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Subject: Daratumumab (Darzalex®) Infusion and Daratumumab-Hyaluronidase-fihj (Darzalex Faspro™) Injection

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

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. In August 2020, the FDA

approved daratumumab in combination with carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.

In May 2020 a new subcutaneously administered version of daratumumab, daratumumab-hyaluronidase-fihj (Darzalex Faspro) was approved by the FDA for five of the eight MM indications approved for intravenous Darzalex. Since the initial approval, Darzalex Faspro has gained the three additional indications and now includes the eight MM indications IV Darzalex has [i.e., "in combination with bortezomib, thalidomide, and dexamethasone for patients with newly diagnosed MM who are eligible for autologous stem cell transplant" (January 2021), "in combination with pomalidomide and dexamethasone for adult patients with multiple myeloma who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor" (July 2021), and "in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy" (December 2021)]. Also, in January 2021, a new indication for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone was approved. In July 2024, the FDA approved a ninth new MM regimen for Darzalex Faspro in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed MM patients who are eligible for autologous stem cell transplant. In November 2025, the FDA approved a new indication for Darzalex Faspro for the treatment of adult patients with high-risk smoldering MM as monotherapy. This is the first FDA-approved treatment for smoldering (asymptomatic) MM. The advantages of Darzalex Faspro (vs. Darzalex) are a shorter administration duration (a 3 to 5-min SQ injection vs. a 3 to 4-hour IV infusion), fewer systemic administration-related reactions (13% vs. 34%) and simplified flat dosing (1,800 mg SQ) vs. weight-based dosing (16 mg/kg IV).

The safety and efficacy of IV 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 5.2026 - January 9, 2026) list four daratumumab triplet drug therapies [daratumumab + bortezomib + dexamethasone, daratumumab + carfilzomib (Kyprolis) + dexamethasone, daratumumab + lenalidomide (Revlimid) + dexamethasone, and daratumumab + pomalidomide (Pomalyst) + dexamethasone], and one doublet therapy [daratumumab + teclistamab (Tecvayli)] as "Preferred" regimens for "Relapsed/Refractory Disease After 1–3 Prior Therapies" as category 1 recommendations for the treatment of previously treated MM. There are numerous other category 1 preferred regimens listed by NCCN. The pomalidomide regimen and the teclistamab regimen are listed under the subsection of "After one prior therapy including lenalidomide and a PI". All of these regimens, except the bortezomib regimen, are listed under the "Bortezomib-Refractory" section, and all regimens, except the lenalidomide regimen,

are listed under the “Lenalidomide-Refractory” section. 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.

The quadruplet regimens of daratumumab + cyclophosphamide + bortezomib + dexamethasone, and daratumumab + carfilzomib + pomalidomide + dexamethasone are listed under “Other Recommended” regimens for “Relapsed/Refractory Disease After 1–3 Prior Therapies” as category 2A recommendations for the treatment of previously treated MM. Daratumumab monotherapy, the regimen of venetoclax + dexamethasone with or without daratumumab or PI [only for t(11;14) patients], and the triplet regimen of daratumumab + selinexor (Xpovio) + dexamethasone are listed under “Useful In Certain Circumstances” for “Relapsed/Refractory Disease After 1–3 Prior Therapies” as category 2A recommendations. The monotherapy regimen is listed under the subsection of “After at least three prior therapies, including a proteasome inhibitor and an immunomodulatory agent, or are double refractory to a proteasome inhibitor and an immunomodulatory agent”. The therapies for previously treated MM include a general footnote of “Regimens included under 1-3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior”.

Regarding first-line MM treatment, the NCCN Guidelines list the triplet regimen of daratumumab + lenalidomide + dexamethasone under “Preferred Regimens” as a category 1 recommended initial primary therapy if hematopoietic cell transplant (HCT)-deferred or if HCT is not indicated. The guidelines also list the quadruplet regimens of daratumumab or isatuximab (Sarclisa) + lenalidomide + dexamethasone as category 1 recommendations in this same section, but only for patients less than 80 years old who are not frail. The triplet regimen is supported by an open-label phase III trial (MAIA, n=737) in which newly diagnosed MM patients ineligible for autologous stem cell transplant were randomized to receive daratumumab + lenalidomide + dexamethasone, or lenalidomide + dexamethasone. The daratumumab-containing regimen had a better 30-month progression free survival (PFS) rate (70.6% vs. 55.6%), and median PFS (not reached vs 31.9 months; HR, 0.56 [95% CI, 0.43 to 0.73]). The daratumumab-containing regimen also had a better ORR (92.9% vs. 81.3%) including a complete response rate or better (47.6% vs. 24.9%). Grade 3 or 4 adverse events occurring in a higher frequency with daratumumab included neutropenia (50% vs. 35.3%), any infection (32.1% vs. 23.3%), and pneumonia (13.7% vs. 7.9%). The NCCN also lists the quadruplet regimen of daratumumab +

cyclophosphamide + bortezomib + dexamethasone under “Useful In Certain Circumstances” as a category 2A recommended initial primary therapy when HCT-deferred or if HCT is not indicated (as a treatment option for patient with renal insufficiency).

For HCT candidates, the NCCN lists the quadruplet regimens of daratumumab or isatuximab + bortezomib + lenalidomide + dexamethasone under “Preferred” as category 1 recommended initial primary therapies. The quadruplet regimen of daratumumab + carfilzomib + lenalidomide + dexamethasone is listed under “Other Recommended” as a category 2A recommendation, and the quadruplet regimen daratumumab + cyclophosphamide + bortezomib + dexamethasone is listed under “Useful in Certain Circumstances” as a category 2A recommendation. Daratumumab + lenalidomide as maintenance therapy, following initial primary therapy for HCT candidates, is listed under “Other Recommended” as a category 2A recommendation. There is a footnote stating, “Two drug maintenance recommended for high-risk MM”. Daratumumab maintenance monotherapy is listed under “Useful in Certain Circumstances” as a category 2A recommendation. Lenalidomide maintenance monotherapy is listed under “Preferred” as a category 1 recommendation for this same patient population; it is the only maintenance therapy under “Preferred”.

The NCCN Guidelines for MM also now include a separate section addressing the treatment of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome. Lenalidomide + dexamethasone with or without daratumumab is listed as a category 2A treatment option for patients with POEMS regardless of HCT status.

Regarding the use of subcutaneous daratumumab-hyaluronidase (Darzalex Faspro), the NCCN Guidelines for MM include a statement of “For any regimen that includes daratumumab, this could be daratumumab for intravenous infusion or daratumumab and hyaluronidase-fihj subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.” The NCCN Guidelines for Systemic Light Chain Amyloidosis (Version 1.2026 - June 11, 2025) list the quadruplet regimen of daratumumab + bortezomib + cyclophosphamide+ dexamethasone under “Preferred Regimens” as initial primary therapy for both transplant and non-transplant candidates (category 1 recommendation for stage I-IIIa with no significant neuropathy, and category 2A recommendations for all stages with significant neuropathy and for stage IIIb disease with no significant neuropathy). Single-agent daratumumab is also listed under “Preferred Regimens” as a category 2A recommendation for stage IIIb disease with no significant neuropathy. Daratumumab monotherapy, daratumumab + lenalidomide + dexamethasone, and venetoclax + daratumumab [for t(11;14) disease] are listed as category 2A recommended options for previously treated disease. The guidelines include a statement to consider repeating initial therapy, especially if relapse-free for several years.

For smoldering (asymptomatic) MM, the NCCN Guidelines stratify their recommendations based on if low-risk or high-risk disease. If low risk, the recommendations include a clinical trial or observe at 3- to 6-month intervals (category 1 recommendation). If high-risk, the recommendations include a clinical trial (preferred), observe at 3- to 6-month intervals (category 2A recommendation), or, in select patients, treatment with daratumumab (category 1 recommendation) or lenalidomide (category 2B recommendation). The clinical trial recommendations include a footnote of “The NCCN Panel strongly recommends enrolling eligible patients with smoldering myeloma in clinical trials”. As for determining risk, the guidelines state that bone marrow plasma cells (BMPCs) >20%, M-protein >2 g/dL, and a serum-

free light chain ratio (FLCr) >20 are variables used to risk stratify patients at diagnosis. Patients with two or more of these risk factors are considered to have a high risk of progression to MM.

The NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia (Version 3.2025 - March 17, 2025) list a clinical trial as the preferred option for patients with relapsed/refractory T-cell ALL. Under "Other Recommended Regimens" a category 2A recommendation is given to a daratumumab-containing regimen (e.g., daratumumab, vincristine, pegaspargase/calaspargase, doxorubicin, and prednisone or dexamethasone).

POSITION STATEMENT:

Initiation of daratumumab (Darzalex) or daratumumab-hyaluronidase (Darzalex Faspro) **meets the definition of medical necessity** when **ANY** of the following criteria is met ("1" to "6"):

1. The member has a diagnosis of smoldering (asymptomatic) multiple myeloma, and **BOTH** of the following ("a" and "b"):
    a. **BOTH** of the following ("i" and "ii"):
        i. The member has **HIGH-RISK** smoldering MM defined has having at least **TWO** of the following risk factors for disease progression:
            - Serum monoclonal protein (M protein) level greater than 2 g/dL
            - Involved-to-uninvolved serum-free light chain ratio (FLCr) greater than 20
            - Bone marrow plasma cells (BMPCs) greater than 20%
        ii. Daratumumab or daratumumab-hyaluronidase will be used as monotherapy for treatment of the member's smoldering disease
    b. The dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase given more often than the following (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)
2. The member has a diagnosis of symptomatic multiple myeloma (MM), and **BOTH** of the following ("a" and "b"):
    a. **ANY** of the following ("i", "ii", "iii", or "iv")
        i. Member has newly diagnosed and previously untreated symptomatic MM, **AND** the member is both eligible for a hematopoietic cell transplant (HCT) (i.e., a transplant candidate) and planning to receive a HCT, and meets the following:
            - Daratumumab or daratumumab-hyaluronidase will be used as primary therapy in combination with any of the following:
                - Quadruplet therapy with bortezomib, lenalidomide (Revlimid), and dexamethasone
                - Quadruplet therapy with bortezomib, thalidomide, and dexamethasone

- Quadruplet therapy with bortezomib, cyclophosphamide, and dexamethasone
- Quadruplet therapy with carfilzomib (Kyprolis), lenalidomide, and dexamethasone

ii. Member has newly diagnosed and symptomatic MM, **AND** the member is both eligible for a hematopoietic cell transplant (HCT) (i.e., a transplant candidate) and planning to receive a HCT, and meets **BOTH** of the following ("1" and "2"):

1. Daratumumab or daratumumab-hyaluronidase will be used as maintenance therapy following a response to primary therapy, **OR** a response or stable disease following a hematopoietic cell transplant
2. **EITHER** of the following ("a" or "b"):
   a. Daratumumab or daratumumab-hyaluronidase will be used as monotherapy (i.e., not in combination with other MM treatments)
   b. Daratumumab or daratumumab-hyaluronidase will be used in combination with lenalidomide, **AND** the member has high-risk disease

iii. Member has newly diagnosed and previously untreated* symptomatic MM, **AND** a hematopoietic cell transplant (HCT) is either **NOT** indicated (i.e., a non-transplant candidate) or **NOT** planned (i.e., transplant-deferred), and meets of the following:

- Daratumumab or daratumumab-hyaluronidase will be used as primary therapy in **ANY** of the following regimens:
  - Triplet therapy with both lenalidomide and dexamethasone
  - Quadruplet therapy with bortezomib, lenalidomide and dexamethasone **AND** the member is both less than 80 years old and not frail
  - Quadruplet therapy with bortezomib, melphalan and prednisone
  - Quadruplet therapy with bortezomib, cyclophosphamide and dexamethasone
  - **ANY** of the following ixazomib (Ninlaro)-containing regimens when the member had intolerable adverse effects (e.g., severe neuropathy) to bortezomib - the specific adverse effect(s) must be provided
    - Quadruplet therapy with ixazomib, cyclophosphamide and dexamethasone
    - Quadruplet therapy with ixazomib, lenalidomide and dexamethasone **AND** the member is both less than 80 years old and not frail

**Exception permitted if using an ixazomib regimen due to bortezomib adverse effects*

iv. Member has relapsed or refractory MM, and meets **BOTH** of the following ("1" and "2"):

1. Member has previously received at least **ONE** appropriate prior line of therapy of adequate duration for the treatment of their MM
2. Daratumumab or daratumumab-hyaluronidase will be used in **ANY** of the following regimens:
   - Monotherapy
   - Doublet therapy with teclistamab (Tecvayli), **AND** the member has received at least **ONE** appropriate prior therapy of adequate duration for the treatment of their MM that include an immunomodulatory agent (e.g., lenalidomide, thalidomide) **AND** a proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib)

- Triplet therapy with both bortezomib and dexamethasone
- Triplet therapy with both carfilzomib and dexamethasone
- Triplet therapy with both lenalidomide and dexamethasone
- Triplet therapy with both pomalidomide (Pomalyst) and dexamethasone, **AND** the member has received at least **ONE** appropriate prior therapy of adequate duration for the treatment of their MM that include an immunomodulatory agent (e.g., lenalidomide, thalidomide) and a proteasome inhibitor (e.g., bortezomib, carfilzomib, ixazomib)
- Triplet therapy with both selinexor (Xpovio) and dexamethasone
- Triplet therapy with both venetoclax (Venclexta) and dexamethasone, **AND** the member has a t(11:14) translocation
- Quadruplet therapy with bortezomib, cyclophosphamide, and dexamethasone
- Quadruplet therapy with carfilzomib, pomalidomide, and dexamethasone

b. The dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase given more often than the following:

i. If used as monotherapy for relapsed disease (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 maintenance monotherapy or maintenance doublet-therapy with lenalidomide: Every 4 weeks

iii. If used as quadruplet therapy in combination with bortezomib, lenalidomide, and dexamethasone, **AND** the member is **NOT** planning to receive a HCT (one cycle is 21 days or 3 weeks):

- Cycles 1 to 2 (weeks 1 to 6): Weekly (i.e., days 1, 8, and 15 of each cycle) for 6 doses*
- Cycles 3 to 8 (weeks 7 to 24): Every 3 weeks (i.e., day 1 of each cycle) for 6 doses
- After cycle 8 (week 25 and beyond): Every 4 weeks

iv. If used as quadruplet therapy in combination with bortezomib, lenalidomide, and dexamethasone, **AND** the member is planning to receive a HCT:

1. If using 21-day or 3-week cycles (GRIFFIN trial protocol):

- Induction therapy:
  - Cycle 1 and 4 (weeks 1 to 12): Weekly (i.e., day 1, 8, and 15 of each cycle) for 12 doses*

- After cycle 4 (week 12): Stop for high-dose chemotherapy and autologous stem cell transplant. Additional doses every week are appropriate if the member's transplant is delayed.

- Consolidation therapy: weekly for a total of 6 doses (weeks 1 to 6) upon re-initiation of treatment following autologous stem cell transplant
- Maintenance therapy (daratumumab + lenalidomide): every 4 weeks following completion of consolidation therapy

2. If using 28-day or 4-week cycles (FDA-label/PERSEUS trial protocol):
    - 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 and 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. Additional doses every 2 weeks are appropriate if the member's transplant is delayed.
    - 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
    - Maintenance therapy (daratumumab + lenalidomide): every 4 weeks following completion of consolidation therapy

v. If used as quadruplet 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. Additional doses every 2 weeks are appropriate if the member's transplant is delayed.
- 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

vi. If used as quadruplet therapy in combination with carfilzomib, lenalidomide, 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 6 (weeks 9 to 24): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 8 doses

- Cycle 7 and 8 (week 25 to 32): Every 4 weeks (i.e., day 1 of each cycle) for 2 doses
- After cycle 8 (week 32): Stop for high-dose chemotherapy and autologous stem cell transplant. Additional doses every 4 weeks are appropriate if the member's transplant is delayed.

vii. If used as quadruplet therapy in combination with cyclophosphamide, bortezomib, and dexamethasone for newly diagnosed, transplant-eligible members (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 6 (weeks 9 to 24): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 8 doses
  - Cycle 7 and 8 (week 25 to 32): Every 4 weeks (i.e., day 1 of each cycle) for 2 doses
  - After cycle 8 (week 32): Stop for high-dose chemotherapy and autologous stem cell transplant. Additional doses every 4 weeks are appropriate if the member's transplant is delayed.
- Maintenance therapy (as daratumumab monotherapy): every 4 weeks upon re-initiation of treatment following autologous stem cell transplant

viii. If used as quadruplet therapy in combination with cyclophosphamide, bortezomib or ixazomib, and dexamethasone for either newly diagnosed, transplant-ineligible members or members with relapsed or refractory disease (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)

ix. If used as quadruplet 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

x. If used as quadruplet therapy in combination with carfilzomib, 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 8 (weeks 9 to 32): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 12 doses
- Cycle 9 and beyond (week 33 and beyond): Every 4 weeks (i.e., day 1 of each cycle)

xi. If used as doublet therapy in combination with teclistamab (Tecvayli) (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)

xii. If used as triplet therapy in combination 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 27): Every 3 weeks (i.e., day 1 of each cycle) for 6 doses
- After cycle 9 (week 27): Every 4 weeks

xiii. If used as triplet therapy with either carfilzomib, lenalidomide, pomalidomide, selinexor, or venetoclax, 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)

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

3. The member has a diagnosis of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome, and **BOTH** of the following ("a" and "b"):

   a. Daratumumab or daratumumab-hyaluronidase is being used in combination with lenalidomide and dexamethasone

   b. The member's dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase given more often than the following:

      i. If the member is planning to receive a hematopoietic cell transplant (HCT):

      - 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. Additional doses every 2 weeks are appropriate if the member's transplant is delayed.

      ii. If the member is **NOT** planning to receive a HCT:

      - 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)

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

4. The member has a diagnosis of systemic light chain amyloidosis, and **BOTH** of the following ("a" and "b"):
    a. **ANY** of the following ("i", "ii', "iii", or "iv"):
        i. **BOTH** of the following:
            - Daratumumab or daratumumab-hyaluronidase is being used in combination with bortezomib, cyclophosphamide, and dexamethasone
            - Member has newly diagnosed disease, **OR** member has relapsed disease and was previously treated with the above four-drug regimen and was relapse-free for at least two years
        ii. Daratumumab or daratumumab-hyaluronidase is being used as monotherapy
        iii. Daratumumab or daratumumab-hyaluronidase is being used in combination with lenalidomide and dexamethasone, **AND** member has relapsed/refractory previously treated disease
        iv. **ALL** of the following:
            - Daratumumab or daratumumab-hyaluronidase is being used in combination with venetoclax
            - Member has relapsed/refractory previously treated disease
            - Member has a t(11:14) translocation
    b. The member's dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase given more often than the following:
        - 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)

        **If given IV, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days (i.e., 8 mg/kg IV on Day 1 and 8 mg/kg IV on Day 2)*
5. The member has a diagnosis of pediatric acute lymphoblastic leukemia (ALL), and **BOTH** of the following ("a" and "b"):
    a. **ALL** of the following ("i" to "iii"):
        i. Member has relapsed/refractory T-cell ALL
        ii. Member is less than 18 years of age
        iii. Daratumumab or daratumumab-hyaluronidase is being used in combination with vincristine, pegaspargase or calaspargase, doxorubicin, **AND** prednisone or dexamethasone
    b. The member's dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) weekly or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase weekly for up to a total of 8 doses (i.e., maximum of 2 cycles of treatment prior to hematopoietic stem cell transplantation)

6. 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 or daratumumab-hyaluronidase 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, except for the following indications:

- Quadruplet therapy with daratumumab or daratumumab-hyaluronidase + cyclophosphamide + bortezomib + dexamethasone when the member is newly diagnosed and planning to receive a HCT - approved for 32 weeks (additional doses every 4 weeks can be approved if the member's transplant is delayed)
- Quadruplet therapy with daratumumab or daratumumab-hyaluronidase + carfilzomib + lenalidomide + dexamethasone - approved for 32 weeks (additional doses every 4 weeks can be approved if the member's transplant is delayed)
- Quadruplet therapy with daratumumab or daratumumab-hyaluronidase + bortezomib + lenalidomide + dexamethasone when the member is newly diagnosed and planning to receive a HCT – approved for 12 weeks if 3-week cycles or 16 weeks if 4-week cycles [additional doses every week (if 3-week cycles) or every 2 weeks (if 4-week cycles) can be approved if the member's transplant is delayed]
- Quadruplet therapy with daratumumab or daratumumab-hyaluronidase + bortezomib + thalidomide + dexamethasone – approved for 16 weeks (additional doses every 2 weeks can be approved if the member's transplant is delayed)
- Quadruplet therapy with daratumumab or daratumumab-hyaluronidase + carfilzomib + pomalidomide + dexamethasone - approved for 32 weeks
- Maintenance monotherapy or maintenance doublet-therapy with lenalidomide for symptomatic MM – approved for 1 year
- Monotherapy for smoldering (asymptomatic) MM - approved for 1 year
- Pediatric ALL – approved for 8 weeks (maximum of 8 total doses)
- POEMS syndrome when the member is newly diagnosed and planning to receive a HCT - approved for 16 weeks [additional doses every 2 weeks can be approved if the member's transplant is delayed]

Continuation of daratumumab (Darzalex) or daratumumab-hyaluronidase (Darzalex Faspro) **meets the definition of medical necessity** when **BOTH** of the following criteria are met ("1" and "2"):

1. An authorization or reauthorization for daratumumab or daratumumab-hyaluronidase has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of smoldering or symptomatic multiple myeloma, systemic light chain amyloidosis, or other FDA-approved or NCCN-supported diagnosis (for POEMS syndrome when the member is newly diagnosed and planning to receive a HCT and pediatric ALL, see initiation criteria); **OR** the member previously met **ALL** indication-specific initiation criteria
2. **ANY** of the following based on the member's diagnosis ("a", "b", "c", or "d"):
    a. Smoldering (asymptomatic) multiple myeloma, and **ALL** of the following ("i", "ii", and "iii"):
        i. Daratumumab or daratumumab-hyaluronidase will be used as monotherapy for treatment of the member's smoldering disease
        ii. The dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase given more often than the following (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)
        iii. Member disease has **NOT** progressed to symptomatic multiple myeloma
    b. Symptomatic multiple myeloma, and **ALL** of the following ("i", "ii", and "iii"):
        i. Daratumumab or daratumumab-hyaluronidase is being used in **ANY** of the following regimens:
            1. Monotherapy
            2. Doublet therapy with lenalidomide
            3. Doublet therapy with teclistamab (Tecvayli)
            4. Triplet therapy with both bortezomib and dexamethasone
            5. Triplet therapy with both carfilzomib and dexamethasone
            6. Triplet therapy with both lenalidomide and dexamethasone
            7. Triplet therapy with both pomalidomide and dexamethasone
            8. Triplet therapy with both selinexor and dexamethasone
            9. Triplet therapy with both venetoclax and dexamethasone
            10. Quadruplet therapy with bortezomib, melphalan, and prednisone
            11. Quadruplet therapy with bortezomib, thalidomide, and dexamethasone
            12. Quadruplet therapy with bortezomib, lenalidomide, and dexamethasone
            13. Quadruplet therapy with bortezomib, cyclophosphamide, and dexamethasone
            14. Quadruplet therapy with carfilzomib, lenalidomide, and dexamethasone
            15. Quadruplet therapy with carfilzomib, pomalidomide, and dexamethasone

16. Quadruplet therapy with ixazomib, cyclophosphamide, and dexamethasone

ii. The member's dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase given more often than the following:

1. If used as monotherapy for relapsed or refractory disease (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 maintenance monotherapy or maintenance doublet-therapy with lenalidomide: Every 4 weeks
3. If used as doublet therapy in combination with teclistamab (Tecvayli)
    - 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)
4. If used as quadruplet therapy in combination with bortezomib, lenalidomide, and dexamethasone when member is **NOT** planning to receive a HCT:
    - Cycles 1 to 2 (weeks 1 to 6): Weekly (i.e., days 1, 8, and 15 of each cycle) for 6 doses
    - Cycles 3 to 8 (weeks 7 to 24): Every 3 weeks (i.e., day 1 of each cycle) for 6 doses
    - After cycle 8 (week 25 and beyond): Every 4 weeks
5. If used as quadruplet therapy in combination with bortezomib, lenalidomide, and dexamethasone when the member is newly diagnosed and planning to receive a HCT:
    a. If using 21-day or 3-week cycles (GRIFFIN trial protocol):
        - Induction therapy:
            - Cycle 1 and 4 (weeks 1 to 12): Weekly (i.e., day 1, 8, and 15 of each cycle) for 12 doses
            - After cycle 4 (week 12): Stop for high-dose chemotherapy and autologous stem cell transplant. Additional doses every week are appropriate if the member's transplant is delayed.
        - Consolidation therapy: weekly for a total of 6 doses (weeks 1 to 6) upon re-initiation of treatment following autologous stem cell transplant
        - Maintenance therapy (daratumumab + lenalidomide): every 4 weeks following completion of consolidation therapy

b. If using 28-day or 4-week cycles (FDA-label/PERSEUS trial protocol):

- 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 and 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. Additional doses every 2 weeks are appropriate if the member's transplant is delayed.
- 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
- Maintenance therapy (daratumumab + lenalidomide): every 4 weeks following completion of consolidation therapy

6. If used as quadruplet 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
7. If used as quadruplet 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. Additional doses every 2 weeks are appropriate if the member's transplant is delayed.
   - 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
8. If used as quadruplet therapy in combination with carfilzomib, lenalidomide, 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 6 (weeks 9 to 24): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 8 doses

- Cycle 7 and 8 (week 25 to 32): Every 4 weeks (i.e., day 1 of each cycle) for 2 doses
- After cycle 8 (week 32): Stop for high-dose chemotherapy and autologous stem cell transplant. Additional doses every 4 weeks are appropriate if the member's transplant is delayed.

9. If used as quadruplet therapy in combination with cyclophosphamide, bortezomib, and dexamethasone when the member is newly diagnosed and planning to receive a HCT (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 6 (weeks 9 to 24): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 8 doses
     - Cycle 7 and 8 (week 25 to 32): Every 4 weeks (i.e., day 1 of each cycle) for 2 doses
     - After cycle 8 (week 32): Stop for high-dose chemotherapy and autologous stem cell transplant. Additional doses every 4 weeks are appropriate if the member's transplant is delayed.
   - Maintenance therapy (as daratumumab monotherapy): every 4 weeks upon re-initiation of treatment following autologous stem cell transplant
10. If used as quadruplet therapy in combination with cyclophosphamide, bortezomib or ixazomib, and dexamethasone for either newly diagnosed, transplant-ineligible members or members with relapsed or refractory disease (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)
11. If used as quadruplet therapy in combination with carfilzomib, 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 8 (weeks 9 to 32): Every 2 weeks (i.e., day 1 and 15 of each cycle) for 12 doses
    - Cycle 9 and beyond (week 33 and beyond): Every 4 weeks (i.e., day 1 of each cycle)
12. 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

13. If used as triplet therapy with either carfilzomib, lenalidomide, pomalidomide, selinexor, or venetoclax, 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 has not had disease progression during daratumumab or daratumumab-hyaluronidase treatment

c. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome and **ALL** of the following ("i" to "iv"):

i. Daratumumab or daratumumab-hyaluronidase is being used in combination with lenalidomide and dexamethasone

ii. The member is **NOT** planning to receive a HCT

iii. The member's dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase given more often than the following:
    - 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)

iv. Member has not had disease progression during daratumumab or daratumumab-hyaluronidase treatment

d. Systemic light chain amyloidosis (SLCA) and **ALL** of the following ("i", "ii", and "iii"):

i. Daratumumab or daratumumab-hyaluronidase is being used as **ANY** of the following:
    - Monotherapy
    - In combination with lenalidomide and dexamethasone
    - In combination with venetoclax
    - In combination with bortezomib, cyclophosphamide and dexamethasone

ii. The member's dosage of IV daratumumab does not exceed 16 mg/kg (based on actual body weight) or the dosage of SQ daratumumab-hyaluronidase does not exceed 1,800 mg daratumumab and 30,000 units hyaluronidase given more often than the following:
    - 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)

iii. Member has not had disease progression during daratumumab or daratumumab-hyaluronidase treatment

e. 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 or daratumumab-hyaluronidase 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 or daratumumab-hyaluronidase 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 or daratumumab-hyaluronidase

Approval duration: 1 year (except for quadruplet therapy with daratumumab or daratumumab-hyaluronidase + bortezomib + thalidomide + dexamethasone; approve for 3 months to allow up to 4 total doses to be given in the consolidation therapy phase; quadruplet therapy with daratumumab or daratumumab-hyaluronidase + carfilzomib + lenalidomide + dexamethasone – allow up to 8 cycles of induction treatment before transplant only, additional doses every 4 weeks can be approved if the member's transplant is delayed).

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

Darzalex

- In combination with lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, **AND** in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- 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 bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three prior lines of 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
- Combination therapy with carfilzomib and dexamethasone (4-week cycle regimen)
    - Week 1: 8 mg/kg on days 1 and 2 (total 2 doses)
    - Weeks 2 to 8: 16 mg/kg weekly (total of 7 doses)
    - Weeks 9 to 24: 16 mg/kg every two weeks (total of 8 doses)

      Week 25 onwards until disease progression: 16 mg/kg 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.

Darzalex Faspro

- In combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in patients with newly multiple myeloma who are eligible 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 lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, **AND** in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- 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 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 in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- 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
- As monotherapy, in patients with high-risk smoldering multiple myeloma
- In combination with bortezomib, cyclophosphamide and dexamethasone for the treatment of patients with newly diagnosed light chain (AL) amyloidosis
- Combination with bortezomib, lenalidomide, and dexamethasone (4-week cycle regimen)
    - The recommended dose is 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously over approximately 3 to 5 minutes 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, melphalan and prednisone (6-week cycle regimen)
    - The recommended dose is 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously over approximately 3 to 5 minutes 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 (including for smoldering MM), or combination therapy with carfilzomib and dexamethasone, lenalidomide and dexamethasone, or pomalidomide and dexamethasone (4-week cycle regimen)
    - The recommended dose is 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously over approximately 3 to 5 minutes 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 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously over approximately 3 to 5 minutes 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 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously over approximately 3 to 5 minutes 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

- Combination therapy with bortezomib, cyclophosphamide and dexamethasone (4-week cycle regimen for light chain amyloidosis)
    - The recommended dose is 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously over approximately 3 to 5 minutes 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
- Pre-medicate patients with a corticosteroid, oral acetaminophen, and oral or IV antihistamine one to three hours prior to every dose. 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. If the patient does not experience a major systemic administration-related reaction after the first 3 doses, consider discontinuing the administration of corticosteroids (excluding any background regimen-specific corticosteroid).
- 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 clinically significant differences in the pharmacokinetics of daratumumab as monotherapy or as combination therapy were observed for mild [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate aminotransaminase (AST)>ULN] and moderate (total bilirubin 1.5 to 3 times ULN and any AST) hepatic impairment. The effect of severe (total bilirubin >3 times ULN and any AST) hepatic impairment on daratumumab pharmacokinetics is unknown.

Drug Availability

Darzalex

- 100 mg/5 mL and 400 mg/20 mL solution for injection in single-dose vials
- Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light. This product contains no preservative.

Darzalex Faspro

- 1,800 mg of daratumumab and 30,000 units of hyaluronidase per 15 mL in a single-dose vial
- Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light. This product contains no preservative.

PRECAUTIONS:

Boxed Warnings

Darzalex

- None

Darzalex Faspro

- None

Contraindications

Darzalex

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

Darzalex Faspro

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

Precautions/Warnings

Darzalex

- **Infusion Reactions**: Daratumumab can cause severe infusion reactions including anaphylactic reactions (e.g., bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema and pulmonary edema). These reactions can be life-threatening and fatal outcomes have been reported. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension. 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. Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred. If ocular symptoms occur, interrupt infusion and seek immediate ophthalmologic evaluation prior to restarting.
- **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.
- **Neutropenia**: Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. A dose delay may be required to allow recovery of neutrophils. No dose reduction is recommended. Consider supportive care with growth factors
- **Thrombocytopenia**: Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's

prescribing information for background therapies. A dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions.

- **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:** Based on the mechanism of action, daratumumab can cause fetal harm when administered to a pregnant woman. Daratumumab may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus.

Darzalex Faspro

- **Hypersensitivity and Other Administration Reactions**: Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur. Fatal reactions have been reported with daratumumab-containing products, including Darzalex Faspro. Permanently discontinue for life-threatening reactions
- **Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis**: Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received Darzalex Faspro in combination with bortezomib, cyclophosphamide and dexamethasone. Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied. Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.
- **Hypersensitivity and Other Administration Reactions**: Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur. Fatal reactions have been reported with daratumumab-containing products, including Darzalex Faspro. In a pooled safety population, 9% of patients experienced a systemic administration-related reaction and 8% had an injection-site reaction. Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue treatment. Consider administering corticosteroids and other medications after the administration of daratumumab depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.
- **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.
- **Neutropenia**: Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding treatment until recovery of neutrophils. In lower body weight patients, higher rates of Grade 3-4 neutropenia were observed.
- **Thrombocytopenia**: Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's

prescribing information for background therapies. Consider withholding treatment until recovery of platelets.

- **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**: Based on the mechanism of action, daratumumab can cause fetal harm when administered to a pregnant woman. Daratumumab may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment and for 3 months after the last dose.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9144	Injection, daratumumab, 10 mg and hyaluronidase-fihj
J9145	Injection, daratumumab, 10 mg

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
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.02	Acute lymphoblastic leukemia, in relapse
D47.2	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified [for POEMS syndrome only]
E85.3	Secondary systemic amyloidosis
E85.4	Organ-limited amyloidosis
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: Florida Blue 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.

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.

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. A serum M-protein of greater than 3 g/dL is consistent with a diagnosis of MM.

Smoldering MM – defined by the International Myeloma Working Group (IMWG) criteria as a serum monoclonal protein ≥3 g/dL,or a urinary monoclonal (Bence-Jones) protein ≥500 mg/24 hr and/or clonal bone marrow plasma cells (BMPCs) 10% to 59%, **AND** absence of myeloma-defining events or amyloidosis

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01
Carfilzomib (Kyprolis) IV, 09-J1000-81
Chimeric Antigen Receptor (CAR) T-Cell Therapies, 09-J3000-94
Doxorubicin HCl Liposome (Doxil) IV, 09-J0000-91
Elotuzumab (Empliciti) IV, 09-J2000-50
Elranatamab-bcmm (Elrexfio) Injection, 09-4000-64
Isatuximab (Sarclisa) Injection, 09-J3000-67
Ixazomib (Ninlaro), 09-J2000-51
Oral Oncology Medications, 09-J3000-65
Talquetamab-tgvs (Talvey) Injection, 09-J4000-63
Teclistamab (Tecvayli) Injection, 09-J4000-46
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 06/11/25.

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.
07/15/20	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, related guidelines, and references.
10/01/20	Revision: Added HCPCS code C9062 (for Darzalex Faspro).
10/15/20	Updated description, position statement, dosage/administration, and references based on new FDA-approved combination regimen with carfilzomib (Kyprolis) and dexamethasone and several new NCCN recommended combination regimens.
01/01/21	Revision: Added HCPCS code J9144 and deleted codes C9062 and J9999.
03/15/21	Updated description section, position statement, dosage/administration, precautions, and references based on an FDA-approved expanded MM indication and new indication for light chain amyloidosis.
07/15/21	Review and revision to guidelines consisting of updating the description section, position statement, related guidelines, and references.

09/15/21	Revision to guidelines consisting of updating the description section, dosage/administration section, precautions, and references based on a newly approved MM regimen for Darzalex Faspro.
01/15/22	Revision to guidelines consisting of updating the description section, dosage/administration section, and references based on a newly approved MM regimen for Darzalex Faspro.
07/15/22	Review and revision to guidelines consisting of updating the description section, position statement, precautions, billing/coding, and references.
07/15/23	Review and revision to guidelines consisting of updating the description section, position statement, related guidelines, and references. For the pomalidomide and dexamethasone triplet regimen, updated criteria to allow treatment after at least one MM regimen. Added daratumumab maintenance therapy for MM per NCCN guidelines.
04/15/24	Revision to guidelines consisting of updating the description section, position statement, billing/coding, and references based on updated NCCN guidelines for MM, pediatric ALL, and SLCA.
07/15/24	Review and revision to guidelines consisting of updating the description section, position statement, related guidelines, and references.
09/15/24	Revision to guidelines consisting of updating the description section, position statement, dosage/administration, and references. The FDA approved a new MM regimen for Darzalex Faspro in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed MM patients who are eligible for ASCT. The FDA-approved regimen is based on 4-week cycles.
07/15/25	Review and revision to guidelines consisting of updating the description section, position statement, related guidelines, and references. Added coverage for POEMS syndrome per new NCCN inclusion. Added new combination regimens for multiple myeloma and systemic light chain amyloidosis per NCCN updates.
10/15/25	Revision to guidelines consisting of updating the position statement to change the max frequency of maintenance dosing from every 8 weeks to every 4 weeks, and removed maintenance duration limits for the regimens for newly-diagnosed transplant-eligible patients with MM. Updated references.
12/15/25	Revision to guidelines consisting of updating the description section, position statement, dosage/administration, definitions, and references. The FDA approved a new indication for Darzalex Faspro for the treatment of adult patients with high-risk smoldering MM as monotherapy.
02/15/26	Revision to guidelines consisting of updating the description section, position statement, and references based on updated NCCN guidelines for MM. Added allowances for: (1) the combination regimen of teclistamab and daratumumab or daratumumab-hyaluronidase as second-line or later MM therapy, (2) first-line MM quadruplet therapy with bortezomib, lenalidomide and dexamethasone (when HCT is not planned) and the member is both less than 80 years old and not frail, and (3) treatment of POEMs when HCT is not planned based on inclusion in the NCCN recommendations for MM. Updated the "transplant ineligible" terminology to "HCT is either NOT indicated (i.e., a non-transplant candidate) or NOT planned (i.e., transplant-deferred)" per NCCN updated wording.