Darzalex® (daratumumab)
(Intravenous)

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I. Length of Authorization [1,6]

- Use for newly diagnosed multiple myeloma in combination with bortezomib, thalidomide, and dexamethasone may not be renewed.
- For use in all other multiple myeloma treatment settings and in systemic light chain amyloidosis, coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

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

- Darzalex 100 mg single-dose vial for injection: 3 vials per dose
  - *Weekly Weeks 1 to 6, then every three weeks Weeks 7-54, then every four weeks Week 55 onwards* ***OR***
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards* ***OR***
  - *Weekly Weeks 1 to 9, then every three weeks Weeks 10-24, then every four weeks Week 25 onwards)* ***OR***
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-16 for induction therapy, then every two weeks Weeks 1 to 8 for consolidation therapy*
- Darzalex 400mg single dose vial for injection: 4 vials per dose
  - *Weekly Weeks 1 to 6, then every three weeks Weeks 7-54, then every four weeks Week 55 onwards* ***OR***
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards* ***OR***
  - *Weekly Weeks 1 to 9, then every three weeks Weeks 10-24, then every four weeks Week 25 onwards)* ***OR***
  - *Weekly Weeks 1 to 8, then every two weeks Weeks 9-16 for induction therapy, then every two weeks Weeks 1 to 8 for consolidation therapy*

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

- Bortezomib/Melphalan/Prednisone Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 6, then every three weeks Weeks 7-54, then every four weeks Week 55 onwards)

- Lenalidomide/Pomalidomide/Carfilzomib Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards)
- Bortezomib Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 9, then every three weeks Weeks 10-24, then every four weeks Week 25 onwards)
- Monotherapy Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 8, then every two weeks Weeks 9-24, then every four weeks Week 25 onwards)
- Bortezomib/Thalidomide Regimen
  - 180 billable units per dose
    (Weekly Weeks 1 to 8, then every two weeks Weeks 9-16 for induction therapy, then every two weeks Weeks 1 to 8 for consolidation therapy)

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is 18 years or older; **AND**

Universal Criteria

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

Multiple Myeloma † Φ [1,2,3,4,5,6,7,8,9,10,27,28,29]

- 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**
- Used in the treatment of newly diagnosed disease in patients who are eligible for autologous stem cell transplant (ASCT) in combination with bortezomib, thalidomide, and dexamethasone (VTd); **OR**
- Used for disease relapse after 6 months following primary induction therapy with the same regimen in combination with lenalidomide and dexamethasone for non-transplant candidates; **OR**
- Used as subsequent therapy in combination with dexamethasone and either lenalidomide, bortezomib, or carfilzomib; **OR**
- Used in combination with pomalidomide and dexamethasone after at least two prior therapies including an immunomodulatory agent (e.g., lenalidomide, pomalidomide, etc.) and a proteasome inhibitor (bortezomib, carfilzomib, etc.); **OR**
- Used as single agent therapy; **AND**
  - Patient 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

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

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

IV. Renewal Criteria [1,2,3]

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: severe infusion reactions including anaphylactic reactions, neutropenia, thrombocytopenia, etc.; **AND**
- Use for newly diagnosed disease in combination with bortezomib, thalidomide, and dexamethasone after 24 weeks of induction/consolidation therapy may not be renewed

V. Dosage/Administration [1,3,5,12]

Indication	Dose
Multiple Myeloma	<u>Newly diagnosed disease in patients ineligible for ASCT in combination with bortezomib, melphalan and prednisone</u> • 16 mg/kg body weight given as an intravenous infusion in a 6 week cycle: – 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 until disease progression (cycle 10 and beyond)
	<u>Newly diagnosed disease in patients ineligible for ASCT in combination with bortezomib, thalidomide and dexamethasone</u> • 16 mg/kg body weight given as an intravenous infusion in a 4 week cycle: • 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>Treatment as one of the following:</u> • Monotherapy for patients with relapsed/refractory multiple myeloma • Combination therapy with lenalidomide and low-dose dexamethasone for newly diagnosed patients ineligible for ASCT • Combination therapy with lenalidomide, pomalidomide, or carfilzomib and low-dose dexamethasone in patients with relapsed/refractory disease

	• 16 mg/kg body weight given as an intravenous infusion in a 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 until disease progression (cycle 7 and beyond)
	Combination therapy with bortezomib and dexamethasone for relapsed/refractory disease • 16 mg/kg body weight given as an intravenous infusion: – Weekly Weeks 1 to 9 (nine doses) – Every three weeks Weeks 10 to 24 (five doses) – Every four weeks Week 25 onwards until disease progression
**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.*	
Note: Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting Darzalex and continue for 3 months following treatment.	

VI. Billing Code/Availability Information

HCPCS Code:

- J9145 - Injection, daratumumab, 10 mg; 1 billable unit = 10 mg

NDC(s):

- Darzalex 100 mg/5 mL single-dose vial: 57894-0502-xx
- Darzalex 400 mg/20 mL single-dose vial: 57894-0502-xx

VII. References

1. Darzalex [package insert]. Horsham, PA; Janssen Biotech, Inc; April 2020. Accessed June 2020.
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14. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Systemic Light Chain Amyloidosis Version 1.2020. National Comprehensive Cancer Network, 2020. 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 NCCN Guidelines, go online to NCCN.org. Accessed June 2020.
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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
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):

Jurisdiction(s): 15	**NCD/LCD/LCA Document (s):** A57243
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A57243&bc=gAAAAAAAAAAA	

Jurisdiction(s): J & M	**NCD/LCD/LCA Document (s):** A56141
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAA	

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

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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; ASCT = autologous stem-cell transplant; TEE = thromboembolic events; AE = adverse event; IMiD = immunomodulatory agent; PI = proteasome inhibitor; MRD = minimal residual disease; sCR = stringent complete response (having a normal serum FLC [Free Light Chain] ratio and absence of clonal cells in bone marrow

Multiple Myeloma

Newly diagnosed disease who are ineligible for autologous stem cell transplant							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab + bortezomib + melphalan + prednisone (DVMP)	1 (other recommended regimen)	Yes	Phase 3 (ALCYONE), randomized	Bortezomib + melphalan + prednisone (VMP)	PFS	Newly diagnosed, ineligible for transplant	• DVMP resulted in a lower risk of disease progression or death compared to VMP
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	• Addition of bortezomib to Rd resulted in significantly improved PFS and OS

						immediate ASCT	
Lenalidomide + high-dose dexamethasone (Rd)	None for high-dose dexameth-asone	Yes	Phase 3 (SWOG S0232), randomized, double-blind, placebo-controlled	High-dose dexamethasone (Dex)	PFS	Newly diagnosed	• Lenalidomide plus dexamethasone is superior to dexamethasone alone as first-line therapy in terms of response rates and PFS • Higher incidence of TEE occurred with Rd despite aspirin prophylaxis
Lenalidomide + low-dose dexamethasone	1 preferred	Yes	Phase 3 (E4A03), randomized, open-label	Lenalidomide + high-dose dexamethasone	ORR	Newly diagnosed prior to ASCT	• Lenalidomide plus low-dose dexamethasone is associated with better short-term OS and lower toxicity compared to lenalidomide plus high-dose dexamethasone
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	1 preferred	Yes	Phase 2	N/A	---------	Untreated transplant ineligible	• CyBorD demonstrated an ORR of 95%
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	1 preferred	Yes	Phase 2 (EVOLUTION), randomized, multicenter	Bortezomib + lenalidomide + dexamethasone (VRd) Bortezomib + lenalidomide + cyclophosphamide + dexamethasone (VDCR) CyBorD-modified	ORR	Untreated regardless of transplant eligibility	• No substantial difference was noted in VDCR over 3-drug combinations
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 + bortezomib + thalidomide + dexamethasone (DVTd)	2A	Yes	Phase 3 (CASSIOPEIA), open-label, randomized, active-controlled	Bortezomib + thalidomide + dexamethasone (VTd)	sCR	Previously untreated disease	• DVTd improved response in transplant-eligible patients with newly diagnosed multiple myeloma
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
Bortezomib + cyclophosphamide + dexamethasone (CyBorD)	1 preferred	Yes	Phase 2	N/A	---------	Untreated transplant ineligible	• CyBorD demonstrated an ORR of 95%
Bortezomib + doxorubicin + dexamethasone (PAD) followed by bortezomib maintenance	2A	No	Phase 3 (HOVON-65/GMMG-HD4), open-label, randomized	Vincristine + doxorubicin + dexamethasone (VAD) followed by thalidomide maintenance	PFS	Newly diagnosed stage II or III, eligible for transplant	• Bortezomib containing regimen during induction and maintenance treatment resulted in a better response, PFS, and OS
Previously Treated Multiple Myeloma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab + bortezomib + dexamethasone (DVd)	1 preferred	Yes after at least one prior therapy	Phase 3 (CASTOR), randomized	Bortezomib + dexamethasone (Vd)	PFS	Second-line and later	• Addition of daratumumab to Vd significantly improved PFS and ORR compared to Vd alone

Daratumumab + lenalidomide + dexamethasone (DRd)	1 preferred	Yes after at least one prior therapy	Phase 3 (POLLUX), randomized	Lenalidomide + dexamethasone (Rd)	PFS	After 1 or more prior therapies	• Addition of daratumumab to Rd significantly lengthened PFS
Daratumumab + carfilzomib + dexamethasone (KdD)	2A	No	Phase 3 (CANDOR), randomized, - open-label	Carfilzomib + dexamethasone (Kd)	PFS	1-3 prior therapies	• The KdD regimen was found to reduce the risk of progression or death by 37% compared to Kd alone
Ixazomib + lenalidomide + dexamethasone	1 preferred	Yes after at least one prior therapy	Phase 3 (TOURMALINE MM1), double-blind, randomized, placebo-controlled	Lenalidomide + dexamethasone (Rd)	PFS	After 1-3 prior therapies	• Addition of ixazomib to Rd significantly increased PFS
Elotuzumab + lenalidomide + dexamethasone (ELd)	1 preferred	Yes in adults who have received 1-3 prior treatments	Phase 3 (ELOQUENT-2), randomized 3-year follow-up	Lenalidomide + dexamethasone (Ld)	PFS ORR	After 1-3 prior therapies	• Patients with relapsed or refractory multiple myeloma who received a combination of elotuzumab, lenalidomide, and dexamethasone had a significant relative reduction of 30% in the risk of disease progression or death
Carfilzomib + lenalidomide + dexamethasone (CLd)	1 preferred	Yes in patients who have received 1-3 prior treatments	Phase 3 (ASPIRE), randomized, multicenter Final analysis of OS	Lenalidomide + dexamethasone (Ld)	PFS	After 1-3 prior therapies	• CLd combination resulted in a significantly improved PFS and OS (improved survival by 7.9 months)

Carfilzomib (twice weekly) + dexamethasone (Cd)	1 preferred	Yes in patients who have received 1-3 prior treatments	Phase 3 (ENDEAVOR), randomized, open-label, multicenter Interim overall survival analysis	Bortezomib + dexamethasone (Bd)	PFS	After 1-3 prior therapies	• Carfilzomib with dexamethasone demonstrated a 2-fold improvement in PFS and a significant increase in OS compared to bortezomib with dexamethasone.
Daratumumab	2A	Yes after at least 3 prior therapies including lenalidomide and a proteasome inhibitor or who are double-refractory to a PI and IMiD	Phase 2	N/A	ORR	After 3 lines of therapy including an IMiD and PI or double refractory to PI and IMiD	• Daratumumab monotherapy demonstrated to be effective in heavily pretreated and refractory patients based on an ORR of 292%
Daratumumab + pomalidomide + dexamethasone (DPd)	2A	Yes after at least 2 prior therapies including lenalidomide and a proteasome inhibitor	Phase 1b (MMY1001), open-label, multicenter	N/A	Safety	After at least 2 prior lines of therapy, including lenalidomide and bortezomib (excluding daratumumab or pomalidomide)	• DPd demonstrated an ORR of 60% • Increased neutropenia was observed with DPd regimen compared to that seen in individual therapies

Systemic Light Chain Amyloidosis

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daratumumab	2A	No	Retrospective analysis	N/A	-----	Relapsed or refractory disease	• Daratumumab is effective with a hematologic response rate of 76% in heavily pretreated systemic light chain amyloidosis patients.