Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Daratumumab (Darzalex®) and daratumumab and hyaluronidase-fihj (Darzalex Faspro)	MP-RX-FP-21-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of daratumumab-containing products approved by the Food and Drug Administration (FDA) for the treatment of certain patients with newly diagnosed and relapsed/refractory multiple myeloma (MM), and light chain (AL) amyloidosis.

Background Information

Daratumumab is a human anti-CD38 monoclonal antibody. Darzalex is administered intravenously, with weight based dosing, over hours. Darzalex Faspro is a subcutaneous dosage form that allows for flat dosing and is administered over 3-5 minutes. The National Comprehensive Cancer Network® (NCCN) provides category 2A recommendations for the use of daratumumab. Approved and recommended uses are listed below:

Newly diagnosed multiple myeloma:

- *Ineligible for stem cell transplant:*
  - In combination with bortezomib, melphalan, and prednisone
  - In combination with lenalidomide and dexamethasone
  - In combination with cyclophosphamide, bortezomib, and dexamethasone (NCCN 2A)
  - In combination with carfilzomib, lenalidomide, and dexamethasone (DP BIIa)
- *Eligible for stem cell transplant:*
  - In combination with bortezomib, thalidomide, and dexamethasone
  - In combination with bortezomib, lenalidomide, and dexamethasone (NCCN 2A)
  - In combination with cyclophosphamide, bortezomib, and dexamethasone (NCCN 2A)
  - In combination with carfilzomib, lenalidomide, and dexamethasone (NCCN 2A)

Relapsed or refractory multiple myeloma:

- In combination with lenalidomide and dexamethasone
- In combination with bortezomib and dexamethasone
- In combination with pomalidomide and dexamethasone in those who have received at least 2 prior therapies (or 1 prior line of therapy) including lenalidomide and a proteasome inhibitor (Label, NCCN 2A)

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- As a single agent in those who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent
- In combination with carfilzomib and dexamethasone
- In combination with cyclophosphamide, bortezomib, and dexamethasone (NCCN 2A)
- In combination with selinexor and dexamethasone (NCCN 2A)

Maintenance therapy for multiple myeloma:

- As a single agent for transplant candidates after response to primary myeloma therapy (NCCN 2A) or for response or stable disease following transplant (NCCN 1)
- In combination with lenalidomide for transplant candidates (high risk disease only) after response to primary myeloma therapy (NCCN 2A) or for response or stable disease following transplant (NCCN 1)

Systemic light chain amyloidosis

Emerging data from prospective and retrospective studies indicate Darzalex and/or Darzalex Faspro produce clinically meaningful responses in patients with systemic light chain amyloidosis. Most recently, the FDA has approved Darzalex Faspro for the treatment of light chain amyloidosis in combination with bortezomib, cyclophosphamide, and dexamethasone. This indication is under accelerated approval and continued approval may be contingent upon confirmatory trials. It is not indicated and not recommended for treatment of light chain amyloidosis in individuals who have NYHA class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials. There is also evidence to support Darzalex as a single agent or in combination with dexamethasone with or without bortezomib in relapsed or refractory systemic light chain amyloidosis (Kimmich 2020, Roussel 2020).

Definitions and Measures

- Line of Therapy:
  - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
  - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
  - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- Multiple myeloma: A type of cancer that begins in plasma cells (white blood cells that produce antibodies).
- Plasma cell leukemia: A rare and aggressive form of multiple myeloma characterized by high levels of plasma cells in the peripheral blood.

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- Proteasome inhibitors: A class of drugs used to treat multiple myeloma that work by blocking the action of proteasomes which are cellular complexes that break down proteins. Examples include bortezomib, carfilzomib and ixazomib.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Approved Indications

See Background section above.

Other Uses

The National Comprehensive Cancer Network® (NCCN) provides a category 2A recommendation for the use of daratumumab in combination with venetoclax and dexamethasone for patients with t(11;14) as useful in certain circumstances for previously treated multiple myeloma. Guidelines have not been updated with literature and discussion support for this recommendation to date.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9145	Injection, daratumumab, 10 mg [DARZALEX]
J9144	Injection, daratumumab, 10 mg and hyaluronidase-fihj [Darzalex Faspro]

ICD-10	Description
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms
C91.00-C91.02	Acute lymphoblastic leukemia
E85.0-E85.9	Amyloidosis
Z51.11-Z51.12	Encounter for antineoplastic chemotherapy and immunotherapy
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues
T86.5	Complications of stem cell transplant

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Z94.84	Stem cells transplant status

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Daratumumab (Darzalex®) and daratumumab and hyaluronidase-fihj (Darzalex Faspro)

A. Criteria For Initial Approval (*Provider must submit documentation (such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information) supporting the patient's diagnosis for the drug and confirming that the patient has met approval criteria)*

B.

i. Individual has a diagnosis of multiple myeloma, including plasma cell leukemia; **AND**

ii. Individual is using for one of the following:

A. Newly diagnosed multiple myeloma for those who are ineligible for stem cell transplantation:

1. In combination with melphalan, prednisone and a proteasome inhibitor (PI) (for example, bortezomib); **OR**
2. In combination with lenalidomide and dexamethasone;

OR

B. Newly diagnosed multiple myeloma for those who are eligible for stem cell transplant, in combination with bortezomib, dexamethasone, and either thalidomide or lenalidomide (Label, NCCN 2A);

OR

C. Newly diagnosed multiple myeloma in combination with carfilzomib, lenalidomide, and dexamethasone;

OR

D. Newly diagnosed multiple myeloma in combination with cyclophosphamide, bortezomib, and dexamethasone;

OR

E. Relapsed or refractory multiple myeloma (Label, NCCN 2A):

1. As a single agent following therapy with at least two prior lines of therapy including a PI (for example, bortezomib, carfilzomib, or ixazomib) and an immunomodulatory agent (for example, thalidomide, lenalidomide, or pomalidomide); **OR**
2. In combination with cyclophosphamide, bortezomib, and dexamethasone; **OR**

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3. In combination with selinexor and dexamethasone; **OR**
4. In combination with venetoclax and dexamethasone for patients with t(11:14); **OR**
5. As combination therapy following treatment with at least one prior line of therapy when used with one of following:
    a. A PI (for example, bortezomib, carfilzomib, or ixazomib) and dexamethasone; **OR**
    b. An immunomodulatory agent (for example, thalidomide, lenalidomide, or pomalidomide) and dexamethasone;

OR

F. As single-agent maintenance therapy for multiple myeloma in transplant candidates (NCCN 2A); **OR**

G. In combination with lenalidomide for maintenance therapy of high-risk multiple myeloma in transplant candidates (NCCN 2A);

OR

iii. Individual has a diagnosis of systemic light chain amyloidosis; **AND**

A. Individual is using as a single agent (NCCN 2A);

OR

B. Individual is using in combination:
    1. Bortezomib, cyclophosphamide, and dexamethasone; **OR**
    2. Dexamethasone with or without bortezomib (DP B IIa)

OR

iv. Individual has a diagnosis of pediatric Acute Lymphoblastic Leukemia (ALL), as T-ALL (NCCN 2A); **AND**

v. Individual is using a daratumumab-containing regimen (e.g. daratumumab, vincristine, pegaspargase or calaspargase, doxorubicin, and prednisone or dexamethasone) for relapsed/refractory T-ALL.

C. Criteria For Continuation of Therapy

i. MMM considers continuation of daratumumab (Darzalex®) and daratumumab and hyaluronidase-fihj (Darzalex Faspro®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:

A. A current oncology note documenting the patient's response to treatment showing no progression of disease.

B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

ii. Maximum duration of therapy:

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A. For the indication of light chain amyloidosis: Up to a maximum of 2 years.
B. For patients with newly diagnosed multiple myeloma eligible for ASCT (in combination with Bortezomib, Thalidomide and Dexamethasone): Up to a total of 16 doses
C. For all other indications: until unacceptable toxicity or disease progression.

D. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

E. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

1. Requests for Darzalex (daratumumab) or Darzalex Faspro (daratumumab and hyaluronidase-fihj) may not be approved if the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications not included above.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

<u>For daratumumab and hyaluronidase-fihj (Darzalex Faspro):</u>

Use	Dosing Schedule	Recommended dose	Duration of Therapy
Multiple Myeloma			
Monotherapy In combination with lenalidomide and	• Weeks 1 to 8: Administer weekly (total of 8 doses)	1,800 mg/30,000 units (1,800 mg daratumumab and	Until disease progression or

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dexamethasone (Darzalex FASPRO-Rd)	• Weeks 9 to 24: Administer every two weeks (total of 8 doses) • Week 25 onwards until disease progression: every 4 weeks	30,000 units hyaluronidase) administered subcutaneously	unacceptable toxicity
In combination with pomalidomide and dexamethasone (Darzalex Faspro-Pd)			
In combination with carfilzomib and dexamethasone (Darzalex Faspro-Kd)			
In Combination with Bortezomib, Melphalan and Prednisone (Darzalex Faspro-VMP)	• 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 4 weeks		
In Combination with Bortezomib, Thalidomide, and Dexamethasone (Darzalex Faspro-VTd)	• Weeks 1 to 8: Administer weekly (total of 8 doses) • Weeks 9 to 16: Every two weeks (total of 4 doses) **Stop for high dose chemotherapy and ASCT** • Consolidation: weeks 1 to 8: Every two weeks (total of 4 doses)	1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously	A total of 16 doses
In Combination with Bortezomib, Lenalidomide, and Dexamethasone (Darzalex Faspro-VTd)	• Weeks 1 to 8: Administer weekly (total of 8 doses) • Weeks 9 to 16: Every two weeks (total of 4 doses) **Stop for high dose chemotherapy and ASCT**	1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously	A total of 16 doses

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	• Consolidation: weeks 1 to 8: Every two weeks (total of 4 doses)		
In Combination with Bortezomib and Dexamethasone (Darzalex Faspro-Vd)	• 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 4 weeks	1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously	Until disease progression or unacceptable toxicity
Light Chain Amyloidosis			
In Combination with Bortezomib, Cyclophosphamide and Dexamethasone (Darzalex Faspro-VCd)	• Weeks 1 to 8: Administer weekly (total of 8 doses) • Weeks 9 to 24: Administer every two weeks (total of 8 doses) • Week 24 onwards until disease progression or a maximum of 2 years: every 4 weeks	1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously	2 years

For daratumumab (Darzalex):

Use	Dosing Schedule	Recommended Dose	Duration of Therapy
Multiple Myeloma			
Monotherapy In combination with lenalidomide and dexamethasone (D-Rd) In combination with pomalidomide and dexamethasone (D-Pd)	• Weeks 1 to 8: Administer weekly (total of 8 doses) • Weeks 9 to 24: Administer every two weeks (total of 8 doses) • Week 25 onwards until disease progression: every 4 weeks	16 mg/kg actual body weight administered as an intravenous infusion	Until disease progression or unacceptable toxicity

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Use	Dosing Schedule	Recommended Dose	Duration of Therapy
In Combination with Bortezomib, Melphalan and Prednisone (D-VMP)	• Weeks 1 to 6: Administer weekly (total of 6 doses) • Weeks 7 to 54: Administer every three weeks (total of 16 doses) • Week 55 onwards until disease progression: every 4 weeks	16 mg/kg actual body weight administered as an intravenous infusion	Until disease progression or unacceptable toxicity
In Combination with Bortezomib, Thalidomide and Dexamethasone (D-VTd)	• Weeks 1 to 8: Administer weekly (total of 8 doses) • Weeks 9 to 16: Administer every two weeks (total of 4 doses) **Stop for high dose chemotherapy and ASCT** • Week 1 to 8: Administer every two weeks (total of 4 doses)	16 mg/kg actual body weight administered as an intravenous infusion	A total of 16 doses
In Combination with Bortezomib and Dexamethasone (D-Vd)	• Weeks 1 to 9: Administer weekly (total of 9 doses) • Weeks 10 to 24: Administer every three weeks (total of 5 doses) • Week 25 onwards until disease progression: every 4 weeks	16 mg/kg actual body weight administered as an intravenous infusion	Until disease progression or unacceptable toxicity
In Combination with Carfilzomib and Dexamethasone (DKd)	• Week 1: Days 1 and 2 (two doses	8 mg/kg/dose	Until disease progression or unacceptable toxicity
	• Weeks 2 to 8: Administer weekly (total of 7 doses)	16 mg/kg/dose	

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Use	Dosing Schedule	Recommended Dose	Duration of Therapy
	• Weeks 9 to 24: Administer every two weeks (total of 8 doses)	16 mg/kg/dose	
	• Week 25 onwards until disease progression: every 4 weeks	16 mg/kg/dose	
Exceptions			
None			

Reference Information

1. Chari A, Martinez-Lopez J, Mateos M, et al. Daratumumab in combination with carfilzomib and dexamethasone in lenalidomide- refractory patients with relapsed multiple myeloma: Subgroup analysis of MMY1001. J Clin Oncol. 2018; 36(15):8002-8002
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 17, 2023.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Jakubowiak A, Chari A, Lonial S, et al. Daratumumab in combination with carfilzomib, lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma (MMY1001). J Clin Oncol. 2017; 35(15):8000-8000.
5. Kimmich CR, Terzer T, Benner A, et al: Daratumumab for systemic AL amyloidosis: prognostic factors and adverse outcome with nephrotic-range albuminuria. Blood 2020; 135(18):1517-1530.
6. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
7. Roussel M, Merlini G, Chevret S, et al. A prospective phase II of daratumumab in previously treated systemic light chain amyloidosis (AL) patients. Blood. 2020; 135: 1531-1540.
8. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed January 2023.
    a. Multiple Myeloma. V1.2024. Revised September 22, 2023.
    b. Systemic Light Chain Amyloidosis. V2.2023. Revised November 28, 2022.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 4/28/2025	Add combination use with venetoclax for consistency. Add regimen included in label information update (bortezomib, lenalidomide and dexamethasone).	6/9/2025	6/19/2025
Select Review	Add NCCN recommendations for combination use with selinexor and maintenance therapy in multiple myeloma; add pediatric acute lymphoblastic leukemia per NCCN. Coding Reviewed: Added ICD-10-CM C91.00-C91.02.	7/29/2024	8/7/2024
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception	Elevance Health's Medical Policy adoption	N/A	11/30/2023