 21] The European regulator deemed the safety profile in the penta-refractory subpopulation (n=83) in STORM part 2 to be consistent with that of the overall population (n=123), including all adverse events (AE), serious AEs and discontinuations due to AEs, with no new safety signals observed. This is reassuring, since these are the most heavily pre-treated patients in the STORM study.[2]

Treatment exposure to selinexor between the two populations were also consistent (median duration of 9.0 weeks).[2] However, there was a lower median total dose received per week in the BCLPD-refractory subpopulation, likely reflective of their fitness.

In the STORM part 2 ITT population (n=123), there were high rates of treatment-related AEs leading to: dose modifications (72%), dose reductions (57%), dose interruptions (52%), and study discontinuation (20%). Treatment-related serious AEs were 31%, whilst treatment-related AEs leading to death was 2.4%.[2]

The economic model uses the rates of all grade 3 to 4 treatment-related AEs associated with selinexor plus dexamethasone from the STORM part 2 safety analysis population, rather than those for the BCLPD-refractory subpopulation. At the September 2019 data cut-off, most treated patients in STORM part 2 (89%) had a severe (≥ grade 3) treatment-related AE. The most frequently occurring (>5% of patients) severe AEs related to selinexor plus dexamethasone treatment were: thrombocytopenia (59%), anaemia (31%), neutropenia (20%), fatigue (19%),

hyponatraemia (18%), leukopenia (13%), lymphopenia (8.9%), nausea (8.9%), hyperglycaemia (7.4%) and diarrhoea (5.9%).[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- The BCLPD-refractory subpopulation in STORM part 2 meets the criteria of penta-refractory multiple myeloma, with all patients receiving four or more prior therapies and being refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab (agents that are used in NHSScotland for the treatment of multiple myeloma before the fifth-line stage).[2, 7, 16] Multiple myeloma studies predominantly report outcomes based on the number of previous lines of therapy, but refractoriness to previous therapies is clinically more relevant.[7, 16] Given that penta-refractory multiple myeloma remains a therapeutic challenge the results of STORM part 2 indicate activity in this population with unmet need.
- Given that ORR decreases with each subsequent therapy in patients with relapsed and refractory multiple myeloma, and complete responses are rarely achieved, the ORR was deemed by regulators to translate into clinically meaningful benefit. Additionally, the median DOR (3.8 months), while short, was considered to have some clinical relevance for patients who have a response and in the context of the penta-refractory stage.[2]

4.2. Key uncertainties

- STORM part 2 was an open-label, phase IIb study with no comparator group. The sample size was small (n=123). Although ORR and DOR can be considered relevant endpoints to conclude on an effect that is likely to translate into clinically meaningful benefit in the penta-refractory setting, the single-arm study design means there is no comparison of PFS and OS in this patient population to other options.[2]
- The median OS in the BCLPD-refractory subpopulation of STORM part 2 was 8.4 months and was longer in patients who had a PR or better. However, these OS results may be confounded by the use of subsequent therapies not routinely used in clinical practice in Scotland.
- There are uncertainties regarding tolerability and the rates of adverse events for selinexor in older patients. In STORM parts 1 and 2 (n=214), only 11% were 75 years of age and over, and these patients had a higher incidence of serious (74% versus 59%) and fatal (22% versus 8.0%) adverse reactions and a higher incidence of discontinuation due to an adverse reaction (52% versus 25%) than patients aged <75 years.[1] There was also an increased frequency of pneumonia and decreased appetite observed in patients 75 years and older.[2] Clinical experts consulted by SMC also raised uncertainties about the number of penta-refractory multiple myeloma patients that would be fit enough to receive this treatment.
- The indirect treatment comparisons had the following limitations which makes the companies' conclusions of superiority of selinexor plus dexamethasone over BSC uncertain:
    - Data in both indirect comparisons came from small subgroups within a single-arm, phase II study (STORM) and an observational, retrospective study (MAMMOTH).

- The included studies may affect the generalisability of the results to Scottish clinical practice. MAMMOTH was a US study and it is unclear whether standard of care treatment is reflective of BSC in Scottish practice.
- Inconsistencies between the MAIC and STC results increase uncertainty. Compared with the naïve analysis (HR of 0.63), the STC adjustment appeared to increase the relative efficacy of selinexor plus dexamethasone (HR of 0.43), while in the MAIC adjustment had the opposite effect on the results (HR of 0.68 in the full model). Overall, the statistician consulted by SMC favoured the naïve comparison due to conflicting results between the ITC analyses and uncertainty about the clinical plausibility of the results. The hazard ratio from the STC was applied in the economic base case.
- Progression-free survival was not reported in the MAMMOTH study and therefore could not be assessed. Moreover, safety and health-related quality of life outcomes were not assessed.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that selinexor plus dexamethasone fills an unmet need in this therapeutic area, and is a therapeutic advancement, as it provides a treatment option to this patient population who have exhausted most available treatments.

4.4. Service implications

Clinical experts consulted by SMC considered that no significant additional service implications are anticipated.

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. There is no established standard of care for treating multiple myeloma at the fifth-line setting and beyond in NHS Scotland.
- The STORM study part 2 showed that selinexor plus dexamethasone has clinical benefits in this heavily pre-treated population. However, there is uncertainty about whether patients

who have a response to this medicine, would be able to maintain good quality of life or return to work. PACE clinicians outlined that selinexor plus dexamethasone would represent a useful treatment option for a small number of fitter patients. However, the significant toxicity profile, which includes manageable side effects, may limit its wider use.

- Families and carers would welcome a treatment that could keep the patient alive and well for longer; with expected benefits to their emotional and psychological wellbeing.
- Selinexor is administered orally, in combination with oral dexamethasone, twice-weekly; this would likely represent a more manageable dosing schedule than some of the other treatments (for example less day unit visits for parenteral administration) used at the fifth-line stage.

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 analysis provided by the submitting company is outlined in table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime horizon, with baseline starting age of 64.5 years in the model. After 30 years <1% of patients remained alive.
Population	In combination with dexamethasone for the treatment of multiple myeloma after at least four prior therapies and whose disease is refectory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody (penta-refractory), and who have demonstrated disease progression on the last therapy.
Comparators	Best supportive care (BSC), which included chemotherapy (cyclophosphamide plus dexamethasone or bendamustine plus methylprednisolone) for 65% of patients. The remaining 35% were assumed to receive symptomatic treatment or end of life care only.
Model description	A partitioned survival model was used with three health states: progression-free, progressed disease and death. Patients were also categorised into on and off treatment in the PFS health state.
Clinical data	The key clinical data source for the selinexor arm was the pre-specified penta-refractory subgroup of patients (n=83) in the STORM part 2 study.[1, 2] For BSC, data were taken from the MAMMOTH study.[7]
Extrapolation	Survival modelling was conducted with distributions selected based on visual fit, statistical fit and plausibility of extrapolated estimates. In the base case, for both PFS and overall survival estimates the log-normal distribution was used, which predicted a 5-year survival rate of 6.4% for selinexor. To estimate OS for the BSC arm, the hazard ratio from the STC

	was applied to the extrapolated STORM OS curve. Due to a lack of PFS data in the MAMMOTH study it was assumed there would be no difference in PFS between selinexor and BSC.
Quality of life	Quality of life data were collected in the STORM part 2 using the disease-specific Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM) patient-reported outcome measure. No published mapping algorithm was identified to map the FACT-MM data to EQ-5D but a mapping algorithm was identified for the broader FACT-G component. In the base case analysis, the company selected the progression-free utility value derived from mapping the STORM FACT-MM data to EQ-5D using the published mapping algorithm for FACT-G to EQ-5D (0.589). For the progressed disease health state, the relative utility decrement from PFS to PD observed in the DREAMM-2 study (9.2%) was applied to the progression-free value resulting in PD value of 0.535.[22, 23] Disutilities associated with grade 3 and 4 adverse events were included in the selinexor arm only.
Costs and resource use	Costs included medicine acquisition, administration, subsequent treatment, health state, concomitant medication and terminal care costs. For BSC, costs of cyclophosphamide plus dexamethasone and bendamustine plus methylprednisolone were included for 65% of patients, with an assumed 80:20 split of the chemotherapy regimens based on clinical expert opinion. Costs of grade 3 and 4 adverse events were included in the selinexor arm resulting in a cost of £3,621 per patient. No adverse event costs were included in BSC.
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.

6.2 Results

The base case results are presented in table 6.2 below.

Table 6.2 Base Case Results (PAS price)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
selinexor	30,967	0.773	14,106	0.968	0.510	27,665
BSC	16,861	0.264	-	-	-	-

Abbreviations: BSC = best supportive care; Incr. = incremental; ICER = incremental cost-effectiveness ratio; LYG= life years gained; PAS = patient access scheme; QALYs =quality-adjusted life years

6.3 Sensitivity analyses

Key sensitivity and scenario analyses are presented in table 6.3.

Table 6.3 Sensitivity and Scenario Analysis Results (PAS price)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			14,106	0.510	27,665
1	Time horizon	Lifetime (30-year)	10 years	13,834	0.471	29,388
2	OS extrapolation	Log-normal	Weibull	13,891	0.324	42,896
3			Exponential	13,846	0.311	44,500
4			Gamma	13,839	0.310	44,705

5	Indirect comparison OS hazard ratio	STC (HR = 0.43)	Upper range of OS lognormal distribution (HR = 0.63)	13,762	0.361	38,076
6	TTD source	TTD data from STORM Part 2	PFS	19,202	0.510	37,660
7	Selinexor weekly dosage	Mean dose from STORM Part 2 (114.4mg)	160mg	17,300	0.510	33,929
8	Utility source	STORM Part 2 (BCLPD) with DREAMM2 relative decrement PFS = 0.589 PD = 0.535	STORM Part 2 (BCLPD) with TA658 relative decrement (0.589, 0.502)	14,106	0.478	29,523
9			DREAMM2 (0.731,0.664)	14,106	0.632	22,303
10			TA658 (0.718,0.611)	14,106	0.582	24,232
11			STORM Part 2 (0.589,0.607)	14,106	0.561	25,138
12	PD utility value	0.535	0.33	14,106	0.311	45,393
13	Adverse event cost per patient in selinexor arm	£3,621	Cost per patient increased to £5,040	15,525	0.510	30,449
14	Combined scenario		Scenarios 1, 2 and 8 combined	13,889	0.303	45,773
Additional scenarios requested post-NDC						
15	Combined scenario	• Upper value for OS distribution (HR = 0.63) • Upper value for selinexor adverse event costs (£5,040 per patient) • 10 year time horizon		14,932	0.324	46,063
16	Combined scenario	As scenario 15 but with a 5 year time horizon		14,396	0.260	55,344

Abbreviations: BCLPD = bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab-refractory subgroup; BSC = best supportive care; HR = hazard ratio; Incr. = Incremental; ICER =incremental cost-effectiveness ratio; OS = overall survival; PAS = patient access scheme; PFS = progression free survival; QALY = quality-adjusted life year; STC = simulated treatment comparison.

6.4 Key strengths

- The analysis was clearly presented with a range of sensitivity analyses provided to test the key uncertainties. Quality of life data were available from the key clinical study.

6.5 Key uncertainties

- Clinical data limitations – the clinical data underpinning the economic model estimates were uncertain and associated with some limitations, such as a lack of comparative data and small sample size. This introduces uncertainty in the cost-effectiveness estimates.
- Indirect comparison uncertainties – An STC was used to estimate the relative effectiveness of selinexor compared to BSC. There are several limitations with the indirect evidence meaning

the hazard ratio used to generate the BSC survival curves is uncertain. Sensitivity analysis was provided using the upper value for OS from the lognormal distribution (hazard ratio = 0.63) which increased the ICER to £38k (scenario 5) and was considered by the Committee to be a more plausible estimate of cost-effectiveness given the limitations associated with the relative effectiveness estimate. Of note, this hazard ratio also aligns with that derived from the naïve indirect comparison.

- Overall survival uncertainties – the results were particularly sensitive to the choice of overall survival extrapolation. Using more conservative predictions of overall survival (table 6.3 scenarios 2 to 4) resulted in a higher ICER. SMC clinical experts were asked to comment on the face validity of the survival estimates and responses received provided some support for the BSC arm. Experts noted it was difficult to comment on the validity of the selinexor estimates due to lack of experience using this treatment.
- Utility values – quality of life data were collected in STORM part 2 using the FACT-MM and mapped to EQ-5D to produce the PFS utility estimate. However, a published mapping algorithm for FACT-MM was not identified so a mapping algorithm for FACT-G was used and assumed to generalise. The impact of this assumption on the validity of the PFS utility estimate is unclear. The PD utility value derived from the FACT-MM data produced a value higher than that for the PFS health state, which lacked face validity. Published evidence was used to estimate the PD utility value by applying a relative decrement to the PFS value. Alternative utility values were explored in sensitivity analysis (table 6.3 scenarios 8 to 12) showing some sensitivity to this parameter, particularly when a much lower PD value is applied (scenario 12).

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 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.[15]

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.[14]

The National Institute for Health and Care Excellence (NICE) published "Myeloma: diagnosis and management" (NG35) in February 2016, which was updated in October 2018.[24]

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.[25, 26]

9. Additional Information

9.1. Product availability date

04 November 2023.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28-day cycle (£)
Selinexor plus dexamethasone	Selinexor orally: 80 mg on days 1 and 3 every week (as part of a 28-day cycle). Dexamethasone orally: 20 mg on days 1 and 3 every week (as part of a 28-day cycle). Treatment should be continued until disease progression or unacceptable toxicity.	**14,736**

Costs from BNF online on 22 May 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be four patients eligible for treatment with selinexor in each year. The estimated uptake rate was 100% in year 1 and year 5, resulting in four patients estimated to receive treatment in each year. SMC clinical expert responses indicate that these numbers may be underestimates.

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 confidential.**

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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.