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Subject: Daratumumab (Darzalex®) Injection

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DESCRIPTION:

Daratumumab (Darzalex) is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody that binds to CD38, a transmembrane glycoprotein expressed on the surface of many hematopoietic cells, and causes lysis of multiple myeloma cells. It was first approved by the FDA in November 2015 as monotherapy for the treatment of patients with multiple myeloma (MM) who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent. Daratumumab was previously granted orphan drug designation for the treatment of MM in May 2013. The indication for use was expanded in November 2016 for use in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy. In June 2017, the FDA-approved indication was expanded again to include use, in combination with pomalidomide (Pomalyst) and dexamethasone, for the treatment of patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. In May 2018, the FDA approved the use of daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem cell transplant. This was the first daratumumab treatment regimen FDA-approved for first-line use in previously untreated patients. In June 2019, the FDA approved daratumumab in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. In September 2019, the FDA approved daratumumab in combination with bortezomib, thalidomide, and dexamethasone for patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. Daratumumab, as sponsored by the innovator drug company, also has orphan drug designations for the treatment of follicular or mantle cell lymphoma (August 2015), diffuse large B-cell lymphoma (November 2015), and systemic amyloid light-chain (AL) amyloidosis (September 2017).

The safety and efficacy of daratumumab, leading to the initial FDA-approval, were assessed in an open-label, multicenter, phase 2, single-arm study (n=106). An overall response rate (ORR) of 29.2% (n=31) was achieved with daratumumab monotherapy in patients with relapsed or refractory MM. Patients had received at least three prior therapies including a PI and an immunomodulatory agent or were double-refractory to a PI and an immunomodulatory agent. A stringent complete response was reported in 2.8% (n=3), complete response (CR) in 0%, very good partial response (VGPR) in 9.4% (n=10), and partial response in 17% (n=18). The median time to response was 1 month, and median duration of response was 7.4 months. In this study, patients had received a median of five prior therapies, 97% of patients had refractory disease to the last therapy, and 80% of patients had received an autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%).

The National Comprehensive Cancer Network (NCCN) Guidelines for MM (Version 2.2020) list two daratumumab triplet drug therapies [daratumumab + bortezomib + dexamethasone, and daratumumab + lenalidomide (Revlimid) + dexamethasone] under “Preferred Regimens” as category 1 recommendations for the treatment of previously treated MM. There are numerous other category 1 preferred regimens listed by NCCN. The triplet regimen with bortezomib is supported by an open-label, phase III trial (n=498) in which subjects were randomized to receive daratumumab + bortezomib + dexamethasone triplet therapy, or bortezomib + dexamethasone doublet therapy. Subjects were excluded if there was previous evidence of refractoriness or intolerance to bortezomib or another PI, like ixazomib and carfilzomib. The ORR was 82.9% with triplet therapy vs. 63.2% with doublet therapy ($p<0.001$). The rates of VGPR and CR were doubled with triplet vs. doublet therapy (59.2% vs. 29.1%, $p<0.001$, and 19.2% vs. 9%, $p<0.001$, respectively). Adverse effects were more common with triplet therapy with grade 3 or 4 thrombocytopenia and neutropenia occurring more frequently (45.3% vs. 32.9%, and 12.8% vs. 4.2%, respectively). The triplet regimen with lenalidomide is supported by a phase III trial (n=569) in which subjects were randomized to receive daratumumab + lenalidomide + dexamethasone triplet therapy, or lenalidomide + dexamethasone doublet therapy. Subjects were excluded if there was previous evidence of refractoriness or intolerance to lenalidomide. The ORR was 92.9% with triplet therapy vs. 76.4% with doublet therapy ($p<0.001$). The CR was more than doubled with triplet vs. doublet therapy (43.1% vs. 19.2%, $p<0.001$). Grade 3 or 4 neutropenia occurred more frequently with triplet therapy (51.9% vs. 37%) and daratumumab-associated infusion-related reactions occurred in 47.7% of patients. Daratumumab monotherapy, the triplet regimen of daratumumab + carfilzomib (Kyprolis) + dexamethasone, and the triplet regimen of daratumumab + pomalidomide (Pomalyst) + dexamethasone are listed under “Other Recommended Regimens” as category 2A recommendations for the treatment of previously treated MM. The monotherapy regimen includes a footnote stating that the regimen is indicated for patients who have received at least three prior therapies, including a proteasome inhibitor and an immunomodulatory agent, or who are double refractory to a proteasome inhibitor and an immunomodulatory agent. The pomalidomide regimen includes a footnote stating, “Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor.”

The NCCN lists the quadruple regimen of daratumumab with bortezomib + melphalan + prednisone (VMP) under “Preferred Regimens” as a category 1 recommended initial primary therapy for non-transplant candidates. The triplet regimen of bortezomib + lenalidomide + dexamethasone and the doublet regimen of lenalidomide + low-dose dexamethasone are the two other category 1 recommended initial primary therapies for non-transplant candidates. The quadruple regimen is supported by an open-label phase III trial (ALCYONE, n=769) in which newly diagnosed MM patients ineligible for autologous stem cell transplant were randomized to receive daratumumab + VMP or VMP. The ORR was 90.9% with D-VMP vs. 73.9% with VMP ($p<0.0001$), and the D-VMP group showed an improvement in PFS (not reached vs. 18.1 months; HR=0.5, 95% CI: 0.38 to 0.65; $p<0.0001$). The most frequent adverse reactions

(≥20% with at least 5% greater frequency in the D-VMP arm) were infusion reactions (28% vs. 0%), upper respiratory tract infection (48% vs. 28%), and peripheral edema (21% vs. 14%). The quadruple regimen of daratumumab with bortezomib + thalidomide + dexamethasone is listed under "Useful in Certain Circumstances" as a category 2 recommended for initial primary therapy for transplant candidates. The triplet regimen of bortezomib + lenalidomide + dexamethasone is the preferred, category 1 recommended regimen for transplant candidates.

POSITION STATEMENT:

Initiation of daratumumab (Darzalex) **meets the definition of medical necessity** when **EITHER** of the following criteria is met ("1" or "2"):

1. The member has a diagnosis of active (symptomatic) multiple myeloma (MM), and **ALL** of the following ("a" to "d"):
    a. **ANY** of the following ("i", "ii", or "iii")
        i. Member has newly diagnosed MM, **AND** is eligible for an autologous stem cell transplant as determined by the treating physician, and meets **BOTH** of the following ("1" and "2"):
            1. Member has not previously received treatment for their MM
            2. Daratumumab will be used as quadruple therapy in combination with bortezomib, thalidomide, and dexamethasone
        ii. Member has newly diagnosed MM, **AND** is ineligible for an autologous stem cell transplant as determined by the treating physician, and meets **BOTH** of the following ("1" and "2"):
            1. Member has not previously received treatment for their MM
            2. Daratumumab will be used as **EITHER** quadruple therapy in combination with bortezomib, melphalan and prednisone; **OR** as triple therapy in combination lenalidomide and dexamethasone
        iii. Member has relapsed or refractory MM, and meets **BOTH** of the following ("1" and "2"):
            1. Member has previously received at least **ONE** prior line of therapy for their MM
            2. **ANY** of the following regimens will be used:
                - Daratumumab will be used as monotherapy for treatment of the member's MM
                - Daratumumab will be used as triplet therapy in combination with both bortezomib and dexamethasone for treatment of the member's MM
                - Daratumumab will be used as triplet therapy in combination with both carfilzomib (Kyprolis) and dexamethasone for treatment of the member's MM
                - Daratumumab will be used as triplet therapy in combination with both lenalidomide (Revlimid) and dexamethasone for treatment of the member's MM
                - Daratumumab will be used as triplet therapy in combination with both pomalidomide (Pomalyst) and dexamethasone for treatment of the member's MM, **AND** the member has received at least two prior therapies for their MM that include an immunomodulatory agent (e.g., lenalidomide, thalidomide) and a proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib)
    b. The 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 daratumumab-containing treatment regimen
    c. The dosage of daratumumab does not exceed 16 mg/kg given more often than the following:

i. If used as monotherapy (one cycle is 28 days or 4 weeks):
   - Cycles 1 and 2 (weeks 1 to 8): Weekly (i.e., day 1, 8, 15, and 22 of each cycle) for 8 doses*
   - Cycles 3 to 6 (weeks 9 to 24): Every two weeks (i.e., day 1 and 15 of each cycle) for 8 doses
   - Cycle 7 and beyond (week 25 and beyond): Every four weeks (i.e., day 1 of each cycle)

ii. If used as quadruple therapy in combination with bortezomib, thalidomide, and dexamethasone (one cycle is 28 days or 4 weeks):
   - Induction therapy:
     - Cycle 1 and 2 (weeks 1 to 8): Weekly (i.e., day 1, 8, 15, and 22 of each cycle) for 8 doses*
     - Cycles 3 to 4 (weeks 9 to 16): Every 2 weeks (i.e., days 1 and 15 of each cycle) for 4 doses
     - After cycle 4 (week 16): Stop for high-dose chemotherapy and autologous stem cell transplant
   - Consolidation therapy: every 2 weeks for a total of 4 doses (weeks 1 to 8) upon re-initiation of treatment following autologous stem cell transplant

iii. If used as quadruple therapy in combination with bortezomib, melphalan and prednisone (one cycle is 42 days or 6 weeks
   - Cycle 1 (weeks 1 to 6): Weekly for 6 doses*
   - Cycles 2 to 9 (weeks 7 to 54): Every 3 weekly (i.e., days 1 and 21 of each cycle) for 16 doses
   - After cycle 9 (week 55): Every 4 weeks

ii. If used as triplet therapy with bortezomib and dexamethasone (one cycle is 21 days or 3 weeks):
   - Cycles 1 to 3 (weeks 1 to 9): Weekly (i.e., days 1, 8, and 15 of each cycle) for 9 doses*
   - Cycles 4 to 9 (weeks 10 to 24): Every 3 weeks (i.e., day 1 of each cycle) for 5 doses
   - After cycle 9 (week 25): Every 4 weeks

iii. If used as triplet therapy with carfilzomib, lenalidomide or pomalidomide, and dexamethasone (one cycle is 28 days or 4 weeks):
   - Cycles 1 to 2 (weeks 1 to 8): Weekly (i.e., day 1, 8, 15, and 22 of each cycle) for 8 doses*
   - Cycles 3 to 6 (weeks 9 to 24): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 8 doses
   - Cycle 7 and beyond (week 25 and beyond): Every 4 weeks (i.e., day 1 of each cycle)

**The first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days (i.e., 8 mg/kg on Day 1 and 8 mg/kg on Day 2)*

b. The member's baseline (i.e., within 90 days prior to initiating treatment with daratumumab) serum monoclonal protein (M-protein) level as detected by serum protein electrophoresis (SPEP) is provided[#]

[#]*If the M-protein is undetectable by SPEP, baseline serum free light chain (SFLC) levels (kappa and lambda), as detected by serum free light chain assay (SFLCA), must also be provided*

2. Member has another FDA-approved or NCCN-supported diagnosis (not previously listed above), and **BOTH** of the following are met ("a" and "b"):
    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 is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    b. The dosage of daratumumab 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 daratumumab (Darzalex) **meets the definition of medical necessity** when **BOTH** of the following criteria are met ("1" and "2"):

1. An authorization or reauthorization for daratumumab 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. **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. Daratumumab is being used in **ANY** of the following regimens:
            1. Quadruple therapy in combination with bortezomib, melphalan, and prednisone
            2. Quadruple therapy in combination with bortezomib, thalidomide, and dexamethasone
            3. Triplet therapy in combination with both bortezomib and dexamethasone
            4. Triplet therapy in combination with both carfilzomib and dexamethasone
            5. Triplet therapy in combination with both lenalidomide and dexamethasone
            6. Triplet therapy in combination with both pomalidomide and dexamethasone
            7. Monotherapy
        ii. The member's dosage of daratumumab does not exceed 16 mg/kg (based on actual body weight) given more often than the following:
            1. If used as monotherapy (one cycle is 28 days or 4 weeks):
                - Cycles 1 to 2 (weeks 1 to 8): Weekly (i.e., day 1, 8, 15, and 22 of each cycle) for 8 doses
                - Cycles 3 to 6 (weeks 9 to 24): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 8 doses
                - Cycle 7 and beyond (week 25 and beyond): Every four weeks (i.e., day 1 of each cycle)
            2. If used as quadruple therapy in combination with bortezomib, melphalan and prednisone (one cycle is 42 days or 6 weeks):
                - Cycle 1 (weeks 1 to 6): Weekly for 6 doses

- Cycles 2 to 9 (weeks 7 to 54): Every 3 weeks (i.e., days 1 and 21 of each cycle) for 16 doses
- After cycle 9 (week 55): Every 4 weeks

3. If used as quadruple therapy in combination with bortezomib, thalidomide, and dexamethasone (one cycle is 28 days or 4 weeks):
   - Induction therapy:
     - Cycle 1 and 2 (weeks 1 to 8): Weekly (i.e., day 1, 8, 15, and 22 of each cycle) for 8 doses*
     - Cycles 3 to 4 (weeks 9 to 16): Every 2 weeks (i.e., days 1 and 15 of each cycle) for 4 doses
     - After cycle 4 (week 16): Stop for high-dose chemotherapy and autologous stem cell transplant
   - Consolidation therapy: every 2 weeks for a total of 4 doses (weeks 1 to 8) upon re-initiation of treatment following autologous stem cell transplant
4. If used as triplet therapy with bortezomib and dexamethasone (one cycle is 21 days or 3 weeks):
   - Cycles 1 to 3 (weeks 1 to 9): Weekly (i.e., days 1, 8, and 15 of each cycle) for 9 doses
   - Cycles 4 to 9 (weeks 10 to 24): Every 3 weeks (i.e., day 1 of each cycle) for 5 doses
   - After cycle 9 (week 25): Every 4 weeks
5. If used as triplet therapy with lenalidomide or pomalidomide and dexamethasone (one cycle is 28 days or 4 weeks)
   - Cycles 1 to 2 (weeks 1 to 8): Weekly (i.e., day 1, 8, 15, and 22 of each cycle) for 8 doses
   - Cycles 3 to 6 (weeks 9 to 24): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 8 doses
   - Cycle 7 and beyond (week 25): Every 4 weeks (i.e., day 1 of each cycle)

iii. Member meets **EITHER** of the following ("1" or "2"):

1. If less than 18 months of treatment – EITHER of the following ("a" or "b"):
   a. A serum M-protein level decrease of 25% or more* compared to baseline, or M-protein is undetectable; **AND** no increase in the size or number of lytic bone lesions after at least two cycles of treatment with daratumumab[†,#]
   b. Member is receiving daratumumab as consolidation therapy following autologous stem cell transplant
2. 18 months or more of treatment - provider attestation that the member has not had disease progression during daratumumab treatment

**If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a decrease of 25% or more in the difference between the light chain produced by the myeloma cells (lambda or kappa) and the other light chain must be achieved*

†If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available a follow-up SFLC level must be submitted

[#]*An exception is permitted if a baseline M-protein level **AND** SFLC level are unavailable. In these cases the physician may provide an attestation of a beneficial clinical response which must include no increase in the size or number of lytic bone lesions.*

b. Other FDA-approved or NCCN-supported diagnosis (not listed above or as an orphan indication), and **ALL** of the following ("i", "ii", and "iii"):
   i. The dosage of daratumumab 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. Daratumumab is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis
   iii. The member has had a beneficial response to treatment with daratumumab

Approval duration: 1 year (except for quadruple therapy with daratumumab + bortezomib + thalidomide + dexamethasone; approve for 3 months to allow up to 4 total doses to be given in the consolidation therapy phase)

Daratumumab (Darzalex) **meets the definition of medical necessity** when used to treat the following orphan indications **AND** all associated criteria are met:

1. Member has a diagnosis of any of the following:
   a. Diffuse large B-cell lymphoma
   b. Follicular lymphoma
   c. Mantle cell lymphoma
   d. Systemic amyloid light-chain (AL) amyloidosis
2. Member has received at least one prior therapy for treatment of their disease
3. The dosage of daratumumab does not exceed 16 mg/kg given more often than the following:
   a. Weeks 1 to 8: Weekly*
   b. Weeks 9 to 24: Every two weeks
   c. Week 25 onwards until disease progression: Every four weeks

   **The first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days (i.e., 8 mg/kg on Day 1 and 8 mg/kg on Day 2)*

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

- In combination with lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant
- In combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant
- In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy
- In combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor
- As monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent
- Combination therapy with bortezomib, melphalan and prednisone (6-week cycle regimen)
    - The recommended dose is 16 mg/kg actual body weight administered as an IV infusion (after dilution) according to the following dosing schedule:
        - Weeks 1 to 6: Weekly (total of 6 doses)
        - Weeks 7 to 54: Every three weeks (total of 16 doses)
        - Week 55 onwards until disease progression: Every four weeks
- Monotherapy, and combination therapy with lenalidomide or pomalidomide and low-dose dexamethasone (4-week cycle regimen)
    - The recommended dose is 16 mg/kg actual body weight administered as an IV infusion (after dilution) according to the following dosing schedule:
        - Weeks 1 to 8: Weekly (total of 8 doses)
        - Weeks 9 to 24: Every two weeks (total of 8 doses)
        - Week 25 onwards until disease progression: Every four weeks
- Combination therapy with bortezomib, thalidomide, and dexamethasone (4-week cycle regimen)
    - The recommended dose is 16 mg/kg actual body weight administered as an IV infusion (after dilution) according to the following dosing schedule:
        - Induction treatment phase:
            - Weeks 1 to 8: Weekly (total of 8 doses)
            - Weeks 9 to 16: Every two weeks (total of 4 doses)
            - Stop for high-dose chemotherapy and autologous stem cell transplant
        - Consolidation treatment phase:
            - Weeks 1 to 8: Every two weeks (total of 4 doses) upon re-initiation of treatment following autologous stem cell transplant
- Combination therapy with bortezomib and dexamethasone (3-week cycle regimen)
    - The recommended dose is 16 mg/kg actual body weight administered as an IV infusion (after dilution) according to the following dosing schedule:
        - Weeks 1 to 9: Weekly (total of 9 doses)

    - Weeks 10 to 24: Every three weeks (total of 5 doses)
    - Week 25 onwards until disease progression: Every four weeks
- To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively.
- The initial infusion rate is 50 mL/hr with a maximum rate of 200 mL/hr. Only increase the rate in the absence of infusion reactions with the previous infusion. See the package insert for more detailed recommendations.
- Administer with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer).
- Pre-medicate patients with a corticosteroid, oral acetaminophen, and oral or IV antihistamine one to three hours prior to every infusion. See the full prescribing information for specific recommendations.
- For monotherapy, post-medicate patients with an oral corticosteroid on the first and second day after all infusions. For combination therapy, consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent, the day after the infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone) is administered the day after the infusion, additional post-infusion medications may not be needed.
- Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting daratumumab and continue for 3 months following treatment.

Dose Adjustments

- Dosage adjustments are not recommended for adverse reactions. Adverse reactions are addressed with treatment interruption and slower infusion rates.
- Renal impairment: no dosage adjustment is necessary for patients with pre-existing renal impairment.
- Hepatic impairment: no dosage adjustments are necessary for patients with mild hepatic impairment (Total Bilirubin [TB] 1× to 1.5× upper limit of normal [ULN] or aspartate aminotransferase [AST] >ULN). Daratumumab has not been studied in patients with moderate to severe hepatic impairment (TB >1.5× ULN and any AST).

Drug Availability

- 100 mg/5 mL and 400 mg/20 mL solution for injection

PRECAUTIONS:

Boxed Warnings

- None

Contraindications

- History of severe hypersensitivity to daratumumab or any of the components of the formulation

Precautions/Warnings

- **Infusion Reactions**: Daratumumab can cause severe infusion reactions (e.g., bronchospasm, hypoxia, dyspnea, and hypertension). Approximately half of all patients experienced a reaction, most during the first infusion. Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt the infusion for infusion reactions of ANY severity. Permanently discontinue the infusion in case of life-threatening infusion reactions (Grade 4). For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

- **Interference with Serological Testing**: Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Type and screen patients prior to starting treatment. Inform blood banks that a patient has received daratumumab.
- **Interference with Determination of Complete Response:** daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.
- **Pregnancy:** There are no human data to inform a risk with use of daratumumab during pregnancy. Animal studies have not been conducted Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, daratumumab may cause fetal myeloid or lymphoid-cell depletion and decreased bone density.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9145	Injection, daratumumab, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C82.00 – C82.99	Follicular lymphoma
C83.10 – C83.19	Mantle Cell lymphoma
C83.30 – C83.39	Diffuse large B-cell lymphoma
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
E85.81	Light chain (AL) amyloidosis
E85.89	Other amyloidosis
E85.9	Amyloidosis, unspecified

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 the last guideline review date.

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.

Minimal response (MR) (according to the Revised Uniform Response Criteria by the International Myeloma Working Group) – **ALL** of the following:

- ≥25% but ≤49% reduction of serum M-protein
- Reduction in 24-hour urine M-protein by 50% to 89%
- In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required
- No increase in size or number of lytic bone lesions (development of compression fractures dose not exclude response).

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

Serum free light chain assay (SFLCA) – a test that detects the amount of unbound or free light chains (i.e., not attached to a heavy chain) in the serum. Normal values - kappa: 3.3 to 19.4 mg/L, lambda: 5.71 to 26.3 mg/L, kappa/lambda ratio: 0.26–1.65 (0.37–3.1 if renal impairment).

Serum Protein Electrophoresis (SPEP) – a test that detects and quantifies the amount of M-protein in the serum. An serum M-protein of greater than 30 g/L is consistent with a diagnosis of MM.

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Bortezomib (Velcade) IV, 09-J0000-92

Carfilzomib (Kyprolis) IV, 09-J1000-81

Doxorubicin HCl Liposome (Doxil) IV, 09-J0000-91

Elotuzumab (Empliciti) IV, 09-J2000

Ixazomib (Ninlaro), 09-J2000-51

Lenalidomide (Revlimid), 09-J0000-80

Panobinostat (Farydak), 09-J2000-37

Pomalidomide (Pomalyst) Capsule, 09-J1000-95

Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/12/19.

GUIDELINE UPDATE INFORMATION:

03/15/16	New Medical Coverage Guideline.
04/15/16	Revision to guideline consisting of clarifying the position statement.
07/01/16	Revision to guideline consisting of HCPCS code updates.
11/15/16	Revision to guideline consisting of updating the position statement, description section, and references based on new NCCN recommendations.
12/15/16	Revision to guideline consisting of updating the position statement with a new triplet regimen and updating the lab documentation requirements.
01/01/17	Revision to guideline consisting of updating the description section, dosage/administration, and references based on new FDA-approved indications. Added HCPCS code J9145.
02/16/17	Revision: Update to Position Statement.
07/15/17	Review and revision to guidelines consisting of updating the description section, position statement, and references.
09/15/17	Revision to guidelines consisting of updating the description section, position statement, dosage/administration section, and references based on new FDA-approved indication for use in combination with pomalidomide and dexamethasone.
07/15/18	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, and references.
07/15/19	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, and references.
08/15/19	Revision to guidelines consisting of updating the description section, position statement, dosage/administration section, and references based on new FDA-approved indication for first-line use in combination with lenalidomide and dexamethasone.
11/15/19	Revision to guidelines consisting of updating the description section, position statement, dosage/administration section, and references based on NCCN guideline updates and a new FDA-approved indication for first-line use in combination with bortezomib, thalidomide, and dexamethasone.