Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2303

isatuximab 20mg/mL concentrate for solution for infusion (Sarclisa®)

Sanofi Aventis

05 March 2021

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 process

isatuximab (Sarclisa®) is accepted for restricted use within NHSScotland.

Indication under review: in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy.

SMC restriction: patients receiving fourth-line therapy.

Addition of isatuximab to pomalidomide plus dexamethasone significantly increased progression-free survival (PFS) in adults with RRMM who had received at least two prior lines of therapy including lenalidomide and a PI.

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

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

Chairman
Scottish Medicines Consortium

Indication

In combination with pomalidomide and dexamethasone, for the treatment of adult patients with RRMM who have received at least two prior therapies including lenalidomide and a PI and have demonstrated disease progression on the last therapy.[1]

Dosing Information

Isatuximab 10mg/kg body weight intravenous (IV) infusion on days 1, 8, 15 and 22 of cycle 1 and on days 1 and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

Isatuximab should be administered in combination with pomalidomide and dexamethasone as specified in the relevant summary of product characteristics (SPC). Premedication should be used prior to isatuximab infusion with the following medicinal products to reduce the risk and severity of infusion reactions: dexamethasone 40mg (or 20mg for patients aged ≥75 years), paracetamol, H_2 antagonist or proton pump inhibitor, and diphenhydramine. See SPC for further information. The above recommended dose of dexamethasone (oral or IV) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide administration.

Isatuximab should be administered by a healthcare professional in an environment where resuscitation facilities are available.[1]

Product availability date

July 2020

Isatuximab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 4 December 2019 (which was withdrawn at the time of marketing authorisation). The indication was for the treatment of adult patients with RRMM in combination with pomalidomide and dexamethasone.

Isatuximab meets SMC end of life and orphan equivalent criteria.

Summary of evidence on comparative efficacy

Isatuximab is a monoclonal antibody that binds to the CD38 receptor, which is highly expressed in multiple myeloma (MM) cells, and induces tumour cell death. The combination of isatuximab and pomalidomide enhances anti-tumour activity.[1,2] The submitting company has requested that SMC consider isatuximab when positioned for use in patients receiving fourth-line therapy.

An open-label phase III study (ICARIA-MM) recruited adults with RRMM who had received at least two prior lines of therapy and whose disease had become non-responsive to lenalidomide and a PI (bortezomib, carfilzomib or ixazomib). Randomisation was stratified by number of previous lines of treatment (2 or 3 versus >3) and age (<75 versus ≥75 years). Patients were equally assigned to 28-

day cycles of pomalidomide 4mg orally on days 1 to 21 plus dexamethasone 40mg (20mg in patients ≥75 years) orally or IV on days 1, 8, 15 and 22 or to these schedules of pomalidomide and dexamethasone plus isatuximab 10mg/kg IV infusion on days 1, 8, 15 and 22 of cycle 1 and on days 1 and 15 of each subsequent cycle. Treatment continued until disease progression or unacceptable toxicity. The primary outcome was PFS, defined as time from randomisation to disease progression assessed by an independent review committee (IRC) using international myeloma working group (IMWG) criteria or death from any cause. This was assessed in the intention-to-treat (ITT) population, which comprised all randomised patients.[2,3]

At the primary analysis of PFS (cut-off 11 October 2018) median follow-up was 11.6 months and isatuximab-pomalidomide-dexamethasone significantly prolonged PFS compared with pomalidomide-dexamethasone. The study was not planned or powered to investigate PFS within the subgroup of patients receiving treatment fourth-line, who are representative of the proposed positioning. Post-hoc analysis within this subgroup indicated that PFS was numerically increased in the isatuximab group as detailed in Table 1.[2-4]

Table 1: IRC-assessed progression-free survival (PFS) in ICARIA-MM study.[2-4]

	Total study population		**Fourth-line subgroup**	
	Isatuximab	**Control**	**Isatuximab**	**Control**
	N=154	**N=153**	**N=52**	**N=58**
Events	73	89	23	33
HR (95% CI), p-value	0.596 (0.436 to 0.814), p=0.001		0.598 (0.348 to 1.030)	
Median* (months)	11.53	6.47	13.31	7.82
1-year PFS rate*	48%	30%	50%	33%

IRC = independent review committee; CI = confidence interval; * estimates from Kaplan-Meier analysis; HR = hazard ratio. Control group and isatuximab group received pomalidomide plus dexamethasone.

A hierarchical statistical testing strategy was applied and the first secondary outcome was overall response rate (ORR), which was defined as a stringent complete response, complete response, very good partial response or partial response on IMWG criteria. ORR was significantly improved in the isatuximab group compared with control as detailed in Table 2. Median duration of response was 13.27 versus 11.07 months; HR 0.828 (95% CI: 0.464 to 1.47).[2,5]

Table 2: IRC-assessed overall response rate (ORR) in ICARIA-MM study.[2-4]

Best overall response	**Total study population**		**Fourth-line subgroup**	
	Isatuximab	**Control**	**Isatuximab**	**Control**
	N=154	**N=153**	**N=52**	**N=58**
Overall response	93 (60%)	54 (35%)	28 (54%)	27 (47%)
	OR: 2.795 (1.715 to 4.562), p<0.001			
Stringent complete response	0	1 (0.7%)	0	0
Complete response	7 (4.5%)	2 (1.3%)	1 (1.9%)	2 (3.4%)
Very good partial response	42 (27%)	10 (6.5%)	13 (25%)	7 (12%)
Partial response	44 (29%)	41 (27%)	14 (27%)	18 (31%)

OR = odds ratio. Control group and isatuximab group received pomalidomide plus dexamethasone.

Data for the next secondary outcome in the hierarchy, overall survival (OS), were not mature at the time of the primary analysis of PFS (cut-off 11 October 2018) and the study is ongoing to assess this, with a final analysis planned after 220 deaths. The interim results for OS are detailed in Table 3 below.[2-4] The submitting company supplied updated overall survival results for the fourth-line subgroup, SMC is unable to publish these due to commercial confidentiality issues.

Table 3: Overall survival in ICARIA-MM study.[2-4]

	Total study population		Fourth-line subgroup	
	Isatuximab	Control	Isatuximab	Control
	N=154	N=153	N=52	N=58
Deaths	43	56	11	23
HR (95% CI), p-value	0.687 (0.461 to 1.023), p=0.0631		0.494 (0.240 to 1.015)	
Median* (months)	NE	NE	NE	14.36
1-year rate*	72%	63%	78%	62%

IRC = independent review committee; CI = confidence interval; * estimates from Kaplan-Meier analysis; HR = hazard ratio; NE = not evaluable. Control group and isatuximab group received

Health Related Quality of Life, assessed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 items (EORTC-QLQ-C30), EORTC Quality of Life Questionnaire Multiple Myeloma module 20 items (EORTC-QLQ-MY20) and EQ-5D-5L questionnaires, did not indicate any significant differences between the treatment groups.[2,3]

The company presented an unanchored matching-adjusted indirect comparison (MAIC) of isatuximab-pomalidomide-dexamethasone (data from the ITT population of ICARIA-MM study)[2,3,5] versus daratumumab monotherapy (data from the phase II, single-arm SIRIUS study)[6], which supported an economic scenario analysis. They noted that the MAIC was not robust and lacked face validity. However, the company suggest that the results indicated that PFS was greater with the isatuximab regimen compared with daratumumab monotherapy and that OS was similar across the treatment groups.

Summary of evidence on comparative safety

The European Medicines Agency (EMA) concluded that the type of adverse events associated with isatuximab are in line with the known toxicity of the pomalidomide-dexamethasone backbone therapy and anti-CD38 therapy and the added toxicity of combining isatuximab with pomalidomide-dexamethasone is considered acceptable.[2]

In the ICARIA-MM study at data cut-off 11 October 2018 within the isatuximab-pomalidomide-dexamethasone and pomalidomide-dexamethasone groups, the median number of cycles was 10 versus 6 cycles and median duration of exposure was 41 versus 24 weeks. Treatment-emergent adverse events were reported by 99% (151/152) and 98% (146/149), respectively, and these were considered treatment-related in 91% and 80%. The incidence of serious adverse events was 62% and 54%, with 35% and 16% treatment-related, respectively. Definitive discontinuation of therapy due to adverse events occurred in 7.2% versus 13% of patients, respectively.[2,3]

Within the isatuximab-pomalidomide-dexamethasone group, compared with pomalidomide-dexamethasone, haematological adverse events were more frequently reported, 59% (89/152) versus 44% (65/149), including neutropenia (47% versus 34%) (febrile neutropenia [12% and 2.0%]), thrombocytopenia (12% and 12%), and anaemia (3.9% and 1.3%), respectively. Also, infection and infestation adverse events were more common in the isatuximab group, including upper respiratory tract infections (28% versus 17%), bronchitis (24% and 9%), pneumonia (20% versus 17%) and nasopharyngitis (9.2% versus 4.7%). Some gastrointestinal adverse events were more common with isatuximab, including diarrhoea (26% versus 20%), nausea (15% versus 9%), vomiting (12% versus 3.4%) and stomatitis (6.6% versus 2.7%). The incidence of cardiac disorders reported as adverse events was higher in the isatuximab group (14% versus 4.0%), and consisted most frequently of cardiac arrhythmias (11% and 2.0%), with atrial fibrillation (4.6% versus 2.0%) the most common. The incidence of nervous system adverse events was higher in the isatuximab group (41% versus 29%). However, because the adverse events were reported as non-serious, not treatment-related, and none led to permanent treatment discontinuation, the EMA concluded there were no serious safety concerns about nervous system disorders. Infusion-related reactions were only reported in the isatuximab group (38% versus 0).[2]

Within a post-hoc analysis of the subgroup of patients in the ICARIA-MM study who received isatuximab-pomalidomide-dexamethasone treatment fourth-line the adverse event profile was generally consistent with the overall study population.[2,5]

Summary of clinical effectiveness issues

Isatuximab is the second anti-CD38 monoclonal antibody (after daratumumab) to be licensed for the treatment of RRMM.[1] In the indication under review, isatuximab meets SMC orphan equivalent and end-of-life criteria.

The choice of therapy for RRMM depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (clinical versus biochemical relapse). Treatment of RRMM is evolving, with novel medicines licensed for this condition including the monoclonal antibody to CD38, daratumumab; the monoclonal antibody to SLAMF7, elotuzumab; the histone deacetylase inhibitor, panobinostat; second-generation immunomodulatory imide drugs (IMiDs), lenalidomide and pomalidomide; and second-generation PIs, carfilzomib and ixazomib.[2]

The submitting company has proposed that isatuximab be positioned for fourth-line use. Clinical experts consulted by SMC advise that the regimens in fourth-line therapy include pomalidomide plus dexamethasone and monotherapy with daratumumab. It is expected that the use of daratumumab in this line of therapy will decline in the future, as it has recently been accepted for restricted use by SMC for second-line treatment of MM and is only used for one line of therapy. However, as there are currently patients who did not receive daratumumab second-line who would be eligible for daratumumab fourth-line in the future, it remains a relevant comparator.

In the main study, ICARIA-MM, the addition of isatuximab to pomalidomide plus dexamethasone increased the primary outcome, PFS, by approximately 5 months in the total study population and by about 5.5 months in the subgroup receiving fourth-line treatment, who are representative of the proposed positioning. This was supported by increases in ORR of about 25% in the total study population and around 7% in the fourth-line subgroup. Quality-of-life data appeared similar across the treatment groups.[2,3]

Currently, immature OS data suggested a possible benefit with isatuximab, although these may be confounded by differences in anti-myeloma treatment post-progression, with 39% versus 54% of patients in the isatuximab and control groups receiving this. In particular, there was a difference in the proportion of patients who subsequently received the anti-CD38 monoclonal antibody, daratumumab: 4% versus 29% in the total study population and 3.8% versus 28% in the fourth-line subgroup.[2-4] A post-hoc analysis of OS in the fourth-line subgroup performed using data from 11 October 2018 cut-off and inverse probability of censoring weighting (IPCW) to adjust for switching to subsequent daratumumab therapy, found a HR of 0.462 (95% CI: 0.209 to 1.018).[7]

The open-label design of the study may limit assessment of subjective outcomes, such as adverse events and health related quality-of-life. The assessment of PFS was performed by an IRC to minimise potential bias. The primary analysis of PFS censored for subsequent anti-myeloma therapy. However, sensitivity analysis that did not include this censoring was consistent with the primary analysis, with a HR of 0.599 (95% CI: 0.447 to 0.801), p<0.001. Isatuximab (similar to daratumumab) can be detected by serum protein electrophoresis and immunofixation assays used to monitor endogenous M-protein. However, the EMA concluded that the impact of possible interference on assessment of disease progression would be limited.[2] The subgroup analyses in patients receiving fourth-line treatment, which support the positioning proposed by the company, were performed post hoc.[2]

The median duration of treatment in the isatuximab group was 10 months and long-term safety data are limited. Also, due to limited data, it was not possible to reach conclusion about effects on minimal residual disease.[2]

There were some imbalances in prognostic factors in the ITT population at baseline however the EMA concluded that overall it seems unlikely that this would have influenced observed efficacy results.[2]

Pre-specified subgroup analysis of PFS indicated that results were generally consistent with the primary analysis across the subgroups defined by age, sex, renal function, prior line of therapy (2-3 versus >3), cytogenetic risk and R-ISS stage.[2,3]

The study excluded patients with primary refractory disease and those with an ECOG performance status of 2 or more. This may limit the application of study results to these groups. Only one patient had received previous treatment with daratumumab and the efficacy of isatuximab in patients who have previously received this anti-CD38 monoclonal antibody is unknown. It has been noted that isatuximab and daratumumab bind to different CD38 epitopes.[2,3] This issue may become more relevant with time as daratumumab was recently accepted for restricted use by SMC for second-line use in RRMM.

The MAIC comparing isatuximab regimen with daratumumab monotherapy, which supported an economic scenario analysis, had limitations as noted by the company. The target population included in the MAIC is broader than the fourth-line population representative of the proposed positioning and the weighted isatuximab group matched with daratumumab in the MAIC differed from the unweighted fourth-line subgroup of the ICARIA-MM study. There were differences in baseline criteria across the treatment groups and, after matching, the effective sample size (ESS) was small, only 42 compared with the initial sample size of 154. Also, some baseline criteria were not matched and, characteristic of this type of unanchored analysis, there was a possibility of unknown unmatched prognostic variables. There were differences in data maturity across the groups and OS data in the ICARIA-MM study were immature. Patient-reported outcomes and safety were not included. Due to these limitations, the company's conclusions are uncertain.

Clinical experts consulted by SMC considered that the isatuximab regimen is a therapeutic advance compared with pomalidomide-dexamethasone due to improved efficacy. They note that it may replace this regimen, although highlight that treatment pathways are complex as therapeutics are evolving in this area. The clinical experts considered that the introduction of this medicine may impact on the patient and/or service delivery as it would introduce an IV administered medicine to a regimen that was orally administered.

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 isatuximab, as an end of life and orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- RRMM is an incurable progressive cancer with a poor prognosis and limited effective treatment options for patients in advanced stages of the disease who have already received multiple treatments. There is an unmet need for therapies that prolong PFS for these patients.
- Isatuximab (in combination with pomalidomide plus dexamethasone) is a reasonably well-tolerated triplet regimen for patients with RRMM in later stages of the disease. It increases PFS in comparison to the current standard of care. This could lead to a prolonged period when the patient's disease is controlled and they are well and able to participate in family and social activities.
- Accessing the isatuximab regimen, which patients regard as innovative, may provide reassurance to patients that they are receiving the optimum treatment for their condition. This can have psychological benefits. Also, some patients may derive hope that the prolonged PFS may provide a bridge to a time when other new medicines become available.

- Patients with RRMM can develop treatment resistance, therefore, practice is changing towards the use of triplet (and quadruplet) regimens to prolong survival in difficult to treat disease in patients who have failed a number of prior therapies.
- Isatuximab is given as an intravenous infusion, requiring attendance at a day ward. This could have implications for the patients, carers and the service as pomalidomide plus dexamethasone is administered orally. However, PACE participants considered that patients will be generally happy to attend for this due to the expected benefits.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 8% 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 considered by SMC.

Summary of comparative health economic evidence

A cost-utility analysis was submitted evaluating isatuximab in combination with pomalidomide and dexamethasone within a subgroup of the licensed indication. The positioning focused on use of the combination at fourth-line. The main comparison was with pomalidomide and dexamethasone alone, although an 'exploratory' comparison with daratumumab was also provided. Clinical expert feedback suggests that both pomalidomide-dexamethasone and daratumumab represent relevant comparators.

A partitioned survival model was used, creating transitions between PFS, 'PPS' (post-progression state) and 'dead'. Time to treatment discontinuation was modelled independently. The analysis used a lifetime (20 year) time horizon.

The main source of clinical evidence for the comparison with pomalidomide and dexamethasone was a post-hoc subgroup analysis of patients treated at fourth-line in the open-label ICARIA-MM study. An unanchored MAIC was used to obtain hazard ratios for PFS and OS of daratumumab, relative to the isatuximab regimen. Separate survival functions were used for extrapolation of OS, with an exponential function for the isatuximab regimen and daratumumab, and a Weibull function for pomalidomide and dexamethasone. The company stated that this was appropriate given the different mode of action of anti-CD38 medicines; however, clinical advice received by the company suggested Weibull or Gompertz curves may be preferable for each of the medicines. A lognormal function was chosen for PFS extrapolation for all medicines.

Utility data were derived from EQ-5D-5L responses collected within ICARIA-MM and adjusted for baseline utility, treatment allocation and health state using a generalised estimating equation regression analysis. Outputs were mapped to the EQ-5D-3L and valued according to UK societal preferences. These resulted in utility estimates of approximately 0.72 for all treatments in PFS and 0.61 in PPS. An end-of-life disutility of -0.23 was also applied.

Costs of medicines acquisition and administration were included, as were costs of subsequent treatment, and those of managing adverse events. Time to treatment discontinuation was modelled using an exponential function applied to the survival data obtained in the ICARIA-MM trial; the MAIC-derived hazard ratio for PFS was applied to estimate treatment duration for daratumumab. Subsequent treatment costs were modelled according to the distribution of treatments observed in the ICARIA-MM study.

A complex 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 simple discount was offered on the list price. A PAS discount is also in place for pomalidomide and daratumumab, and these were included in the results used for decision-making by using estimates of the comparator PAS price.

The results presented do not take account of the PASs for pomalidomide and daratumumab or the PAS for isatuximab, 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 pomalidomide and daratumumab due to commercial confidentiality and competition law issues.

The base case results are shown in Table 4. The largest proportion of QALY gains versus pomalidomide and dexamethasone were estimated to be in the post-progression setting, whilst a greater proportion of QALYs are gained in the PFS state against daratumumab (although there is a shortfall of 0.5 QALYs post-progression for this comparison). There is a significant increase in medicines costs versus both comparators, with a degree of cost-savings observed for subsequent therapy costs versus pomalidomide and dexamethasone.

Table 4: Base case comparisons

Comparison	Incremental QALYs	ICER (all list price)
Isatuximab vs pomalidomide and dexamethasone	1.309	£135,079
Isatuximab vs daratumumab	0.164	£1,288,492

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year

A number of scenario analyses were presented for the pomalidomide and dexamethasone comparison (Table 5), while a one-way deterministic sensitivity analysis was provided upon request for the comparison with daratumumab. The comparison with pomalidomide was particularly sensitive to the approach to survival extrapolation, the assumptions regarding subsequent treatments administered and associated cost, and the duration of treatment and dose of isatuximab. The tornado plot for the comparison with daratumumab highlighted particular sensitivity to changes in utility for the PFS and PPS states, as well as approaches to estimating medicines acquisition costs.

Table 5: Key scenario analyses (pomalidomide + dexamethasone comparison)

	Scenario name	ICER vs Pd, £/QALY (all list price)
	Base case	£135,079
1.	Subsequent therapy (proportions and duration) based on expert feedback	£150,815
2.	10-year time horizon	£149,530
3.	Isa dosing based on ICARIA-MM weight distribution	£104,192
4.	Use of Scottish costs book for unit costs	£157,211
5.	Two previous scenarios combined: 1 and 4	£174,941
6.	Extrapolation of OS using Weibull distribution for IsaPd and Pd	£227,736
7.	Extrapolation of OS using Gompertz distribution for IsaPd and Pd	£245,774
8.	Extrapolation of time to treatment discontinuation using log-logistic function	£235,247
9.	No subsequent treatment with Dara and applying OS HR based on IPCW analysis	£139,634
10.	No subsequent treatment with Dara and Len and applying OS HR based on IPCW analysis	£153,157
11.	Extrapolation of OS using exponential distribution for IsaPd and Pd (plus use of NHS England unit costs and trial-based subsequent therapy distributions)	£159,848

Isa: isatuximab; Pd: pomalidomide and dexamtherasone; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; OS: overall survival; HR: hazard ratio; IPCW: inverse probability of censoring weighting

The economic analyses are associated with a number of limitations:

- Uncertainty exists regarding the most appropriate comparator. Based on current market share data up to December 2019 it would appear that daratumumab is the predominant comparator. Although the company have provided an 'exploratory' comparison with daratumumab, the level of reporting was lower than provided for the base case comparison with pomalidomide and dexamethasone. In addition, the results of the daratumumab comparison are significantly worse (Table 4).

- The choice of survival distributions assumes that the hazard of survival will follow a different pattern for the isatuximab regimen versus pomalidomide and dexamethasone alone. The company argue this is due to a different mechanism of action and use this justification to select an exponential function for isatuximab and a Weibull function for pomalidomide and dexamethasone. Clinical advisors consulted by the company suggested that the Weibull or Gompertz distributions may be preferable for both regimens; this approach of using the same survival functions also aligns with standard methods in survival extrapolation.[8] Use of these alternative distributions results in a significantly higher ICER

(Scenarios 6 and 7). Based on updated survival data the exponential distribution was considered a reasonable alternative, again resulting in an increase to the ICER (Scenario 11).

- Patients in the ICARIA-MM study received daratumumab and lenalidomide as subsequent treatment following progression on pomalidomide and dexamethasone. The costs and effects of these treatments were factored into the base case analysis. Scenarios were provided where these costs were removed, and the OS for pomalidomide and dexamethasone was adjusted using the Inverse Probability of Censoring Weighting (IPCW) approach. These scenarios were felt more representative of clinical practice and resulted in increased ICERs (Scenarios 9 and 10).
- Minimal differences were observed in the goodness-of-fit statistics for the extrapolation of time to treatment discontinuation. Although an exponential function was chosen in the base case, no alternative approaches were tested as scenarios. The model is likely to be sensitive to the choice of function: a more conservative approach has been obtained from the submitting company (Scenario 8).

The Committee considered the benefits of isatuximab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as isatuximab 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 isatuximab for restricted use in NHSScotland.

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published in 2017 'Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up'. 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. For patients who have experienced disease progression after a second or subsequent relapse, the guidelines recommend pomalidomide in combination with dexamethasone (as a backbone) plus cyclophosphamide, ixazomib, bortezomib, daratumumab or elotuzumab; or daratumumab alone or in combination; or enrolment in a clinical trial.[9]

The National Institute for Health and Care Excellence (NICE) published in 2016 and updated in 2018 'Myeloma: diagnosis and management'. For patients who have had a subsequent relapse, these guidelines recommend lenalidomide in combination with dexamethasone only in people who have received two or more prior therapies. In addition, pomalidomide, in combination with dexamethasone, is not recommended within its marketing authorisation for treating relapsed and

refractory multiple myeloma in adults who have had at least 2 previous treatments, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy.[10]

Additional information: comparators

In the proposed fourth-line proposed positioning, clinical experts consulted by SMC advised that the main comparators are the pomalidomide plus dexamethasone regimen and monotherapy with daratumumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per cycle (£)
Isatuximab Pomalidomide Dexamethasone	10mg/kg IV on day 1, 8, 15 and 22 or cycle 1 and on day 1 and 15 of each subsequent 28-day cycle 4mg orally daily on day 1 to 21 of each 28-day cycle 40mg (20mg if ≥75 years) orally or IV on day 1, 8, 15 and 22 of each 28-day cycles	15,990 (23,087 in first cycle)

Costs from BNF online on 2 October 2020 based on body weight of 70kg and age <75 years. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: 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.

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

References

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This assessment is based on data submitted by the applicant company up to and including 13 November 2020.

**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*

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.