SMC2804

isatuximab concentrate for solution for infusion (Sarclisa®)

Sanofi

10 October 2025

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 assessed under the orphan equivalent medicine process

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

Indication under review: in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

In a phase III study of patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant, the addition of isatuximab to bortezomib, lenalidomide, and dexamethasone significantly improved 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

Isatuximab is an IgG1 monoclonal antibody that binds to the CD38 receptor, which is highly expressed on multiple myeloma cells, and induces cell death.[1]

For this indication (in combination with bortezomib, lenalidomide, and dexamethasone), the recommended dose of isatuximab is 10 mg/kg body weight by intravenous infusion on days 1, 8, 15, 22, and 29 of cycle one and days 1, 15, and 29 of cycles two to four. From cycles five to 17, isatuximab is administered on days 1 and 15, and from cycles 18 onwards isatuximab is administered on day 1 only. Treatment cycles consist of a 42-day treatment period from cycle one to four and a 28-day treatment period from cycle five onwards. Treatment is repeated until disease progression or unacceptable toxicity. Further details are included in the summary of product characteristics (SPC).[1] For dosing and administration directions for the other medicines administered with isatuximab, see their individual SPC.

1.2. Disease background

The incidence of multiple myeloma in Scotland is estimated to be 8.8 per 100,000 people.[2] Multiple myeloma 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 years 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.[2]

Multiple myeloma is a 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.[4, 5]

1.3. Treatment pathway and relevant comparators

For multiple myeloma, first line 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). Older people are generally not considered eligible for ASCT due to comorbidities.[6]

For patients in Scotland with newly diagnosed multiple myeloma who are ineligible for ASCT, clinical experts consulted by SMC advise that combination therapy with the anti-CD38 monoclonal antibody, daratumumab plus lenalidomide and dexamethasone is the predominant treatment and the relevant comparator. Clinical experts also advised that other less common treatment options include lenalidomide and dexamethasone for frailer patients or those unable to regularly travel to hospital; bortezomib and dexamethasone for patients with renal impairment; and clinical trials.

Cancer Medicines Outcome Programme Public Health Scotland (CMOP-PHS) data indicate that most patients received daratumumab, lenalidomide and dexamethasone. Small proportions received lenalidomide and dexamethasone; daratumumab and lenalidomide; bortezomib and dexamethasone; and lenalidomide monotherapy.[7]

1.4. Category for decision-making process

Eligibility for a PACE meeting

Isatuximab 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 the efficacy and safety of isatuximab for this indication comes from IMROZ.[8] Details are presented in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	IMROZ [5, 8]
Study design	International, randomised, open-label, phase III study.
Eligible patients	• Adult patients ≥18 to ≤80 years of age. • Multiple myeloma (as defined by IMWG 2022 criteria). • Evidence of measurable disease: serum M-protein ≥1.0 g/dL using serum protein immunoelectrophoresis, and/or urine M-protein ≥200 mg/24 hours using urine protein immunoelectrophoresis, and/or serum free light chain multiple myeloma without measurable M-protein in serum or urine as per previous criteria (serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio <0.26 or >1.65). • Newly diagnosed and ineligible for high-dose chemotherapy due to age ≥65 years or <65 years with comorbidities likely to have a negative impact on tolerability of high-dose chemotherapy with stem cell transplant.
Treatments	Patients were randomised to receive bortezomib, lenalidomide, and dexamethasone with or without isatuximab 10 mg/kg by intravenous infusion on days 1, 8, 15, 22, and 29 of cycle one; days 1, 15, and 29 of cycles two to four; on days 1 and 15 of cycles five to 17; and on day 1 from cycles 18 onwards. Treatment cycles consisted of a 42-day treatment period from cycle one to four (induction period) and a 28-day treatment period from cycle five onwards (continuous treatment period). Treatment was to continue until disease progression, unacceptable toxicity or the patient's decision to discontinue study. Bortezomib, lenalidomide, and dexamethasone were dosed and administered per the IMROZ study protocol. Patients in the bortezomib, lenalidomide, and dexamethasone group (the control group) who had confirmed disease progression as assessed by the investigator during the continuous phase were allowed to cross-over to the isatuximab in combination with bortezomib, lenalidomide, and dexamethasone group (the isatuximab-containing group).
Randomisation	Patients were randomised in a 3:2 ratio. Randomisation was stratified according to country (not China versus China), age (<70 versus ≥70 years) and R-ISS disease stage (stage I or II versus III versus not classified).
Primary outcome	PFS, defined as the time between date of randomisation to the date of first progression (assessed by IRC per IMWG 2022 criteria) or death due to any cause.

Secondary outcomes	Key secondary outcomes in hierarchical order: • CR rate. Defined as proportion of patients with sCR and CR, as defined by IMWG 2022 criteria assessed by IRC. • MRD negativity rate in patients with CR. Defined as the proportion of patients with CR and MRD negativity by next-generation sequencing at any time point after first dose of study intervention. • VGPR or better rate. Defined as the proportion of patients with sCR, CR, and VGPR, as defined by IMWG 2022 criteria assessed by IRC. • OS. Defined as the time from date of randomisation to death from any cause.
Statistical analysis	Efficacy analyses were performed in the ITT population, which included all randomised patients. A hierarchical statistical testing strategy was applied with no formal testing of outcomes after the first non-significant outcome, with these remaining results reported descriptively (no p-values reported).

Abbreviations: CR = complete response; IRC = independent review committee; IMWG = International Myeloma Working Group; ITT = intention-to-treat; MRD = minimal residual disease; OS = overall survival; PFS = progression-free survival; R-ISS = Revised International Staging System; sCR = stringent complete response; VGPR = very good partial response.

At the second progression-free survival (PFS) interim analysis (data cut-off 26 September 2023), after a median follow-up of 59.7 months, the addition of isatuximab to bortezomib, lenalidomide, and dexamethasone resulted in a statistically significant improvement in PFS and the key secondary outcomes: complete response (CR) and minimal residual disease (MRD) negativity in those with CR. As the key secondary outcome, very good partial response (VGPR) was not significant, overall survival (OS) was not tested inferentially.[5, 8] See Table 2.2 for details.

Table 2.2: Primary and selected secondary outcomes from IMROZ (data-cut 26 September 2023, ITT).[5, 8]

	Isatuximab, bortezomib, lenalidomide, dexamethasone (n=265)	**Bortezomib, lenalidomide, dexamethasone (n=181)**
Primary outcome: PFS assessed by IRC per IMWG 2022 criteria		
Median duration of exposure, months	53	31
PFS events, n	84	78
Median PFS, months	NR	54
Stratified HR (98.5% CI), p-value	0.60 (0.41 to 0.88), p<0.001	
KM-estimated PFS at 12 months	93%	86%
Secondary outcome: CR rate assessed by IRC per IMWG 2022 criteria		
CR or better, %	75	64
Stratified OR (95% CI), p-value	1.66 (1.10 to 2.50), p=0.008	
Secondary outcome: MRD negativity rate in patients with CR assessed by IRC		
MRD negativity in CR or better, %	56	41
Stratified OR (95% CI), p-value	1.80 (1.23 to 2.65), p=0.001	
Secondary outcome: VGPR or better assessed by IRC per IMWG 2022 criteria		
VGPR or better, %	89	83
Stratified OR (95% CI), p-value	1.73 (0.99 to 3.01), p=0.026 [a]	
Secondary outcome: OS		
Deaths, n	69	59
Median OS, months	NR	NR

Stratified HR (99.97% CI)	0.78 (0.41 to 1.48)	
KM-estimated OS at 12 months	95%	93%

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; IMWG = International Myeloma Working Group; IRC = independent review committee; ITT = intention-to-treat; KM = Kaplan=Meier; MRD = minimal residual disease; NR = not reached; PFS = progression-free survival; OS = overall survival; OR = odds ratio; sCR = stringent complete response; VGPR = very good partial response.

[a] The efficacy p-value boundary was 0.025 therefore results for subsequent outcomes are descriptive only and not inferential (no p-values reported).

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using three questionnaires: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Cancer specific module with 30 items (EORTC QLQ-C30), the EORTC QLQ myeloma specific module with 20 items (MY20) and 5Q-5D-5L. Data were collected on day 1 of each cycle in the induction and continuous treatment periods, until the end of treatment. Additional data were collected at 30 and 90 days following the last treatment administration.[8]

Overall, quality of life measured by EORTC QLQ-C30 Global Health Score was maintained over time and similar in both treatment groups. Functioning, disease, treatment-related symptoms, health status and health utility measured by EORTC QLQ-C30, EORTC QLQ-MY20, and 5Q-5D-5L were also maintained in both treatment groups and did not significantly differ over time.[5]

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

In the absence of direct evidence versus relevant comparators, the submitting company performed indirect treatment comparisons (ITCs). The results of three unanchored matching-adjusted indirect comparisons (MAIC) for three comparators (daratumumab, lenalidomide, and dexamethasone; lenalidomide and dexamethasone; and bortezomib, melphalan, and prednisone) and an unanchored inverse probability weighting (IPW) analysis for one comparator (bortezomib, cyclophosphamide, and dexamethasone) were used to inform the economic base case. However, the main results that inform the economic analysis are from the MAIC versus daratumumab, lenalidomide, and dexamethasone. A network meta-analysis (NMA) was also conducted which informed an economic scenario analysis. Further details are presented in Table 2.2.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored MAIC, IPW analysis and Bayesian NMA.
Population	Adults with newly diagnosed multiple myeloma who are ineligible for ASCT.
Comparators	• Daratumumab, lenalidomide, and dexamethasone (MAIC and NMA) • Lenalidomide and dexamethasone (MAIC and NMA) • Bortezomib, melphalan, and prednisone (MAIC and NMA) • Bortezomib, cyclophosphamide, and dexamethasone (IPW only)
Studies included	Four studies were included in the MAICs (IMROZ[8], MAIA[9-11], ALCYONE[12, 13] and FIRST[14, 15]); two studies were included in the IPW (IMROZ[8] and Flatiron[16]); ten studies were included in the NMA (IMROZ[8], VISTA[17], FIRST[14, 15], MAIA[9-11], IFM 01/01[18], HOVON 49[19], Beksac 2011[20], Sacchi 2011[21], REAL MM[22, 23] and SWOG S0777[24, 25]).
Outcomes	PFS, OS, TTD and MRD negativity (TTD and MRD negativity were only assessed in MAIC versus daratumumab, lenalidomide, and dexamethasone).
Results	The MAIC and IPW results suggest that isatuximab has superior efficacy, for PFS and OS, to all comparators except daratumumab, lenalidomide and dexamethasone in terms of OS, as

	the results did not suggest evidence of a difference for this outcome. Isatuximab has superior efficacy for MRD negativity and similar efficacy for TTD versus daratumumab, lenalidomide and dexamethasone. The NMA results suggest that isatuximab has superior efficacy in terms of PFS to all comparators except daratumumab, lenalidomide and dexamethasone, as the results did not suggest evidence of a difference for this outcome. There was no evidence of a difference in OS versus any comparator.

Abbreviations: ASCT = autologous stem cell transplant; CI = confidence interval; CrI = credible interval; HR = hazard ratio; IPW = inverse probability weighting; MAIC = matching-adjusted indirect comparison; MRD = minimal residual disease; NMA = network meta-analysis; OR = odds ratio; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation.

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

3. Summary of Safety Evidence

In the IMROZ study at data cut-off 26 September 2023, the median duration of treatment in the isatuximab-containing group was 53.2 months and in the control group was 31.3 months.[8]

In the isatuximab-containing group and control group, respectively, patients reporting a grade 3 or higher adverse event (AE) were 92% (241/263) versus 84% (152/181), these were considered treatment-related in 77% versus 68% of patients. Patients with a reported serious AE were 71% versus 67%, which were treated-related in 33% and 32%, and patients discontinuing therapy due to an AE was 23% versus 26%. The rate of fatal AEs was higher in the isatuximab-containing group versus the control group: 11% versus 5.5%.[5, 8]

The most frequently reported treatment-related grade 3 or higher AEs with an incidence of ≥5% in any group, in the isatuximab-containing group versus the control group were: neutropenia (29% versus 20%), thrombocytopenia (11% versus 9.4%), pneumonia (9.1% versus 6.6%), and cataract (8.0% versus 6.1%).[5]

Infusion related reactions and secondary primary malignancies were AEs of special interest. The incidence of treatment-related infusion related reactions of any grade was higher in the isatuximab-containing group versus the control group (23% versus 0). Secondary primary malignancies that occurred during the treatment and post-treatment periods were 16% versus 8.8%, in the isatuximab-containing group versus the control group respectively.[5]

The regulator considered that the addition of isatuximab to bortezomib, lenalidomide, and dexamethasone is associated with higher toxicity compared with bortezomib, lenalidomide, and dexamethasone due to infusion related reactions, pneumonia, severe neutropenia and secondary primary malignancies. These AEs reflect the known safety profile of isatuximab and advice is provided in the SPC to minimise these risks.[1, 5]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- At the interim analysis (26 September 2023) with a median follow-up of 59.7 months, isatuximab in combination with bortezomib, lenalidomide, and dexamethasone was

associated with a statistically significant and clinically meaningful improvement in PFS compared with bortezomib, lenalidomide, and dexamethasone.[8]

- This was supported by hierarchically tested secondary outcomes: the percentage of patients with a CR was significantly higher in the isatuximab-containing group than in the control group (75% versus 64%), as was the percentage of patients with CR who achieved MRD negative status (56% versus 41%).[8]
- Isatuximab is the second anti-CD38 monoclonal antibody licensed for the first line treatment of multiple myeloma in patients who are ineligible for ASCT.

4.2. Key uncertainties

- Clinical experts consulted by SMC consider that daratumumab, lenalidomide, and dexamethasone is the most relevant comparator for patients with newly diagnosed multiple myeloma ineligible for ASCT in NHSScotland. No direct comparative evidence was available versus relevant comparators and ITCs were performed. The submitting company used unanchored ITCs which have much stronger assumptions and substantial bias than anchored ITCs. Other limitations of the ITCs included methodological differences between studies that could not be adjusted for and safety and HRQoL outcomes were not assessed.[26] Overall, due to these limitations the results of the comparisons are uncertain.
- More mature data are required before conclusions about the impact of isatuximab on OS can be reached. At the 26 September 2023 data-cut off, estimated median OS were not reached in either treatment group. The European regulator has requested additional OS analyses, which are expected from future data-cuts.[5]
- Patients in the control group were permitted to cross-over during the continuation phase to receive the isatuximab-containing regimen following confirmed disease progression as assessed by the investigator and at the 26 September 2023 data-cut off, 14% (25/181) of patients had crossed over.[8] Inverse probability of censoring weighting analyses to adjust for cross-over suggest that the treatment effect was similar if patients had not crossed over.[26]These are difficult to interpret for a number of reasons, including small numbers of deaths and immature survival data.
- IMROZ excluded patients >80 years and patients with Eastern Cooperative Oncology Group (ECOG) performance status scores >2, therefore the treatment effect for older patients and those with poorer performance status is unknown.[8] However, SMC clinical experts consider that the place in therapy for isatuximab in combination with bortezomib, lenalidomide, and dexamethasone would be for younger, fitter patients who are able to tolerate quadruplet therapy.
- The treatment effect of isatuximab in patients with high-risk cytogenic features remains uncertain due to small numbers in this subgroup. Additionally, the definition of high-risk multiple myeloma used in the IMROZ study is now outdated.[5, 28]
- IMROZ had an open-label design; this could introduce potential bias for subjective safety and quality of life outcomes. Furthermore, HRQoL data was not adjusted for multiplicity and should therefore be interpreted with caution.[8]

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

4.3 Clinical expert input

Clinical experts consulted by SMC consider that isatuximab in combination with bortezomib, lenalidomide, and dexamethasone fills an unmet need for younger, fitter patients who can tolerate quadruplet therapy and those with high-risk disease who have poor outcomes with current standard of care treatments. Despite the lack of direct data versus the relevant comparator for this patient population, clinical experts generally considered that isatuximab in this indication was a therapeutic advancement due to PFS results in the key study.

4.4 Service implications

Clinical experts consulted by SMC consider that isatuximab may impact on the patient and the service. Administration of isatuximab requires intravenous access and regular attendance at chemotherapy day units. Increased resource may be required from chemotherapy day units and pharmacy aseptic units to prepare doses.

5. 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 orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Multiple myeloma is an incurable, relapsing and remitting blood cancer which can be treated with sequential lines of combination drug regimens. Patients relapse after each line of treatment as myeloma becomes resistant to the drugs used. The first remission is usually the longest and subsequent relapses are worse, more frequent and harder to treat. The complications of myeloma can be significant, debilitating, and painful; they include severe bone pain, fractures, kidney damage, fatigue and a depleted immune system that can lead to increased infections. Approximately two-thirds of patients diagnosed with multiple myeloma cannot receive a stem cell transplant.
- There is unmet need for treatment that delivers comparable outcomes to stem cell transplantation specifically for transplant ineligible patients but who are still fit enough to benefit from intensification of treatment. Currently, transplant eligible patients benefit from quadruplet therapy. However, transplant ineligible patients are limited to triplet or doublet regimens, contributing to a survival gap between transplant eligible and ineligible groups. Quadruplet therapy allows more patient centred tailoring of doses of each drug depending on the specific patient toxicity.
- PACE participants highlighted that while current treatments have improved, there remains a need for more effective treatment options at first line when the most durable remissions can be obtained.
- This isatuximab quadruplet combination may offer improved progression-free survival, improved chance of MRD negativity, increased depth of response and longer remission times than current treatments. Increased remission time results in improved quality of life,

psychological benefits, gives patients and families a period of stability and reduces risks of myeloma related complications.

- This isatuximab quadruplet combination offers the best available treatment for patients who are borderline transplant eligibility or for whom transplant is not a viable treatment option. This ensures that transplant ineligible patients are not compromised in terms of treatment efficacy.
- Patients may be willing to accept the risk of additional side effects with a quadruplet regimen if it offers improved survival outcomes. Neuropathy associated with bortezomib is expected to be better tolerated by patients eligible for the regimen, who are typically fitter. However, bortezomib may be administered in later treatment cycles regardless of patient fitness. Furthermore, the quadruplet regimen provides more flexibility to manage side effects, which can have a huge impact on quality of life.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK which is a registered charity. Myeloma UK has received 4.8% 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.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An economic case was presented and is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	A lifetime time horizon of 29 years.
Population	Newly diagnosed multiple myeloma patients who are ineligible for a stem cell transplant.
Comparators	Four comparators were included: daratumumab, lenalidomide, and dexamethasone (DRd); lenalidomide and dexamethasone (Rd); bortezomib, cyclophosphamide, and dexamethasone (VCd); and bortezomib, melphalan, and prednisone (VMP). DRd was considered the most relevant comparator by SMC clinical experts.
Model description	A three-state partitioned survival model was used with health states of progression-free, post-progression and death. Patients enter the model in the progression-free health state. Within the progression-free health state, patients can be on or off treatment. Patients may either remain progression-free, transition to post-progression, or transition directly to death. Patients in the post-progression state may subsequently transition to death.
Clinical data	Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (IsaVRd) PFS, OS, time to treatment discontinuation (TTD) and adverse event data were from the IMROZ ITT population.[5, 8] For all comparators, PFS and OS clinical data were sourced from the ITCs. Unanchored MAICs were used for comparisons with DRd, Rd and VMP. An IPW was used for the comparison with VCd. DRd TTD was sourced from the MAIC, with other comparator TTD relying on median DoT and PFS from clinical studies. Adverse events for all comparators were from relevant clinical studies.[5, 8-11, 17]

Extrapolation	IsaVRd PFS was extrapolated using a gamma distribution. Comparator PFS was estimated by applying time-varying hazard ratios obtained from the ITCs to the extrapolated IMROZ ITT PFS data. IsaVRd OS was extrapolated using a generalised gamma distribution. Comparator OS was estimated by applying time-varying hazard ratios obtained from the ITCs to the extrapolated IMROZ ITT OS data. The OS time-varying hazard ratios were fixed at the end of IMROZ follow-up (5.67 years). The submitting company highlighted this as conservative due to continued improvements in the relative treatment effect for OS of IsaVRd versus comparators. IsaVRd TTD was extrapolated using an exponential distribution. DRd TTD was estimated by applying a DRd versus IsaVRd TTD hazard ratio estimated from the MAIC to the extrapolated IsaVRd ITT TTD data. TTD for other comparators was estimated by applying hazard ratios derived using the median PFS and DoT to the PFS extrapolation of each comparator.
Quality of life	EQ-5D-5L data from IMROZ were used to derive the progression-free health state utility values. These were 0.728 for IsaVRd (with DRd assumed the same) and 0.688 for other comparators (assumed equivalent to the VRD progression-free utility value). A utility value of 0.557 for post-progression across all treatment arms was sourced from NICE TA587 (FIRST Study). The submitting company highlighted that due to limited post-progression EQ-5D-5L data collection in IMROZ, the literature value was used. Adverse event disutilities were also included.
Costs and resource use	Costs included in the model were medicine acquisition, administration, concomitant treatment, subsequent treatments, adverse events, monitoring and end of life.
PAS	A Patient Access Scheme (PAS) was submitted by the submitting 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 daratumumab, lenalidomide, bortezomib, carfilzomib, panobinostat, and pomalidomide, and these were included in the results used for decision-making by using estimates of the comparator PAS price.

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

6.2. Results

The base case analysis compared IsaVRd with DRd. SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 6.2.

Table 6.2: Sensitivity analysis for DRd

	Parameter	Base case	Scenario
1a	Time horizon	Lifetime (29 years)	10 years
1b			20 years
2	Subsequent treatments attrition rates	Clinical trials and Yong et al.	Same for all comparators (Yong et al.)
3	Subsequent treatment cost method	Applied after first line progression.	Applied after first line discontinuation
4	OS–IsaVRd	Gen. Gamma	Gompertz
5	PFS–IsaVRd	Gamma	Weibull
6	TTD–IsaVRd	Exponential	Gompertz
7	TTD–DRd	TTD MAIC HR applied to IsaVRd TTD	TTD = PFS (applies to IsaVRd also)
8a	Comparative efficacy		Standard NMA constant HRs (VRd reference)

8b		Time-varying hazard ratios derived from ITCs	Standard NMA constant HRs (IsaVRd reference)
8c			Time-varying hazard ratios PFS=OS=1
8d			Extrapolate MAIC-adjusted DRd and IsaVRd PFS and OS
8e			Extrapolate MAIC-adjusted DRd and IsaVRd PFS and OS. OS HR = 1.
9	Utilities PPS	All treatments FIRST literature value of 0.557.	IMROZ - PPS with treatment effect IsaVRd and DRd = 0.710 Other comparators = 0.670
10	Utilities (PFS and PPS)	IMROZ–PFS with treatment effect IsaVRd and DRd = 0.728 Other comparators = 0.688 Literature–PPS All treatments = 0.557.	IMROZ–PFS with no treatment effect All treatments = 0.713 IMROZ–PPS with no treatment effect All treatments = 0.694
11	Utilities (PFS and PPS)	IMROZ – PFS with treatment effect IsaVRd and DRd = 0.728 Other comparators = 0.688 Literature - PPS All treatments = 0.557.	IMROZ – PFS with treatment effect IsaVRd and DRd = 0.728 Other comparators = 0.688 Literature – PPS decrement from Hatswell et al., 2019 of 0.03
12	Medicine costs	BNF	Contract pricing
C1	Scenarios 2 and 10. Same attrition rate applied to all comparators and IMROZ utilities (PFS and PPS)		
C2	C1 and Scenario 8d. C1 and extrapolate MAIC DRd and IsaVRd PFS and OS.		
C3	C1 and Scenario 8e. C1 and extrapolate MAIC DRd and IsaVRd PFS and OS. OS HR = 1.		
C4	Scenarios 8d and 11. Extrapolate MAIC DRd and IsaVRd PFS and OS and use Hatswell et al., 2019 utility decrement.		

Abbreviations: BNF = British National Formulary; C = combined scenario; DRd = daratumumab, lenalidomide, and dexamethasone; ICER = incremental cost-effectiveness ratio; Incr. = incremental; IPW = inverse probability weighting; IsaVRd = isatuximab, bortezomib, lenalidomide and dexamethasone; HR = hazard ratio; ITC = indirect treatment comparison; ITT = intention-to-treat; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PPS = post=progression state; QALYs = quality-adjusted life years; Rd = lenalidomide and dexamethasone; RDI = relative dose intensity; TTD = time to treatment discontinuation; VCd = bortezomib, cyclophosphamide, and dexamethasone; VMP = bortezomib, melphalan, and prednisone; VRd = bortezomib, lenalidomide and dexamethasone. Note: All IsaVRd alternative OS and PFS extrapolations also apply the same parametric distribution for the comparator time-varying hazard ratios.

6.4. Key strengths

- The economic analysis included the most relevant comparator of DRd.
- The efficacy data for IsaVRd comes from IMROZ, a randomised phase III study.
- The sources used to value resource use costs were appropriate.

6.5. Key uncertainties

- There were uncertainties in the extrapolation of OS and PFS, affecting the estimated relative efficacy of IsaVRd. Firstly, the time-varying hazard ratios were derived from the MAIC and IPW adjusted data but subsequently applied to the IMROZ ITT data. The submitting company highlighted this approach was used to maintain a consistent reference curve for IsaVRd PFS and OS. However, SMC statistical support highlighted that the submitting company's approach introduced a fundamental inconsistency, and highlighted preference for the direct modelling of extrapolated MAIC and IPW adjusted data for each comparator. This was considered in a scenario analysis for DRd (Scenario 8d), with an additional scenario setting the OS hazard ratio to 1 given the lack of a statistically significant improvement in OS for ISaVRd compared to DRd (Scenario 8e). Additionally, the

extrapolated IsaVRd PFS and OS estimates all exceeded the submitting company's clinical expert expectations. Although, alternative IsaVRd PFS and OS curves were explored in scenario analyses (Scenarios 4 and 5), uncertainty remained about the face validity of survival extrapolations.

- There were uncertainties with the base case post-progression utility value sourced from NICE TA587 (FIRST study). Firstly, the submitting company justified this approach due to the limited EQ-5D data collection in IMROZ (97 patients post-progression, with a total of 272 records). However, the post-progression EQ-5D data collection in FIRST also had a similar limitation with only 257 and 269 progressed observations in the Rd and thalidomide plus melphalan plus prednisone (MPT) arms, respectively, derived from one post progression visit. Secondly, the FIRST study started in 2008 with EQ-5D data collected for a maximum of 18 months or until disease progression. The relevance of these health-related quality of life data to the current multiple myeloma treatment pathways may therefore be limited. Finally, the FIRST EQ-5D regression from which the post-progression utility value was derived showed a much smaller decrement upon progression (of 0.028) than is observed in this submission (of 0.171 for IsaVRd and DRd). A study by Hatswell et al., 2019 also demonstrated a smaller decrement upon progression of 0.03.[29] Given these limitations, scenario analyses were conducted using post-progression utility values derived from IMROZ, based on two separate utility regressions (Scenarios 9 and 10). One regression incorporated the treatment effect associated with IsaVRd, while the other excluded it. To address uncertainty in this area, the submitting company also provided an additional scenario analysis that applied the progression decrement from Hatswell et al., 2019 to the base case PFS utility values (Scenario 11).
- There was uncertainty in the modelling of subsequent treatment proportions, given the higher attrition rates in the IsaVRd arm compared to comparator arms. The submitting company noted that the IMROZ population had a mean age of 71.6 years, and given the longer observed PFS, more patients are expected to die due to age-related factors or comorbidities before receiving further treatment. However, the imbalance in subsequent treatment proportions may have underestimated subsequent treatment costs for IsaVRd. Therefore, a scenario applied equal proportions of subsequent treatment across all arms (Scenario 2).[30]
- There was uncertainty in the TTD extrapolations. While the base case TTD estimates for IsaVRd and DRd were similar, IsaVRd showed an improved PFS compared to DRd. This resulted in a larger gap between PFS and TTD for IsaVRd than DRd. The submitting company justified this by noting a MAIC analysis demonstrated that IsaVRd significantly increased the odds of achieving MRD negativity compared to DRd. In addition, the submitting company noted the equivalent TTD was supported by its MAIC TTD results. However, there remains a potential face validity concern, and a conservative scenario was considered assuming equivalence between TTD and PFS to explore the bounds of this uncertainty (Scenario 7).
- The treatment pathway for multiple myeloma is complex, often involving several successive lines of therapy. Modelling the second line onwards using a single post-

progression health state may not adequately reflect the implications of disease progression. However, whilst a more granular modelling approach may improve accuracy, it also increases demands on data requirements and interpretability.

- The cost of bortezomib and lenalidomide in NHS practice is lower than the price used in the economic model due to the existence of a national framework agreement for these medicines. Using the national framework contract prices has a substantial impact on the cost-effectiveness results.

7. Conclusion

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 use in NHSScotland.

8. Guidelines and Protocols

The European Haematology Association (EHA) and European Myeloma Network (EMN) published guidelines on the diagnosis, treatment and follow-up of patients with multiple myeloma in July 2025.[31]

The British Society for Haematology and UK Myeloma Forum published guidelines on the diagnosis, investigation and initial treatment of myeloma in March 2021.[6]

The European Haematology Association (EHA) and European Society of Medical Oncology (ESMO) published clinical practice guidelines for diagnosis, treatment and follow-up of multiple myeloma in March 2021.[32]

The National Institute for Health and Care Excellence (NICE) updated its guideline 35 Myeloma: diagnosis and management in October 2018.[33]

9. Additional Information

9.1. Product availability date

27 January 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
isatuximab (in combination with bortezomib, lenalidomide, and dexamethasone)	**10 mg/kg by intravenous infusion according to treatment cycle.** **Cycle one: days 1, 8, 15, 22, and 29** **Cycles two to four: days 1, 15, and 29** **Cycles five to 17: days 1 and 15** **Cycles 18 onwards: day 1 only**	**Cycle 1: 17,743** **Cycles 2 to 4: 10,646** **Cycles 5 to 17: 7,097** **Cycle 18 onwards: 3,549**

Costs from BNF online on 27 June 2025. Costs calculated using the full cost of vials assuming wastage and a body weight of 70 kg. 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.

*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 15 August 2025.

**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