Belantamab mafodotin (Blenrep®) as monotherapy for the treatment of relapsed or refractory multiple myeloma (MM)

General information [1]

Drug description	Indication
Belantamab mafodotin (also known as GSK2857916) is a humanised IgG1κ monoclonal antibody against the BCMA conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F.	Belantamab mafodotin is indicated as monotherapy for the treatment of MM 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.

Current treatment [2]

- Lenalidomide in combination with dexamethasone is recommended for the treatment of MM in transplant-eligible patients who have received at least two prior therapies.
- The following are recommended as subsequent (post-second line) therapies for treating MM in transplant in-eligible patients:
  - daratumumab monotherapy
  - ixazomib, with lenalidomide and dexamethasone
  - pomalidomide, in combination with low-dose dexamethasone
  - panobinostat in combination with bortezomib and dexamethasone
  - lenalidomide in combination with dexamethasone.

Regulatory status

EMA [1, 3]	FDA [4]
Approval status for this indication: On 23 July 2020, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Blenrep®, intended for the treatment of relapsed and refractory MM. On 16 October 2017, orphan designation was granted by the European Commission. Date of issue of marketing authorisation valid throughout the European Union: **25/08/2020** **UPDATE December 2023 [5]:** on 15 December 2023, the CHMP has confirmed its initial recommendation to not renew the conditional marketing authorisation for Blenrep® (belantamab mafodotin) because recent data did not confirm its effectiveness; the benefits of Blenrep® are therefore considered to no longer outweigh its risks. **UPDATE September 2023 [6]:** on 15 September 2023, the CHMP has recommended **not renewing the conditional marketing authorisation for Blenrep®**. This recommendation follows a review of available data by the CHMP as part of the renewal of Blenrep®'s marketing authorisation. In its review, the CHMP considered that results from a new study (DREAMM-3) did not confirm the effectiveness of Blenrep® as agreed when conditional marketing authorisation was granted. On 21 September 2023, the company that markets Blenrep® asked for re-examination of the CHMP opinion. Upon receipt of the grounds of the request, the CHMP will re-examine its recommendation and issue a final recommendation. Once the re-examination has been finalised, EMA will send the CHMP's final opinion on the renewal application to the European Commission, which will issue a final legally binding decision applicable in all EU Member States. **Information for healthcare professionals, according to the EMA:** ❖ Blenrep® will no longer be available following non-renewal of its conditional marketing authorisation. ❖ Healthcare professionals should not start any new patients on Blenrep®. ❖ For patients currently using Blenrep®, healthcare professionals should explain to patients that the medicine is no longer available and discuss with them suitable treatment alternatives. ❖ Blenrep® received a conditional marketing authorisation in August 2020; the marketing authorisation was subject to annual renewals based on the results of additional studies imposed on the marketing authorisation holder.	**Approval status for this indication**: On 5 August 2020, the FDA granted accelerated approval to belantamab mafodotin-blmf (Blenrep®) for adult patients with relapsed or refractory MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. **UPDATE:** On 6 February 2023, the **FDA withdraw** the accelerated approval of Blenrep® (belantamab mafodotin-blmf) [7].

- ❖ The recent DREAMM-3 study failed to show that patients treated with Blenrep® lived longer without their disease getting worse than those treated with pomalidomide and low-dose dexamethasone.
- ❖ This phase 3, open-label, randomised (2:1) study compared Blenrep® with pomalidomide and low-dose dexamethasone in 325 patients with relapsed/refractory multiple myeloma. The primary endpoint agreed as part of the specific obligation was superiority in investigator-assessed progression-free survival (PFS). The study found no statistically significant difference in PFS between the two groups (HR 1.03; 95% confidence interval: 0.72, 1.47).

Other indications: none

✓ **Orphan status**
✓ **Additional monitoring**

Costs

Currently, there is no cost information available.

Administration of belantamab mafodotin: Recommended supportive care [8]

- ❖ Patients should have an ophthalmic examination (including visual acuity and slit lamp examination) performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and as clinically indicated whilst on treatment.
- ❖ Physicians should advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment as this may reduce corneal symptoms.
- ❖ For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional.

Special warnings and precautions for use [8]

- ❖ **Traceability**: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- ❖ **Corneal adverse reactions**: Corneal adverse reactions have been reported with the use of belantamab mafodotin. The most commonly reported adverse reactions were keratopathy or microcyst-like epithelial changes in corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye symptoms. Patients with a history of dry eyes were more prone to develop changes in the corneal epithelium. Changes in visual acuity may be associated with difficulty in driving or operating machinery. Ophthalmic examinations, including assessment of visual acuity and slit lamp examination, should be performed at baseline, before the subsequent 3 treatment cycles and during treatment as clinically indicated. Patients should be advised to administer preservative-free artificial tears at least 4 times a day during treatment. Patients should avoid using contact lenses until the end of treatment. Patients experiencing keratopathy with or without changes in visual acuity may require a dose modification (delay and/or reduction) or treatment discontinuation based on severity of findings. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. These should be managed promptly and as clinically indicated by an eye care professional. Treatment with belantamab mafodotin should be interrupted until the corneal ulcer has healed.
- ❖ **Thrombocytopenia**: Thrombocytopenic events (thrombocytopenia and platelet count decreased) were frequently reported in study 205678. Thrombocytopenia may lead to serious bleeding events, including gastrointestinal and intracranial bleeding. Complete blood counts should be obtained at baseline and monitored during treatment, as clinically indicated. Patients experiencing Grade 3 or 4 thrombocytopenia or those on concomitant anticoagulant treatments may require more frequent monitoring and should be managed with a dose delay or dose reduction. Supportive therapy (e.g. platelet transfusions) should be provided according to standard medical practice.
- ❖ **Infusion-Related Reactions (IRR)**: IRRs have been reported with belantamab mafodotin. Most IRRs were Grade 1-2 and resolved within the same day. If a grade 2 or higher infusion- related reaction occurs during administration, the infusion rate should be reduced or the infusion should be stopped depending on the severity of the 6 symptoms. Appropriate medical treatment should be instituted and infusion should be started at a slower rate, if the patient's condition is stable. If Grade 2 or higher IRR occurs, premedication for subsequent infusions should be administered.
- ❖ **Excipients:** This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially "sodium-free".

Study characteristics [8-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Reference(s)
DREAMM-2, Study 205678 NCT03525678	196	belantamab mafodotin 2.5 mg/kg IV every 3 weeks on day 1 of each cycle	belantamab mafodotin 3.4 mg/kg IV every 3 weeks on day 1 of each cycle	the proportion of randomly assigned patients in the ITT population who achieved an overall response (as assessed by an IRC)	open-label, two-arm, multicenter, international, phase 2 trial	-	GlaxoSmithKline	[9]

Efficacy (I vs. C) | **Safety** (I vs. C)

Overall response (by IRC): 30 (31%; 97.5% CI 20.8-42.6) of 97 patients vs. 34 (34%; 23.9-46.0) of 99 patients **Very good partial response or better:** 18 (19%) of 97 patients vs. 20 (20%) of 99 patients **Clinical benefit** (minimal response or better, by IRC): 33 (34%; 95% CI 24.7-44.3) of 97 patients vs. 39 (39%; 29.7-49.7) of 99 patients. **Median duration of response:** not reached in both groups. At the data cutoff date, 18 vs. 25 patients had a duration of response of 4 months or longer with PFS follow-up ongoing and continued to be on treatment. **OS data (at the time of data cutoff):** not mature; 32 (33%) of 97 patients and 31 (31%) of 99 patients died. **Median OS in patients receiving belantamab mafodotin at a dose of 2.5 mg/kg**: 13.7 months (95% CI, 9.9-not reached) **Survival probability at 12 months in patients receiving belantamab mafodotin at a dose of 2.5 mg/kg**: 0.5 **Median PFS:** 2.9 months (95% CI, 2.1–3.7) vs. 4.9 months (2.3–6.2); at the time of data cutoff, 58% and 56% of patients had disease progression or died. **QoL**: not available[1]	**SAEs:** n=38/95 (40%) vs. n=47/99 (47%) **Death[2]:** n=3/95 (3%) vs. n=7/99 (7%) **Discontinuation[3]:** n=8/95 (8%) vs. n=10/99 (10%)

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	no	no	unclear[4]	yes[5]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, BCMA=B-cell maturation antigen, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, FDA=Food and Drug Administration, HR=hazard ratio, I=intervention, Int.=intention, IRC=independent review committee, IRRs=infusion-related reactions, IV=intravenously, MM=multiple myeloma, n=number, NR=not reported, OS=overall survival, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event.

References:

1. European Medicines Agency (EMA). Medicines. Blenrep. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/blenrep].
2. National Institute for Health Research (NIHR). Belantamab mafodotin for relapsed / refractory multiple myeloma – Fourth line. [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2019/08/24271-Belantamab-Mafodotin-for-Multiple-Myeloma-V1.0-AUGUST2019-NON-CONF.pdf].

[1] According to the authors, patient-reported outcomes and health-related QoL outcomes will be reported separately.
[2] death due to SAE(s); two deaths were potentially treatment related (one case of sepsis in the 2.5 mg/kg cohort and one case of haemophagocytic lymphohistiocytosis in the 3.4 mg/kg cohort
[3] Permanent treatment discontinuation due to AE(s); keratopathy was the most common reason for treatment discontinuation
[4] Primary analysis data; NCT03525678 is ongoing until 11/2020
[5] The sponsor was involved in study design and implementation, data collection, data analysis, data interpretation, and writing of the report.

3. European Medicines Agency (EMA). Medicines. EU/3/17/1925. [Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171925].
4. U.S. Food and Drug Administration (FDA). FDA granted accelerated approval to belantamab mafodotin-blmf for multiple myeloma. [Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-granted-accelerated-approval-belantamab-mafodotin-blmf-multiple-myeloma].
5. European Medicines Agency (EMA). EMA confirms recommendation for non-renewal of authorisation of multiple myeloma medicine Blenrep. [Available from: https://www.ema.europa.eu/en/news/ema-confirms-recommendation-non-renewal-authorisation-multiple-myeloma-medicine-blenrep].
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7. U.S. Food and Drug Administration (FDA). Withdrawn | Cancer Accelerated Approvals. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/withdrawn-cancer-accelerated-approvals].
8. European Medicines Agency (EMA). Blenrep: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/blenrep-epar-product-information_en.pdf].
9. Lonial S, Lee H, Badros A, Trudel S, Nooka AK, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol 2020: 21: 207–21.
10. Supplement to: Lonial S LH, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol 2020: 21: 207–21; published online Dec 16. 2019.