09-J3000-80

Original Effective Date: 11/15/20

Reviewed: 11/12/25

Revised: 12/15/25

Subject: Belantamab Mafodotin-blmf (Blenrep®) IV Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Belantamab mafodotin (Blenrep) is an antibody-drug conjugate (ADC) that targets B-cell maturation antigen (BCMA), a protein expressed on normal B lymphocytes and multiple myeloma cells. It was initially approved by the Food and Drug Administration (FDA) in August 2020 for the treatment of adults with relapsed or refractory multiple myeloma (MM) who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication was approved under accelerated approval based on response rate. In November 2022, the DREAMM-3 Phase III confirmatory trial failed to show that Blenrep was any better than on-market treatment, thus failing to meet the requirements of the FDA accelerated approval regulations. As such, the FDA requested that GSK withdraw the US marketing authorization. Blenrep was off the US market for several years. However, in October 2025, the FDA re-approved Blenrep as combination therapy based on the results of the DREAMM-7 trial. The new indication is Blenrep in combination with bortezomib and dexamethasone for the treatment of adult patients with relapsed or refractory MM who have received at least two prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent. Belantamab mafodotin has 3 components consisting of an afucosylated, humanized immunoglobulin G1 (IgG1) monoclonal antibody covalently linked to a microtubule inhibitor [monomethyl auristatin F (MMAF)] via a protease-resistant maleimidocaproyl linker. Belantamab mafodotin is internalized after binding to BCMA and then MMAF is released via proteolytic cleavage which causes disruption in the microtubule network and eventually cell cycle arrest and apoptosis. Belantamab mafodotin was the first approved therapy that targets BCMA, and provided a novel mechanism of action for the treatment of MM. The chimeric antigen receptor (CAR) T-cell therapies,

idecabtagene vicleucel (Abecma) and ciltacabtagene autoleucel (Carvykti), that also target BCMA were approved in March 2021 and February 2022, respectively, for relapsed or refractory MM.

At a median follow-up of 28.2 months, belantamab mafodotin plus bortezomib and dexamethasone (BVd) showed significant and clinically meaningful progression-free survival (36.6 months vs. 13.4 months; HR 0.41 [95% CI, 0.31 to 0.53), overall survival, minimal residual disease negativity, and duration of response benefits compared with daratumumab plus bortezomib and dexamethasone (DVd) in the randomized DREAMM-7 study of adult patients with relapsed or refractory MM after at least one prior line of therapy; ocular events were more frequent with BVd but manageable with dose modifications.

The National Comprehensive Cancer Network (NCCN) Guidelines for MM (Version 3.2026) include the triplet regimen of belantamab mafodotin + bortezomib + dexamethasone as a category 1 recommendation for previously treated MM under the sections of "Other Recommended" and "After two prior therapies including an IMiD and a PI". The NCCN guidelines also include belantamab mafodotin monotherapy as category 2A recommendation for relapsed/refractory MM after three prior lines of therapy under the section of "Useful in Certain Circumstances".

POSITION STATEMENT:

Initiation of belantamab mafodotin (Blenrep) **meets the definition of medical necessity** when **EITHER** of the following criteria are met ("1" or "2"):

1. Member has a diagnosis of relapsed or refractory multiple myeloma (MM) and **ALL** of the following ("a" to "e"):
    a. **EITHER** of the following ("i" or "ii"):
        i. **ALL** of the following ("1", "2", and "3"):
            1. Member has received **TWO or more** appropriate prior lines of therapy of adequate duration for the treatment of their MM

                NOTE: Primary therapy, with or without subsequent hematopoietic cell transplant, followed by maintenance therapy is considered a single line of therapy

            2. Member's prior MM treatments have included **BOTH** of the following ("a" and "b"):
                a. A proteasome inhibitor [for example - bortezomib, carfilzomib (Kyprolis), or ixazomib (Ninlaro)]
                b. An immunomodulatory agent [for example - lenalidomide (Revlimid), pomalidomide (Pomalyst), or thalidomide (Thalomid)]
            3. Belantamab mafodotin will be used at triplet therapy in combination with **BOTH** bortezomib AND dexamethasone
        ii. **ALL** of the following ("1", "2", and "3"):
            1. Member has received **THREE** or more appropriate prior lines of therapy of adequate duration for the treatment of their MM

                NOTE: Primary therapy, with or without subsequent hematopoietic cell transplant, followed by maintenance therapy is considered a single line of therapy

2. Member's prior MM treatments have included **ALL** of the following (i.e., triple-class exposed):
    a. An anti-CD38 monoclonal antibody [for example - daratumumab (Darzalex), daratumumab-hyaluronidase (Darzalex Faspro), or isatuximab (Sarclisa)]
    b. A proteasome inhibitor [for example - bortezomib, carfilzomib (Kyprolis), or ixazomib (Ninlaro)]
    c. An immunomodulatory agent [for example - lenalidomide (Revlimid), pomalidomide (Pomalyst), or thalidomide (Thalomid)]
3. Belantamab mafodotin will be used as single-agent therapy (i.e., not used in combination with other MM treatments)

b. Member's MM was **NOT** previously refractory (i.e., disease progression on treatment or progression within 60 days after the last dose of a given therapy) to a belantamab mafodotin-containing treatment regimen

c. A baseline ophthalmic examination (visual acuity and slit lamp), within 4 weeks prior to the first dose of belantamab mafodotin, has been or will be completed

d. The ordering provider and the infusing healthcare facility is certified with, and the treated member enrolled in, the Blenrep REMS program

e. Dosage of belantamab mafodotin does not exceed 2.5 mg/kg (based on actual body weight) every 3 weeks

2. Member has another FDA-approved or NCCN-supported diagnosis, and **ALL** of the following are met ("a" to "e"):
    a. **EITHER** of the following ("i" or "ii"):
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
        ii. Indication **AND** usage are recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    b. Belantamab mafodotin is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis
    c. A baseline ophthalmic examination (visual acuity and slit lamp), within 4 weeks prior to the first dose of belantamab mafodotin, has been or will be completed
    d. The ordering provider and the infusing healthcare facility is certified with, and the treated member enrolled in, the Blenrep REMS program
    e. Dosage of belantamab mafodotin does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Approval duration: 6 months

Continuation of belantamab mafodotin (Blenrep) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. An authorization or reauthorization for belantamab mafodotin has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of multiple myeloma, or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria
2. The member is receiving regularly scheduled ophthalmic examinations (visual acuity and slit lamp) occurring before each dose of belantamab mafodotin
3. The ordering provider and the infusing healthcare facility is certified with, and the treated member enrolled in, the Blenrep REMS program
4. **EITHER** of the following based on the member's diagnosis ("a" or "b"):
    a. Multiple myeloma, and **ALL** of the following ("i", "ii", and "iii"):
        i. **EITHER** of the following:
            1. Belantamab mafodotin is being used at triplet therapy in combination with **BOTH** bortezomib **AND** dexamethasone, **AND** does **NOT** exceed eight 21-day cycles of combination treatment (i.e., eight total doses of belantamab mafodotin given with combination therapy)
            2. Belantamab mafodotin is being used as single-agent therapy (i.e., not used in combination with other MM treatments)
        ii. Dosage of belantamab mafodotin does not exceed 2.5 mg/kg (based on actual body weight) every 3 weeks.
        iii. Provider attestation that the member has not had disease progression during belantamab mafodotin treatment
    b. Other FDA-approved or NCCN-supported diagnosis, and **ALL** of the following ("i", "ii", and "iii"):
        i. Dosage of belantamab mafodotin does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guideline for the specific diagnosis
        ii. Belantamab mafodotin is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis
        iii. Member has had a beneficial response to treatment with belantamab mafodotin

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least two prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent.

- The recommended dosage of Blenrep, in combination with bortezomib and dexamethasone, is 2.5 mg/kg as an IV infusion over 30 minutes once every 3 weeks for 8 cycles, followed by 2.5 mg/kg every 3 weeks as a single agent.

Dose Adjustments

- Adverse Drug Reactions - The recommended dose reduction for adverse reactions is 1.9 mg/kg every 3 weeks. A second dose reduction to 1.9 mg/kg every 8 weeks can be considered for ocular toxicity based on ophthalmic exam findings. Refer to the product labeling for the specific recommendations for the different adverse reactions.
- Hepatic Impairment – No dosage adjustment is necessary in patients with mild hepatic impairment (total bilirubin level less than or equal to the upper limit of normal (ULN) and an AST level greater than the ULN, OR total bilirubin level of 1 to 1.5-times the ULN and any AST level). The recommended dose of Blenrep has not been established in patients with moderate or severe hepatic impairment.
- Renal Impairment - No dosage adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) of 30 to 89 mL/min/1.73 m^2). Specific guidelines for dosage adjustments in severe renal impairment (eGFR of 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (eGFR of less than 15 mL/min/1.73 m^2) with or without dialysis are not available; it appears that no dosage adjustments are needed.

Drug Availability

- 70-mg single-dose vial as a sterile, preservative-free, white to yellow lyophilized powder for reconstitution.
- Store vials refrigerated at 36ºF to 46ºF (2ºC to 8ºC).

PRECAUTIONS:

Boxed Warning

- WARNING: OCULAR TOXICITY
    - Blenrep caused changes in the corneal epithelium resulting in changes in vision, including severe visual impairment, and symptoms such as blurred vision and dry eyes. In the clinical study, corneal ulcers, including cases with infection, also occurred.
    - Conduct ophthalmic exams at baseline, before each dose, promptly for worsening symptoms, and as clinically indicated. In the clinical study, 83% of patients required a dosage modification due to ocular toxicity. Withhold Blenrep until improvement and resume or permanently discontinue, based on severity.
    - Because of the risk of ocular toxicity, Blenrep is available only through a restricted program called the BLENREP Risk Evaluation and Mitigation Strategy (REMS).

Contraindications

- None

Precautions/Warnings

- **Ocular Toxicity:** Belantamab mafodotin causes ocular toxicity, defined as changes in the corneal epithelium and changes in BCVA based on ophthalmic exam (including slit lamp exam), or other ocular adverse reactions as defined by the CTCAE. In DREAMM-7, ocular toxicity occurred in 92% of patients, including Grade 3 or 4 in 77% of patients. The most common ocular toxicities (>25%) were reduction in BCVA (89%) and corneal exam findings (86%) based on ophthalmic exam findings, blurred vision (66%), dry eye (51%), photophobia (47%), foreign body sensation in eyes (44%), eye irritation (43%), and eye pain (33%). Ocular toxicity based on ophthalmic exam findings was reported as Grade 2 in 9% of patients, Grade 3 in 56% of patients, and Grade 4 in 21% of patients. The median time to onset of the first Grade 2 to 4 ophthalmic exam findings was 43 days (range: 15 to 611 days). The median duration of all Grade 2 to 4 ophthalmic exam findings was 85 days (range: 5 to 813 days). Patients experienced a median of 3 episodes (range: 1 to 11 episodes) of ocular toxicity based on ophthalmic exam findings. Of the patients with Grade 2 to 4 ophthalmic exam findings, 42% had improvement of the last event to Grade 1 or better; 22% had resolution of the last event based on return to baseline or normal ophthalmic exam findings. The most commonly reported corneal exam findings included superficial punctate keratopathy, microcyst-like deposits, epithelial changes, and haze. Cases of corneal ulcer, including cases with infection, have been reported and should be managed promptly by an eye care professional. A reduction in BCVA to 20/50 or worse in at least one eye occurred in 69% of patients, including 29% who experienced a change in BCVA to 20/100 or worse, and 12% who experienced a change in BCVA to 20/200 or worse. Of the patients with reduced BCVA to 20/50 or worse in at least one eye, 61% had resolution of the last event to baseline or better. Of the patients with reduced BCVA to 20/100 or worse, 57% had resolution of the last event. Of the patients with reduced BCVA to 20/200 or worse, 48% had resolution of the last event.
- Ophthalmic exams (including slit lamp exam and BCVA assessment) should be conducted by an eye care professional, such as an ophthalmologist or optometrist, at baseline, before each dose of belantamab mafodotin, promptly for new or worsening symptoms, and as clinically indicated. Perform baseline exam within 4 weeks prior to the first dose. Perform each follow-up exam within 10 days prior to the next planned dose. All effort should be made to schedule the exam as close to belantamab mafodotin dosing as possible. Withhold belantamab mafodotin until improvement in both corneal exam findings and change in BCVA to Grade 1 or less and resume at same or reduced dose or permanently discontinue based on severity. Counsel patients to promptly inform their healthcare provider of any ocular symptoms. Counsel patients to use preservative-free artificial tears at least 4 times a day starting with the first infusion and continuing until the end of treatment, and to avoid wearing contact lenses for the duration of therapy. Bandage contact lenses may be used under the direction of an eye care professional. Changes in visual acuity may be associated with difficulty for driving and reading. Counsel patients to use caution when driving or operating machinery.
- **Blenrep REMS**: Belantamab mafodotin is available only through a restricted program called the BLENREP REMS because of the risks of ocular toxicity. Notable requirements of the BLENREP REMS include the following:
    - Prescribers must be certified with the BLENREP REMS by enrolling and completing training.
    - Prescribers must counsel patients receiving belantamab mafodotin about the risk of ocular toxicity, the need for monitoring via ophthalmic examinations before each dose, and provide patients with the BLENREP REMS Patient Guide.
    - Patients must be enrolled in the BLENREP REMS and adhere to monitoring.
    - Healthcare setting that dispense belantamab mafodotin must be certified in the BLENREP REMS by enrolling and must obtain authorization prior to dispensing.
    - Wholesalers and distributers must distribute belantamab mafodotin only to certified healthcare settings.

  Further information is available, at www.BLENREPREMS.com and 1-855-690-9572.
- **Thrombocytopenia**: Thrombocytopenia of any grade occurred in 100% of patients in DREAMM-7. Grade 2 thrombocytopenia occurred in 10% of patients, Grade 3 in 29% of patients, and Grade 4 in 45% of patients. Clinically significant bleeding (Grade ≥2) occurred in 7% of patients with concomitant

low platelet levels (Grade 3 or 4). Monitor complete blood cell counts at baseline and periodically during treatment as clinically indicated. Withhold or reduce the dose of belantamab mafodotin based on severity.

- **Embryo-Fetal Toxicity**: Based on its mechanism of action, belantamab mafodotin can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with belantamab mafodotin and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with belantamab mafodotin and for 6 months after the last dose.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9999	Not otherwise classified, antineoplastic drugs

ICD-10 Diagnosis Codes That Support Medical Necessity

C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Heavy chain – the larger component of an immunoglobulin. There are five types: IgG, IgA, IgM, IgD, and IgE.

Immunoglobulins (a.k.a., antibodies) – proteins made by normal plasma cells that have an important role in fighting infection as part of the humoral immune response. Antibodies are composed of two heavy chains and two light chains that form a larger complex. Each plasma cell produces only one type of heavy chain and one type of light chain.

Light chain – the smaller component of an immunoglobulin. There are two types: kappa and lambda.

Myeloma Protein (M-Protein) – a nonfunctional immunoglobulin protein or protein fragment produced by malignant plasma cells (or myeloma cells). Since myeloma cells are monoclonal, the M-proteins for a given patient are structurally identical. Both portions of an immunoglobulin (the heavy chain and light chain) can be found in the serum, while only light chains can be found in the urine.

Plasma cell - a fully differentiated B lymphocyte (a type of white blood cell) that is specialized for immunoglobulin production and is found primarily in bone marrow.

Primary refractory MM - patients who never achieve at least a MR to initial induction therapy and progress while on therapy

Progressive MM - at least a 25% increase from nadir in the serum M-protein (absolute increase must be ≥0.5 g/dL) or urine M-protein (absolute increase must be ≥200mg/24 hours), or in the difference between involved and uninvolved serum-free light-chain (FLC) levels (with an abnormal FLC ratio and FLC difference >100 mg/L).

Relapsed and refractory MM - patients who never achieve at least a MR or who progress within 60 days of their last therapy

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01
Bortezomib Injection, 09-J0000-92
Carfilzomib (Kyprolis) IV, 09-J1000-81
Chimeric Antigen Receptor (CAR) T-Cell Therapies, 09-J3000-94
Daratumumab (Darzalex) Infusion and Daratumumab-Hyaluronidase-fihj (Darzalex Faspro), 09-J2000-49
Doxorubicin HCl Liposome (Doxil) IV, 09-J0000-91
Elotuzumab (Empliciti) IV, 09-J2000
Isatuximab (Sarclisa) Injection, 09-J3000-67
Ixazomib (Ninlaro), 09-J2000-51
Oral Oncology Medications, 09-J3000-65
Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None

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8. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 11/04/25.
9. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 3.2026 – November 3, 2025. Multiple Myeloma. Available at http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf. Accessed 11/04/25.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/12/25.

GUIDELINE UPDATE INFORMATION:

11/15/20	New Medical Coverage Guideline.
01/01/21	Revision: Added HCPCS code C9069.
04/01/21	Revision: Added HCPCS code J9037 and deleted codes C9069 and J9999.
07/15/21	Review and revision including updates to the description section, position statement, related guidelines, and references.
07/15/22	Review and revision of guideline including updates to the description section and references.
07/15/23	MCG retired as Blenrep is no longer available in the US.
12/15/25	MCG reactivated due to Blenrep being re-approved by the FDA, in combination with bortezomib and dexamethasone, for the treatment of adult patients with relapsed or refractory MM who have received at least 2 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent.