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

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Document Number: EOCCO-0585

Last Review Date: 09/01/2021
Date of Origin: 02/02/2021
Dates Reviewed: 02/2021, 09/2021

I. Length of Authorization [1,9,19,20]

Coverage will be provided for 6 months and may be renewed unless otherwise specified.

- Use for newly diagnosed multiple myeloma in combination with bortezomib, thalidomide, and dexamethasone may not be renewed.
- Use for newly diagnosed disease in combination with bortezomib, lenalidomide and dexamethasone may be renewed for up to a maximum of 2 years of maintenance therapy.
- Use for newly diagnosed or relapsed disease in combination with cyclophosphamide, bortezomib and dexamethasone may be renewed for up to a maximum of 80 weeks (32 weeks of induction therapy and 48 weeks of maintenance therapy).
- Use for newly diagnosed systemic light chain amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone may be renewed for up to a maximum of 2 years.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Darzalex Faspro 1,800 mg/30,000 unit single-dose vial for injection: 1 vial per dose
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards*

B. Max Units (per dose and over time) [HCPCS Unit]:

- Up to 180 billable units per dose
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards*

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria [1]

- Therapy will not be used in combination with other anti-CD38 therapies (i.e., daratumumab, isatuximab, etc.); **AND**

Multiple Myeloma † Φ [1,2,6-14,16,17,19,20,1e]

- Used in the treatment of newly diagnosed disease in patients who are ineligible for autologous stem cell transplant (ASCT) in combination with ONE of the following regimens:
  - Lenalidomide and dexamethasone; **OR**
  - Bortezomib, melphalan and prednisone; **OR**
  - Cyclophosphamide, bortezomib, and dexamethasone; **OR**
- Used in the treatment of newly diagnosed disease in patients who are eligible for autologous stem cell transplant (ASCT) in combination with ONE of the following regimens:
  - Bortezomib, lenalidomide, and dexamethasone; **OR**
  - Bortezomib, thalidomide, and dexamethasone (VTd); **OR**
  - Cyclophosphamide, bortezomib, and dexamethasone; **OR**
- Used for disease relapse after 6 months following primary induction therapy with the same regimen in combination with ONE of the following regimens:
  - Lenalidomide and dexamethasone for non-transplant candidates; **OR**
  - Cyclophosphamide, bortezomib, and dexamethasone; **OR**
- Used as subsequent therapy in combination with dexamethasone and ONE of the following:
  - Selinexor; **AND**
    - Used after at least three prior lines of therapy including a proteasome inhibitor (e.g., bortezomib, carfilzomib, etc.) and an immunomodulatory agent (e.g., lenalidomide, pomalidomide, etc.); **OR**
    - Patient is double-refractory to a proteasome inhibitor and an immunomodulatory agent; **OR**
  - Lenalidomide; **OR**
  - Bortezomib; **OR**
  - Carfilzomib; **OR**
  - Cyclophosphamide and bortezomib; **OR**
- Used in combination with pomalidomide and dexamethasone; **AND**
  - Used after at least ONE prior line of therapy including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, etc.); **OR**
  - Used after at least TWO prior therapies including an immunomodulatory agent (e.g., pomalidomide, etc.) and a proteasome inhibitor (bortezomib, carfilzomib, etc.); **OR**
- Used as single agent therapy; **AND**
  - Patient must have received at least three previous lines of therapy including a proteasome inhibitor (e.g., bortezomib, carfilzomib, etc.) and an immunomodulatory agent (e.g., lenalidomide, pomalidomide, etc.); **OR**
  - Patient is double-refractory to a proteasome inhibitor and an immunomodulatory agent

Systemic Light Chain Amyloidosis † ‡ [1,2,15,18,21]

- Patient must NOT have NYHA Class IIIB or Class IV, or Mayo Stage IIIB cardiac disease; **AND**
  - Used in the treatment of newly diagnosed disease in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd); **OR**
  - Used as single agent therapy for the treatment of relapsed/refractory disease

† FDA Approved Indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,2,6,9,19,20]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease and decrease in size of tumor of tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: hypersensitivity and other administration reactions (e.g., systemic administration-related reactions, local injection-site reactions, etc.), neutropenia, thrombocytopenia, cardiac toxicity, etc.; **AND**

Multiple Myeloma

- Use for newly diagnosed disease in combination with bortezomib, thalidomide and dexamethasone after 24 weeks of induction/consolidation therapy may not be renewed.
- Use for newly diagnosed disease in combination with bortezomib, lenalidomide and dexamethasone may be renewed for up to a maximum of 2 years of maintenance therapy.
- Use for newly diagnosed or relapsed disease in combination with cyclophosphamide, bortezomib and dexamethasone may be renewed for up to a maximum of 80 weeks *(32 weeks of induction therapy and 48 weeks of maintenance therapy).*

Systemic Light Chain Amyloidosis (newly diagnosed disease)

- Use for newly diagnosed disease in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) may be renewed for a maximum of 2 years of therapy.

V. Dosage/Administration [1,6,8,15]

Indication	Dose
Multiple Myeloma	Administer 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) as a 15 mL injection subcutaneously into the abdomen. Treatment as one of the following:
	<u>Newly diagnosed disease in patients ineligible for ASCT in combination with bortezomib, melphalan and prednisone (D-VMP) (6-week cycle)</u> – Weekly Weeks 1 to 6 (six doses; cycle 1) – Every three weeks Weeks 7 to 54 (16 doses; cycles 2 to 9) – Every four weeks Week 55 onwards (cycle 10 and beyond) *Treat until disease progression or unacceptable toxicity.*
	<u>Newly diagnosed disease in patients eligible for ASCT in combination with bortezomib, thalidomide and dexamethasone (4-week cycle):</u> Induction – – Weekly Weeks 1 to 8 (eight doses; cycles 1 and 2) – Every two weeks Weeks 9 to 16 (four doses; cycles 3 and 4) *Stop for high dose chemotherapy and ASCT.* Consolidation –

	– Every two weeks Weeks 1 to 8 (four doses; cycles 5 and 6)
	<u>Newly diagnosed disease in patients eligible for ASCT in combination with bortezomib, lenalidomide and dexamethasone:</u> Induction – **3 week cycle** – Weekly Weeks 1 to 12 (twelve doses; cycles 1 to 4) Consolidation – *(after ASCT)* – **3 week cycle** – Weekly Weeks 13 to 18 (six doses; cycles 5 and 6) Maintenance – **4 week cycle** – Every 4 or 8 weeks Weeks 1 to 102 for a maximum of 2 years of maintenance treatment
	<u>Newly diagnosed OR relapsed disease in combination with cyclophosphamide, bortezomib and dexamethasone (4-week cycle):</u> Induction – – Weekly Weeks 1 to 8 (eight doses; cycles 1 and 2) – Every two weeks Weeks 9 to 24 (eight doses; cycles 3 to 6) – Every four weeks Week 25 to 32 (two doses; cycles 7 and 8) Maintenance *(after ASCT)* – – Every 4 weeks Weeks 33-48 for up to 12 cycles
	<u>Treatment as one of the following:</u> o Monotherapy for patients with relapsed/refractory multiple myeloma (4-week cycle) o Combination therapy with lenalidomide and low-dose dexamethasone for newly diagnosed patients ineligible for ASCT (4-week cycle) o Combination therapy with lenalidomide or pomalidomide and dexamethasone in patients with relapsed/refractory disease (4-week cycle) o Combination therapy with selinexor and dexamethasone for relapsed/refractory disease (4-week cycle) – Weekly Weeks 1 to 8 (eight doses; cycles 1 and 2) – Every two weeks Weeks 9 to 24 (eight doses; cycles 3 to 6) – Every four weeks Week 25 onwards (cycle 7 and beyond) *Treat until disease progression or unacceptable toxicity.*
	<u>Combination therapy with carfilzomib and dexamethasone for relapsed/refractory disease (4-week cycle):</u> – Weekly Weeks 1 to 8 (eight doses; cycles 1 to 2) – Every two weeks Weeks 9 to 24 (eight doses; cycles 3 to 6) – Every four weeks Week 25 onwards (cycle 7 and beyond) *Treat until disease progression or unacceptable toxicity.*
	<u>Combination therapy with bortezomib and dexamethasone for relapsed/refractory disease (3-week cycle):</u> – Weekly Weeks 1 to 9 (nine doses; cycles 1 to 3) – Every three weeks Weeks 10 to 24 (five doses; cycles 4 to 8) – Every four weeks Week 25 onwards (cycle 9 and beyond) *Treat until disease progression or unacceptable toxicity.*
Systemic Light Chain Amyloidosis	<u>Newly diagnosed disease in combination therapy with bortezomib, cyclophosphamide and dexamethasone (D-VCd) (4-week cycle):</u> – Weekly Weeks 1 to 8 (eight doses; cycles 1 and 2) – Every two weeks Weeks 9 to 24 (eight doses; cycles 3 to 6) – Every four weeks Week 25 onwards (cycle 7 and beyond) *Treat until disease progression or unacceptable toxicity or a maximum of 2 years*
	<u>Single agent therapy for relapsed/refractory disease (4-week cycle):</u> – Weekly Weeks 1 to 8 (eight doses; cycles 1 and 2) – Every two weeks Weeks 9 to 24 (eight doses; cycles 3 to 6) – Every four weeks Week 25 onwards (cycle 7 and beyond) *Treat until disease progression or unacceptable toxicity*

**Keep refrigerated. Darzalex Faspro should only be administered subcutaneously by a healthcare professional. Do NOT administer Darzalex Faspro intravenously.*
Note: Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting Darzalex and continue for 3 months following treatment. Refer to the PI for other pre- and post-medication therapies.

VI. Billing Code/Availability Information

HCPCS Code:

- J9144 - Injection, daratumumab, 10 mg and hyaluronidase-fihj; 1 billable unit=10 mg

NDC:

- Darzalex Faspro 1,800 mg of daratumumab and 30,000 units of hyaluronidase per 15 mL single-dose vial: 57894-0503-xx

VII. References (STANDARD)

1. Darzalex Faspro [package insert]. Horsham, PA; Janssen Biotech, Inc; July 2021. Accessed August 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for daratumumab and hyaluronidase-fihj. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed August 2021.
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18. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Systemic Light Chain Amyloidosis Version 1.2022. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed August 2021.
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VIII. References (ENHANCED)

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2e. Kastritis E, Palladini G, Minnema MC, et al. Subcutaneous daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (CyborD) in patients with newly diagnosed light chain (AL) amyloidosis: primary results from the phase 3 Andromeda study. Abstract LB2604. Presented as part of EHA25 Virtual, June 14, 2020.

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5e. Magellan Health, Magellan Rx Management. Darzalex Faspro Clinical Literature Review Analysis. Last updated August 2021. Accessed August 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma, in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse
E85.81	Light chain (AL) amyloidosis
E85.89	Other amyloidosis
E85.9	Amyloidosis, unspecified
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-

database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; VGPR = very good partial response; CHR = complete hematologic response

Multiple Myeloma

Newly Diagnosed Disease – ineligible for autologous stem cell transplant							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab SQ + bortezomib + melphalan + prednisone (D-VMP)	2A	Yes	Phase 2 (PLEIADES), multi-cohort, open-label	N/A	ORR	Newly diagnosed MM, ineligible for transplant	• Subcutaneous daratumumab in combination with standard-of-care regimens demonstrated comparable clinical activity (ORR) and safety to corresponding intravenous daratumumab regimens with substantially shorter durations of administration.
Daratumumab + lenalidomide + dexamethasone (DRd)	1 preferred	Yes	Phase 3 randomized, open-label, multi-center	Lenalidomide + dexamethasone (Rd)	PFS	Newly diagnosed MM ineligible for ASCT	• Among patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation, the risk of disease progression or death was significantly lower among those who received daratumumab plus lenalidomide and dexamethasone than among those who received lenalidomide and dexamethasone alone.
Bortezomib + lenalidomide + dexamethasone (VRd)	1 preferred	Yes	Phase 3 (SWOG S0777), randomized, open-label	Lenalidomide + dexamethasone (Rd)	PFS	Newly diagnosed, not planned for immediate ASCT	• Addition of bortezomib to Rd resulted in significantly improved PFS and OS.
Daratumumab + cyclophosphamide + bortezomib + dexamethasone (D-VCd)	2A certain circum-stances	No	Phase 2 (LYRA), multi-center, single-arm	N/A	ORR	Newly diagnosed (transplant eligible and ineligible) and relapsed disease	• In newly diagnosed patients, very good partial response or better (≥VGPR) and overall response rates after 4 induction cycles were 44% (primary endpoint) and 79%, respectively, and 56% and 81% at end of induction. Similar response rates were observed in the small number of patients with relapsed multiple myeloma.

Newly diagnosed disease in patients eligible for autologous stem cell transplant							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab + lenalidomide + bortezomib + dexamethasone (DRVd)	2A other	No	Phase 2 (GRIFFIN), randomized	Bortezomib + lenalidomide + dexamethasone (RVd)	sCR	Newly diagnosed transplant-eligible	• Daratumumab with RVd induction and consolidation improved depth of response (sCR) compared to RVd alone in patients with transplant-eligible NDMM, with no new safety concerns.
Bortezomib + lenalidomide + dexamethasone (VRd)	1 preferred	Yes	Phase 3 (SWOG S0777), randomized, open-label	Lenalidomide + dexamethasone (Rd)	PFS	Newly diagnosed	• Addition of bortezomib to Rd resulted in significantly improved PFS and OS.
Relapsed or Refractory Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab SQ + lenalidomide + dexamethasone (D-Rd)	2A	Yes	Phase 2 (PLEIADES), multi-cohort, open-label	N/A	ORR	Relapsed or refractory disease	• Subcutaneous daratumumab in combination with standard-of-care regimens demonstrated comparable clinical activity (ORR) and safety to corresponding intravenous daratumumab regimens with substantially shorter durations of administration.
Daratumumab SQ	2A	Yes	Phase 3 (COLUMBA), open-label, randomized, non-inferiority study	Daratumumab IV	ORR Maximum trough concentration (C_{trough}; cycle 3, day 1)	After ≥ 3 previous lines of therapy, including a proteasome inhibitor and immunomodulatory drug, or were double refractory to both a proteasome inhibitor and immunomodulatory drug	• Subcutaneous daratumumab was non-inferior to intravenous daratumumab in terms of efficacy and pharmacokinetics and had a comparable safety profile in patients with relapsed or refractory multiple myeloma.

Daratumumab SQ + pomalidomide (P) + dexamethasone (d)	2A	Yes after at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor	Phase 3 (APOLLO), open-label, randomized	Pomalidomide + dexamethasone (Pd)	PFS	Relapsed or refractory MM after at least one prior lie of therapy including lenalidomide and a proteasome inhibitor	• Among patients with relapsed or refractory multiple myeloma, daratumumab plus pomalidomide and dexamethasone reduced the risk of disease progression or death versus pomalidomide and dexamethasone alone.

Systemic Light Chain Amyloidosis

Newly Diagnosed Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab hyaluronidase-fihj + CyBorD (bortezomib + cyclophosphamide + dexamethasone)	1 preferred	Yes	Phase 3 (ANDROMEDA), open-label, randomized, active-controlled	CyBorD	CHR	Newly diagnosed disease	• The addition of daratumumab to CyBorD was superior to CyBorD alone, resulting in deeper and more rapid hematologic responses and improved clinical outcomes with an acceptable safety profile.
Relapsed or Refractory Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab	2A	No	Phase 2	N/A	Safety	Relapsed or refractory disease	• In a single-center phase 2 trial that enrolled 22 patients with a median of two prior therapies, hematologic very good partial response (VGPR) or better was seen in 86% of patients with a median time to first response of four weeks.
Daratumumab	2A	No	Phase 2, single-arm, multi-center	N/A	ORR	Relapsed or refractory disease	• In a multicenter phase 2 trial that enrolled 40 patients with a median of three prior therapies, hematologic VGPR or better was seen in 48 percent with a median time to first response of one week.