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SMC2597

belantamab mafodotin powder for concentrate for solution for infusion (Blenrep®)

GlaxoSmithKline

08 December 2023

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 end of life and orphan medicine process

belantamab mafodotin (Blenrep®) is not recommended for use within NHSScotland.

Indication under review: as monotherapy 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 one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

In a phase II, open-label study of belantamab mafodotin, the overall response rate was 32% in patients with multiple myeloma that was triple-class refractory.

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

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

Belantamab mafodotin (referred to as belantamab hereafter) is an immunoglobulin G1 kappa (IgG1K) monoclonal antibody, conjugated with a cytotoxic agent, which binds specifically to B-cell maturation antigen (BCMA), leading to immune mediated tumour cell death.

The recommended dose of belantamab is 2.5mg/kg every three weeks, administered as an intravenous (IV) infusion over at least 30 minutes; treatment may be continued until disease progression or unacceptable toxicity.[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, kidney dysfunction and neurological complications.[2, 3] Multiple myeloma predominantly affects older people and the median age at diagnosis is approximately 70 years.[4] Approximately 47% of patients will be alive 5 years after their diagnosis. The incidence of multiple myeloma in Scotland is estimated to be 8.8 per 100,000 people.[5, 6]

1.3. Treatment pathway and relevant comparators

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'; this encompasses patients with disease that is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent, and an anti-CD38 monoclonal antibody. Generally, these patients have been exposed to all medicines that have demonstrated efficacy as monotherapy (with or without glucocorticoids); this includes bortezomib (PI), carfilzomib (PI), lenalidomide (immunomodulatory agent), pomalidomide (immunomodulatory agent), and daratumumab (an anti-CD38 monoclonal antibody).[2, 7-9]

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, carfilzomib plus dexamethasone, bortezomib plus dexamethasone, and best-supportive care. The company considered that pomalidomide plus dexamethasone or panobinostat plus bortezomib and dexamethasone were the most relevant comparators.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option:
Belantamab received an Innovation Passport allowing entry into the Medicines and Healthcare Products Regulatory Agency (MHRA) Innovative Licensing and Access Pathway. Belantamab has a conditional marketing authorisation from the MHRA.

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

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support belantamab comes from the DREAMM-2 study. Details are summarised in Table 2.1.

Table 2.1. Overview of the relevant study.

Criteria	DREAMM-2 study.[1, 2]
Study Design	International, open-label, randomised, two-arm (no comparator arm) phase II study.
Eligible Patients	• Aged ≥18 years, with an ECOG PS of 0 to 2. • Histologically or cytologically confirmed diagnosis of multiple myeloma as defined according to IMWG criteria. • Had measurable disease and no prior allogenic SCT. • Had undergone a autologous SCT or was considered transplant ineligible; **and** • Had failed at least three prior lines of anti-myeloma treatments, including an anti-CD38 antibody (for example daratumumab) alone or in combination, and was refractory[a] to an immunomodulatory agent (that is lenalidomide or pomalidomide), and to a proteasome inhibitor (for example bortezomib, ixazomib, or carfilzomib).[b]
Treatments	IV belantamab every three weeks at a dose of either: 2.5mg/kg (licensed dose and focus of this submission) or 3.4mg/kg; treatment continued until disease progression or unacceptable toxicity. Patients received full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, anti-diarrhoeal, and analgesics, as appropriate. Concomitant therapy with bisphosphonates was allowed. Patients were permitted to receive local irradiation for pain or stability control.
Randomisation	Eligible patients were randomised equally to either treatment group. Randomisation was stratified according to the number of prior lines of therapy (≤4 or >4) and cytogenetic risk categories (high risk vs. non-high risk).[c]
Primary outcome	Overall response rate (ORR), defined as sCR + CR + VGPR + PR, assessed by an IRC based on the 2016 IMWG response criteria. Participants with unknown or missing response were treated as non-responders and were included in the percentage ORR calculations.
Secondary & exploratory outcomes	These included but were not limited to: duration of response (DOR), progression-free survival (PFS), overall survival (OS), time to treatment discontinuation (exploratory), and time to next treatment (exploratory).
Statistical analysis	No formal statistical analysis was conducted; the results are descriptive only.

[a]Refractory myeloma is defined as disease that is non-responsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Non-responsive disease is defined as either failure to achieve at least minimal response or development of PD while on therapy.

[b]The number of prior lines of therapy was determined according to guidelines.[10]

[c]High-risk was defined as the following cytogenics: t(4;14), t(14;16), and 17p13del; non-high risk were all other cytogenics.

CR = complete response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IMWG = International Myeloma Working Group; IRC = independent review committee (IRC); IV = intravenous; PR = partial response; sCR = stringent complete response; SCT = stem cell transplant; VGPR = very good partial response.

The submitting company presented results from the interim analysis (January 2020 data cut-off) and the final analysis (March 2022 data cut-off) and results are presented in Table 2.2. The results of the primary outcome at the final analysis were similar to those at the interim analysis.

Table 2.2: Results of primary and selected secondary outcomes of the DREAMM-2 study in the ITT population for patients in the 2.5mg/kg belantamab cohort (data cut-off March 2022, unless specified otherwise).[1, 11, 12]

	IV Belantamab 2.5mg/kg every three weeks (n=97)
Median duration of follow-up	12.5 months (range: 0.1 to 40.4 months)
Primary outcome: ORR as per IRC assessment[a] (data cut-off January 2020)	
Overall response rate, % (n)	32% (31)
Stringent Complete Response, % (n)	2% (2)
Complete Response, % (n)	5% (5)
Very Good Partial Response, % (n)	11% (11)
Partial Response, % (n)	13% (13)
Secondary outcome: DOR as per IRC assessment	
Median DOR	12.5 months
Secondary outcome: PFS as per IRC assessment	
KM estimated median PFS, months (95% CI)	2.8 months (1.6 to 3.6)
Secondary outcome: Overall survival	
KM-estimated median overall survival	15.3 months
IRC = independent review committee (IRC); IV = intravenous.	

Time to treatment discontinuation (TTD) and time to next treatment (TTNT) were exploratory outcomes that were analysed post-hoc. The results from these analyses informed the cost-effectiveness analysis. At the final analysis (data cut-off March 2022), the median TTD was 2.1 months.[12]

Five patients (5%) received three lines of treatments prior to belantamab, which is outside the population considered for this submission (≥4 prior therapies). However, results for this fifth line or beyond (5L+) subgroup (n=92) were consistent with the full study population that received the 2.5mg/kg belantamab dose (n=97) for ORR, progression-free survival (PFS), overall survival, TTD, and TTNT.[2]

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and the myeloma-specific questionnaire (EORTC-QLQ-MY20).[13, 14] From baseline to week 61, there was a reduction in the EORTC-QLQ-C30 scores for global health status/QoL however, belantamab appeared to result in improvements in all other domains for EORTC-QLQ-C30; the results from the EORTC-QLQ-MY20 questionnaire appear to be supportive of these results.[13]

2.3. Supportive studies

DREAMM-3 (NCT04162210) is an ongoing phase III, open-label, randomised, international study to evaluate the efficacy and safety of belantamab monotherapy (n=218) compared with

pomalidomide plus dexamethasone (n=107). The study includes patients with relapsed and/or refractory multiple myeloma who received at least 2 prior lines of anti-myeloma treatments (including at least 2 consecutive cycles of both lenalidomide and a proteasome inhibitor [given separately or in combination], and who have failed their last line of treatment.[15, 16]

The primary outcome was PFS; at the primary analysis (median follow-up 11.5 months [belantamab] and 10.8 months [pomalidomide plus dexamethasone]) median PFS was longer for belantamab (11.2 months; 95% CI: 6.4 to 14.5) compared with pomalidomide plus dexamethasone (7.0 months; 95% CI: 4.6 to 10.6). However, this difference was not statistically significant.[16]

The submitting company highlighted that very few patients in this study were triple-class refractory and on their fifth line of multiple myeloma treatment.

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

In the absence of direct evidence, the submitting company provided a naïve unadjusted comparison using data from the DREAMM-2 study and the National Cancer Registration and Analysis Service (NCRAS) study. Comparisons of belantamab with pomalidomide plus dexamethasone in adults with triple-class refractory multiple myeloma at fifth line and beyond (5L+) were made; the outcomes assessed were overall survival, TTNT and TTD – these were used to inform the base-case analysis of the economic evaluation and are described in Table 2.3. The submitting company initially conducted an unanchored matching-adjusted indirect comparison (MAIC) using individual patient data from DREAMM-2 and aggregate data from the English-based NCRAS study but were unable to match the majority of key patient characteristics, resulting in a small effective sample size for DREAMM-2 after matching; they deemed the MAIC results to be too uncertain to inform the base-case analysis of the economic evaluation.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Naïve unadjusted comparison using data from the studies mentioned below.
Population	Adults with triple-class refractory multiple myeloma 5L+.
Comparators	Pomalidomide plus dexamethasone.
Studies included	DREAMM-2 (n=97)[11, 12, 14] and aggregate data from the NCRAS study.
Outcomes	Overall survival, TTNT, and TTD.
Results	The results from the naïve comparison appear to show numerical evidence favouring belantamab compared with pomalidomide plus dexamethasone for overall survival. For TTNT and TTD, there appears to be numerical evidence favouring pomalidomide plus dexamethasone compared with belantamab.

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

3. Summary of Safety Evidence

The European regulator deemed the safety profile of belantamab to be acceptable in the target population and noted ocular toxicities and their clinical management to be the most important safety concern. However, they did outline that additional data is needed to support the overall

safety profile of belantamab; as such they have outlined this in the obligations of the conditional marketing authorisation (see section 4.3).[2]

In the DREAMM-2 study at the January 2020 data cut-off, the median duration of treatment in the 2.5mg/kg cohort was 9 weeks. Any treatment-emergent adverse event (AE) was reported by 98% (93/95) of patients, and these were treatment-related in 88% of patients. Patients reporting a grade 3 or higher AE were 83%, and 57% were treatment-related. Patients with a reported serious AE were 42%, and 12% of these were treatment-related. Patients with a dose reduction due to treatment emergent AEs were 35%, the proportion of AEs that led to dose interruptions/delays were 54%, and patients discontinuing therapy due to an AE was 9.0%; 7.0% had treatment-related AEs that led to permanent treatment discontinuation.[2, 11] Fatal serious AEs (SAEs) occurred in 3 of 95 patients (3.0%); one of these events (sepsis) was considered treatment-related.[11]

Overall, updated AE safety data from the final analysis (data cut-off March 2022) showed no new safety signals were observed.[12] However, there were increases in the proportion of patients: with serious AEs, discontinuing therapy due to an AE, had treatment-related AEs that led to permanent treatment discontinuation (9.0%), and those who had a fatal serious AE.

At the January 2020 data cut-off, the most frequently reported grade ≥3 AEs with an incidence of ≥3% were: keratopathy (31%), thrombocytopenia/decreased platelet count (22%), anaemia (21%), lymphopenia/decreased lymphocyte count (17%), neutropenia/decreased neutrophil count (11%), pneumonia (7.0%), hypercalcaemia (7.0%), leukopenia/decreased leukocyte count (6%), blurred vision events (4.0%), pyrexia (4.0%), infusion-related reactions (3.0%) and increased gamma glutamyltransferase (3.0%).[1, 2, 11]

Eye disorders were very common and include: keratopathy (71%), blurred vision (23%), best-corrected visual acuity (BCVA) reduction to 20/50 (18%) and dry eyes (15%); keratopathy was the most common reason for dose modification in the DREAMM-2 study (27%)[1, 2], and 3.0% discontinued belantamab treatment permanently due to ocular AEs.[12] However, BCVA changes and blurred vision were transient; up to 86% of all patients who had experienced blurred vision or worsening BCVA had resolution by the end of follow up; no permanent complete loss of vision has been reported.[12] The Summary of Product Characteristics describes required ophthalmic examinations and dose modifications in response to toxicity.[1]

Infusion-related reactions (IRRs) occurred in 21% of patients in DREAMM-2; most IRRs (90%) occurred during the first infusion and most were grade 1 (6.0%) or 2 (12%).[1]

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

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- At the final analysis (data cut-off March 2022) in the DREAMM-2 study, treatment with belantamab resulted in an ORR of 32% in the cohort of patients with TCR multiple myeloma at 5L+, who received the licensed 2.5mg/kg dose; median overall survival was 15.3 months. These results were considered clinically meaningful in this heavily pre-treated population.[2]

- In the DREAMM-2 study, all patients were refractory to at least one immunomodulator, proteasome inhibitor, and anti-CD38 antibody; the majority of patients (95%) had previously received at least four prior therapies. Overall, the study population aligns with the licensed indication.[2]
- The company provided some observational data from the UK, including patients treated in Scotland, that was supportive.

4.2. Key uncertainties

- DREAMM-2 was an open-label, phase II study with no comparator arm. The sample size of patients treated with the 2.5mg/kg dose was small (n=97), and no patients have been treated with the commercially available lyophilised formulation at the licensed 2.5mg/kg dose.[2]
- The DREAMM-3 study offers some direct comparison for belantamab with pomalidomide plus dexamethasone, however, the study population is wider than the licensed indication, the study was not powered for subgroup analysis, and relevant subgroup data for 5L+ triple-class refractory patients have not been provided..[2]
- There is uncertainty over the most relevant comparator. Clinical experts contacted by SMC indicated that pomalidomide plus dexamethasone would most likely be used before the fifth-line stage for multiple myeloma patients in NHSScotland; most experts indicated that cyclophosphamide or best-supportive care would be more relevant comparators. Other potential treatment options that could be considered relevant include: cyclophosphamide +/- dexamethasone, bendamustine, panobinostat plus bortezomib and dexamethasone, carfilzomib plus dexamethasone, bortezomib plus dexamethasone.
- There were a number of limitations identified in the MAIC and the naïve comparison. The company did not consider the use of best supportive care as a comparator, which is also more reflective of SMC expert opinion. There was heterogeneity between the studies used in the comparisons including in study design, outcome definitions, key patient characteristics (such as previous lines of therapy and international staging system) and assessment timepoints. Furthermore, time to next treatment was used as a proxy to estimate the relative PFS between the treatments, which may bias the clinical inputs used in the cost-effectiveness analysis. In terms of generalisability, the NCRAS study uses NHSEngland patient data up to 2019, and due to the differences in treatments available between NHSEngland and NHSScotland, this data source is not considered reflective of practices in NHSScotland. Given these limitations, the results are considered highly uncertain and should be interpreted with caution.

4.3. MHRA conditional marketing authorisation specific obligations / Innovative Licensing and Access Pathway (ILAP) and ongoing studies

The MHRA specific obligations and the ongoing DREAMM-3 study are unlikely to address the key uncertainties in the clinical evidence presented.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that belantamab 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. They considered that the place in therapy for belantamab is fifth-line or beyond.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the patient and/or service delivery due to the requirement for ophthalmology monitoring. Some experts highlighted that they have already been able to use belantamab (as per the licensed indication) through an early access scheme.

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 **belantamab (Blenrep**)**,** as an **orphan and end of life** 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; treatment is generally palliative in nature in this setting. Belantamab would be a potential treatment option for fitter, heavily pre-treated patients with multiple myeloma who would have a limited chance of responding to these existing therapies and who have a poor prognosis.
- The DREAMM-2 study showed that belantamab has clinical benefits in this heavily pre-treated population; PACE clinicians shared their positive experiences of using belantamab in practice through the UK early patient access scheme and consider belantamab to be an effective medicine for these patients who have run out of treatment options. Real-world evidence from the entire UK early access scheme treated with belantamab was reassuring and confirmed a positive objective response rate greater than that seen in DREAMM-2.
- Families and carers would welcome a treatment that could keep the patient alive and well for longer; this could translate into substantial health benefits to their emotional and psychological wellbeing.
- Belantamab is administered as a 30-minute infusion every three weeks, which would likely represent a more manageable dosing schedule than some of the other treatments used at the fifth line stage.
- Ocular toxicity is very common and there is a need for patients to self-administer eye drops several times per day whilst on belantamab treatment. It is reported that the ocular toxicity is usually reversible with dose reductions or delays. There will be a need for regular eye

examinations for patients whilst on belantamab treatment and would require each health board across NHSScotland to establish a service link-up with local ophthalmology departments.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 9.5% 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

The economic analysis submitted by the company is summarised in table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime horizon (25 years) with a 1 week cycle length. Shorter time horizons of 10 and 15 years were explored in sensitivity analysis.
Population	The patient population in the economic analysis reflects the licensed indication i.e. patients with multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.
Comparators	Pomalidomide plus dexamethasone was considered the most relevant comparator by the submitting company. A comparison with panobinostat plus bortezomib plus dexamethasone was provided as a sensitivity analysis.
Model description	A cohort-based partitioned survival model was used with four health states: progression-free on treatment, progression-free off-treatment, progressed disease and death. The separate health states for patients on and off treatment in the progression-free state were included to reflect some patients in DREAMM-2 withdrawing from active treatment before disease progression. Different utility values were applied in the progression-free health states depending on whether patients were on or off treatment.
Clinical data	Efficacy data were taken from the DREAMM-2 study for belantamab and the observational, retrospective NCRAS dataset for pomalidomide plus dexamethasone. These data sources were used in a naïve indirect comparison to estimate the belantamab treatment effect as described above. As no PFS data were available for pomalidomide plus dexamethasone, TTNT data were used as a proxy for PFS in both the pomalidomide plus dexamethasone arm and the belantamab arm of the model.
Extrapolation	Clinical data were extrapolated for proxy PFS (TTNT), OS and TTD using parametric survival modelling. Curve selection for each outcome was based on goodness of fit statistics (AIC/BIC), visual fit and clinical plausibility. This resulted in the selection of the Weibull distribution for proxy PFS and OS in both arms, with the lognormal selected for TTD.
Quality of life	EORTC-QLQ-C30 data were collected in DREAMM-2 and mapped to EQ-5D using a published algorithm to derive utility values. Age-related utility decrements were applied. Disutilities due to adverse events were taken from published literature with most values from the NICE TA510 of daratumumab in fourth-line MM.
Costs and resource use	Costs included medicine acquisition and administration, management of adverse events, and monitoring and disease management costs. Costs of subsequent treatments were included based on the proportions from DREAMM-2 and NCRAS. In line with the SmPc, the cost of

	ophthalmology visits and artificial tears were included for belantamab patients. This was estimated to result in a cost of £721 in year 1 and £203 in subsequent years. Health state costs relating to routine management and monitoring were included based on those identified in the NICE TA510 and included physician visits, complete blood counts and biochemistry. Adverse events costs were included for grade ≥3 events occurring in ≥5% of patients plus keratopathy where mild, moderate and severe grading was included. The average cost of managing keratopathy was estimated to be £408.
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 simple discount was offered on the list price. A PAS discount is in place for pomalidomide and this was 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 PAS for pomalidomide 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 due to commercial confidentiality and competition law issues.

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

6.2 Results

The base case results estimated by the company showed that belantamab (with PAS) was dominant compared to pomalidomide plus dexamethasone (at list prices) meaning it was estimated as resulting in lower costs and better health outcomes for patients.

6.3 Sensitivity analyses

Selected sensitivity analysis provided by the company are summarised in table 6.2 below.

Table 6.2 Selected sensitivity analysis results (with belantamab PAS, list price for pomalidomide)

	Scenario Analysis	**Base case assumption**	**ICER**
1	10 year time horizon	Lifetime (25 years)	dominant
2	Three-state model	Four-state model	dominant
3	MAIC used as source of comparative effectiveness	Naïve comparison	dominant
4	DREAMM-3 data used as source of comparative effectiveness		Not provided
5	Panobinostat/bortezomib/ dexamethasone comparison	Pomalidomide plus dexamethasone	dominant
6	Subsequent treatment costs informed by Scottish clinical opinion	Subsequent treatment costs informed by DREAMM-2 and NCRAS	dominant

7	No waning or cap on PFS	Waning and cap on PFS	dominant
8	Including 15% wastage	No drug wastage included	dominant

PAS = patient access scheme; MAIC = matched-adjusted indirect comparison; PFS = progression-free survival; ICER = incremental cost-effectiveness ratio; dominant = the assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

6.4 Key strengths

- The model structure was appropriate and consistent with the approach used in the assessment of other multiple myeloma treatments.
- The availability of quality of life data from the DREAMM-2 study which were mapped to EQ-5D to estimate utility values in the model was a key strength.

6.5 Key uncertainties

- There is some uncertainty regarding the choice of comparator used in the analysis. SMC clinical expert responses indicated pomalidomide plus dexamethasone, while used in practice, is likely to be used earlier in the treatment pathway. Cyclophosphamide was highlighted by the majority of clinical experts as the treatment most likely to be displaced with some experts suggesting no active treatment/best supportive care (BSC) may be a more relevant comparator. The company was requested to provide an analysis comparing belantamab with cyclophosphamide or BSC but chose not to provide this comparison as they maintained that more active comparator treatments were more appropriate. The cost-effectiveness of belantamab versus cyclophosphamide or BSC remains unknown.
- The source of comparative effectiveness in the model was a naïve comparison using DREAMM-2 data to estimate the efficacy of belantamab and NCRAS data for pomalidomide plus dexamethasone. However, there are direct comparative data available from the ongoing phase III DREAMM-3 study comparing belantamab with pomalidomide plus dexamethasone which were omitted from the analysis. The company noted limitations with using DREAMM-3 as the key data source in the model on the basis that only a small proportion of patients were triple class refractory and on their fifth line of treatment. Despite these limitations, the New Drugs Committee (NDC) considered it would be preferable to explore using DREAMM-3 data in the model given the uncertainties associated with the naïve indirect comparison. The company was asked to provide cost-effectiveness estimates using the DREAMM-3 study but chose not to provide these on the basis that it was not possible to provide cost-effectiveness estimates using these data that could be interpreted.
- The relative treatment effect of belantamab versus pomalidomide plus dexamethasone is based on a naïve indirect comparison. A MAIC was also conducted but the company argued the naïve comparison was more appropriate. There are a number of limitations with the indirect comparisons as described above and the results of the analysis showed some sensitivity to the choice of indirect approach.
- There were no PFS data available from the NCRAS data to use in the model meaning TTNT data were used as a proxy for PFS. The company noted this may result in an overestimation

of the QALY gains in the model although it is not clear if this will introduce a bias in favour of one treatment. This uncertainty further strengthens the argument of using the DREAMM-3 study data which would allow PFS data to be used directly in the model, albeit there will also be uncertainties remaining with this approach.

- The mix of subsequent treatments in the pomalidomide plus dexamethasone arm of the model was based on estimates from the NCRAS study and as noted above, this study may not be generalisable to current practice in NHSScotland. A scenario analysis was provided where subsequent treatments were based on Scottish clinical expert opinion (scenario 6) which is more appropriate than the base case approach.
- No wastage was included in the base case analysis on the assumption that in practice vial sharing would be possible. SMC clinical experts commented that this is unlikely and therefore the sensitivity analysis where some wastage is included (scenario 8) is more relevant to Scottish practice.

7. Conclusion

The Committee considered the benefits of belantamab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as belantamab is an orphan 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 was unable to accept belantamab 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.[18]

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.[19]

The National Institute for Health and Care Excellence (NICE) published “Myeloma: diagnosis and management” (NG35) in February 2016, which was updated in October 2018.[20]

9. Additional Information

9.1. Date of licensing

27 August 2020

9.2. Product availability date

May 2021

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per three-week cycle* (£)
Belantamab mafodotin	**2.5mg/kg as an intravenous infusion every three weeks until disease progression**	**£11,415**

Costs from BNF online on 05 September 2023. Costs calculated using an average weight of 70kg and the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimated there would be 39 patients eligible for treatment with belantamab mafodotin in year 1, rising to 193 patients in year 5, to which confidential uptake rates were applied. SMC is unable to publish the budget impact due to commercial in confidence issues.

*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 24 October 2023.

**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.