Darzalex® (daratumumab)
(Intravenous)

-E-

Document Number: OHSU HEALTHSERVICES-0383

Date Reviewed: 07/2025

Date of Origin: 01/07/2019

Dates Approved: 01/2019, 04/2019, 07/2019, 10/2019, 11/2019, 01/2020, 04/2020, 07/2020, 10/2020, 01/2021, 05/2021, 07/2021, 10/2021, 01/2022, 04/2022, 07/2022, 10/2022, 01/2023, 04/2023, 07/2023, 10/2023, 01/2024, 04/2024, 06/2024, 09/2024, 12/03/2024, 03/04/2025, 06/05/2025, 06/24/2025, 09/04/2025

I. Length of Authorization [1,16,17,19,21,24,29,30]

- Initial: Prior authorization validity will be provided initially for 6 months.
- Renewal: Prior authorization validity may be renewed every 6 months thereafter, unless otherwise specified.
  - Prior authorization validity may NOT be renewed for the following:
    - ❖ Newly diagnosed multiple myeloma in combination with bortezomib, thalidomide, and dexamethasone.
    - ❖ Pediatric Acute Lymphoblastic Leukemia.
  - Prior authorization validity may be renewed for up to a maximum of 2 years of therapy for the following:
    - ❖ Newly diagnosed multiple myeloma in combination with bortezomib, lenalidomide and dexamethasone as maintenance therapy *(for patients eligible for ASCT)*.
    - ❖ Maintenance therapy for multiple myeloma in combination with lenalidomide or as a single agent.
    - ❖ Newly diagnosed OR repeat of initial therapy if relapse-free for several years, systemic light chain amyloidosis in combination with bortezomib, cyclophosphamide, and dexamethasone.
  - Prior authorization validity may be renewed for up to a maximum of 32 weeks of therapy for the following:
    - ❖ Newly diagnosed multiple myeloma in combination with carfilzomib, lenalidomide, and dexamethasone.
  - Prior authorization validity may be renewed for up to a maximum of 80 weeks of therapy for the following:

- ❖ Newly diagnosed OR relapsed or refractory/progressive multiple myeloma in combination with cyclophosphamide, bortezomib and dexamethasone *(32 weeks of induction therapy and 48 weeks of maintenance therapy).*

– Prior authorization validity may be renewed for up to a maximum of 36 months of therapy for the following:

- ❖ Monotherapy for primary treatment of high-risk smoldering myeloma (asymptomatic).

II. Dosing Limits

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

- **Multiple Myeloma:** 180 billable units every 7 days for 12 doses, every 14 days for 8 doses, every 21 days for 16 doses, then every 28 days
- **Systemic Light Chain Amyloidosis:** 180 billable units every 7 days for 8 doses, every 14 days for 8 doses, then every 28 days
- **Pediatric ALL:** 180 billable units every 7 days for 8 doses

III. Initial Approval Criteria [1]

Prior authorization validity is provided in the following conditions:

- Patient is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria

- Therapy will not be used in combination with other anti-CD38 therapies; **AND**

Multiple Myeloma † ‡ Φ [1-11,13,14,16-19,22,23,15e-17e]

- 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**
  - Bortezomib, lenalidomide, 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**

- Carfilzomib, lenalidomide, and dexamethasone; **AND**

  - Use of daratumumab in combination with carfilzomib, lenalidomide, and dexamethasone will be restricted to patients with a contraindication or intolerance to one of the following regimens:
    - Bortezomib/lenalidomide/dexamethasone
    - Daratumumab/lenalidomide/bortezomib/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 for relapsed or refractory/progressive disease in combination with dexamethasone and ONE of the following:
  - Lenalidomide; **OR**
  - Bortezomib; **OR**
  - Carfilzomib; **OR**
  - Carfilzomib and pomalidomide; **OR**
  - Cyclophosphamide and bortezomib; **OR**
  - Selinexor; **OR**
  - Venetoclax *(for patients with t(11:14) ONLY)*; **OR**
- Used in combination with pomalidomide and dexamethasone after prior therapy with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, etc.); **OR**
- Used as single agent therapy; **AND**
  - Patient received 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**
- Used as maintenance therapy for symptomatic disease in transplant candidates; **AND**
  - Used as a single agent or in combination with lenalidomide; **AND**
    - Used after response to primary myeloma therapy; **OR**
    - Used for response or stable disease following an autologous hematopoietic cell transplant (HCT); **OR**
    - Used for response or stable disease following a tandem autologous or allogeneic HCT for high risk patients; **OR**

– Used as primary treatment for high-risk smoldering myeloma (asymptomatic) as a single agent

Systemic Light Chain Amyloidosis ‡ [2,12,15,25-27]

- Used for newly diagnosed disease OR as a repeat of initial therapy if relapse-free for several years; **AND**
  - Used in combination with bortezomib, cyclophosphamide, and dexamethasone (D-VCd); **OR**
- Used for relapsed or refractory disease; **AND**
  - Used as a single agent

Pediatric Acute Lymphoblastic Leukemia (ALL) ‡ [2, 20,21]

- Patient age ≥ 1 and ≤ 30 years; **AND**
- Patient has relapsed/refractory T-cell ALL; **AND**
- Used in combination with vincristine, pegaspargase/calaspargase, doxorubicin, and prednisone/dexamethasone

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.

Enhanced Oncology Value (EOV) Program – Redacted indications
Uses not listed above have inadequate data to support efficacy and are excluded from prior authorization validity. Other treatment options including, but are not limited to, the following may be appropriate: radiation therapy, surgery, traditional chemotherapy (e.g., platinum, taxane), compassionate use/expanded access programs, clinical trials, supportive care, integrative and complementary therapies.

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

IV. Renewal Criteria [1]

Prior authorization validity can be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Duration of authorization has not been exceeded (*refer to Section I*); **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion-related reactions including anaphylactic reactions, neutropenia, thrombocytopenia, etc.

V. Dosage/Administration [1,12,16-19,22-24,27,29,30-36]

Indication	Dose
Multiple Myeloma	<u>Newly diagnosed disease in patients eligible 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>Newly diagnosed disease in combination with bortezomib, lenalidomide and dexamethasone</u> ▪ 16 mg/kg body weight given as an intravenous infusion as follows: <u>For patients *eligible* for ASCT:</u> ▪ Induction – **3 week cycle** – Weekly Weeks 1 to 12 (twelve doses; cycles 1 to 4) ▪ Consolidation – *(after ASCT)* – **3 week cycle** – Every 3 weeks Weeks 13 to 18 (two doses; cycles 5 and 6) ▪ Maintenance – **4 week cycle** – Every 4 or 8 weeks Weeks 1 to 104 for a maximum of 2 years of maintenance treatment <u>For patients *ineligible* for ASCT:</u> ▪ Induction – **3 week cycle** – Weekly Weeks 1 to 6 (six doses; cycles 1 and 2) ▪ Consolidation – **3 week cycle** – Every 3 weeks Weeks 7 to 24 (six doses; cycles 3 to 8) ▪ Maintenance – **4 week cycle** – Every 4 weeks Weeks 25 (cycle 9) and beyond *treat until disease progression or unacceptable toxicity*
	<u>Newly diagnosed disease in patients eligible for ASCT in combination with carfilzomib, lenalidomide, and dexamethasone</u> ▪ 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 to 32 (two doses; cycles 7 and 8)
	<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 (cycle 10 and beyond) *Treat until disease progression or unacceptable toxicity*
	<u>Newly diagnosed OR relapsed or refractory/progressive disease in combination with cyclophosphamide, bortezomib and dexamethasone</u> Induction ▪ 8 mg/kg body weight given as an intravenous infusion on days 1 and 2 (Week 1; total 2 doses) ▪ Followed by 16 mg/kg body weight given as an intravenous infusion in a 4 week cycle: – Weekly Weeks 2 to 8 (seven 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)* ▪ 16 mg/kg body weight given as an intravenous infusion every 4 weeks for up to 12 cycles (48 weeks)
	<u>Treatment as one of the following:</u> • Monotherapy for patients with relapsed/refractory multiple myeloma • Combination therapy with lenalidomide and dexamethasone for newly diagnosed patients ineligible for ASCT • Combination therapy with lenalidomide, pomalidomide, or selinexor AND dexamethasone in patients with relapsed or refractory/progressive disease • Combination therapy with carfilzomib, pomalidomide, and dexamethasone in patients with relapsed or refractory/progressive disease • Combination therapy with venetoclax and dexamethasone for relapsed or refractory/progressive t(11;14) disease • Monotherapy as primary treatment for high-risk smoldering myeloma (asymptomatic)^ ▪ 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 (cycle 7 and beyond) *treat until disease progression or unacceptable toxicity* *^For high-risk smoldering myeloma (asymptomatic): Treat until disease progression or unacceptable toxicity for a maximum of 36 months*
	<u>Combination therapy with carfilzomib and dexamethasone for relapsed or refractory/progressive disease</u> ▪ 8 mg/kg body weight given as an intravenous infusion on days 1 and 2 (Week 1; total 2 doses) ▪ Followed by 16 mg/kg body weight given as an intravenous infusion in a 4 week cycle: – Weekly Weeks 2 to 8 (seven 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*

	Combination therapy with bortezomib and dexamethasone for relapsed or refractory/progressive disease ▪ 16 mg/kg body weight given as an intravenous infusion in a 3 week cycle: – 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*
	Maintenance treatment for transplant candidates ▪ Combination with lenalidomide: 16 mg/kg body weight given as an intravenous infusion every 4 or 8 weeks until disease progression or unacceptable toxicity. For a maximum of 2 years of maintenance treatment. ▪ Single agent: 16 mg/kg body weight given as an intravenous infusion every 8 weeks until disease progression or unacceptable toxicity. For a maximum of 2 years of maintenance treatment.
Pediatric ALL	▪ 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)
Systemic Light Chain Amyloidosis	Combination with bortezomib, cyclophosphamide, and dexamethasone for newly diagnosed disease OR repeat of initial therapy if relapse-free for several years ▪ 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 and onwards (cycle 7 and beyond) *Treat until disease progression or unacceptable toxicity or a maximum of 2 years*
	▪ Single agent therapy for 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 and onwards (cycle 7 and beyond) *Treat until disease progression or unacceptable toxicity*
**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 100 mg/5mL single-dose vial: 57894-0505-xx
- Darzalex 400 mg/20 mL single-dose vial: 57894-0502-xx
- Darzalex 400 mg/20 mL single-dose vial: 57894-0505-xx

VII. References (STANDARD)

1. Darzalex [package insert]. Horsham, PA; Janssen Biotech, Inc; April 2025. Accessed July 2025.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for daratumumab. National Comprehensive Cancer Network, 2025. 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 July 2025.
3. Chari A, Martinez-Lopez J, Mateos MV, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. Blood. 2019 Aug 1;134(5):421-431. doi: 10.1182/blood.2019000722. Epub 2019 May 21.
4. Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019 May 30;380(22):2104-2115. doi: 10.1056/NEJMoa1817249.
5. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018 Feb 8;378(6):518-528. doi: 10.1056/NEJMoa1714678. Epub 2017 Dec 12.
6. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019 Jul 6;394(10192):29-38. doi: 10.1016/S0140-6736(19)31240-1. Epub 2019 Jun 3.
7. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Oct 6;375(14):1319-1331.
8. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Aug 25;375(8):754-66. doi: 10.1056/NEJMoa1606038.
9. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood. 2017 Aug 24;130(8):974-981. doi: 10.1182/blood-2017-05-785246. Epub 2017 Jun 21.
10. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016 Apr 9;387(10027):1551-1560. doi: 10.1016/S0140-6736(15)01120-4. Epub 2016 Jan 7.

11. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med. 2015 Sep 24;373(13):1207-19. doi: 10.1056/NEJMoa1506348. Epub 2015 Aug 26.
12. Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood. 2017 Aug 17;130(7):900-902. doi: 10.1182/blood-2017-01-763599. Epub 2017 Jun 14.
13. Dimopoulous M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet. 2020 July 18;396(10245):186-197.
14. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Multiple Myeloma Version 2.2026. National Comprehensive Cancer Network, 2025. 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 July 2025.
15. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Systemic Light Chain Amyloidosis Version 1.2026. National Comprehensive Cancer Network, 2025. 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 July 2025.
16. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020 Aug 20;136(8):936-945.
17. Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study. Br J Haematol. 2019 May;185(3):492-502.
18. Gasparetto C, Lentzsch S, Schiller G, et al. Selinexor, daratumumab, and dexamethasone in patients with relapsed or refractory multiple myeloma. eJHaem. 2020;1-10. https://doi.org/10.1002/jha2.122.
19. Landgren O, Hultcrantz M, Diamond B, et al. Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma: The MANHATTAN Nonrandomized Clinical Trial. JAMA Oncol. 2021 Jun 1;7(6):862-868. doi: 10.1001/jamaoncol.2021.0611.
20. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia Version 3.2025. National Comprehensive Cancer Network, 2025. 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 July 2025.

21. Hogan LE, Bhatla T, Teachey DT, et al. Efficacy and safety of daratumumab (DARA) in pediatric and young adult patients (pts) with relapsed/refractory T-cell acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL): Results from the phase 2 DELPHINUS study. Journal of Clinical Oncology 2022;40:10001-10001.
22. Moreau P, Hulin C, Perrot A, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:1378-1390.
23. Bahlis NJ, Baz R, Harrison SJ, et al. Phase I Study of Venetoclax Plus Daratumumab and Dexamethasone, With or Without Bortezomib, in Patients With Relapsed or Refractory Multiple Myeloma With and Without t(11;14). J Clin Oncol. 2021 Nov 10;39(32):3602-3612. doi: 10.1200/JCO.21.00443. Epub 2021 Aug 13. PMID: 34388020; PMCID: PMC8577687.
24. Laubach JP, Kaufman JL, Sborov DW, et al. Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients (Pts) with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin after 24 Months of Maintenance. Blood 2021; 138 (Supplement 1): 79. doi: https://doi.org/10.1182/blood-2021-149024.
25. Sanchorawala V, Boccadoro M, Gertz M, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. Amyloid 2022;29:1-7.
26. Wechalekar AD, Cibeira MT, Gibbs SD, et al. Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group. Amyloid 2023;30:3-17.
27. Kastritis E, Minnema MC, Dimopoulos MA, et al. Daratumumab Monotherapy in Previously Untreated High-Risk Patients with Stage 3B Light Chain (AL) Amyloidosis: A Phase II Multicenter Study By European Myeloma Network (EMN). Blood 2019; 134 (Supplement_1): 1868. doi: https://doi.org/10.1182/blood-2019-126524.
28. Sonneveld, P, Zweegman, S, Cavo, M, et al. Carfilzomib, Pomalidomide, and Dexamethasone As Second-line Therapy for Lenalidomide-refractory Multiple Myeloma. Hemasphere. 2022 Sep 30;6(10):e786.
29. Palladini, G, Kastritis E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood. 2020; 136:71-80.
30. Chakraborty, R, Rosenbaum C, Kaur G, et al. First report of outcomes in patients with stage IIIb AL amyloidosis treated with Dara-VCD frontline therapy. Br J Haematol. 2023;201:913-916.
31. Kawano Y, Hata H, Takashio S, et al. Daratumumab, lenalidomide and dexamethasone in newly diagnosed systemic light chain amyloidosis patients associated with multiple myeloma. Br J Haematol. 2022;198:e38-e41.

32. Dispenzieri, A. POEMS Syndrome: 2019 Update on diagnosis, risk-stratifications, and management. Am J Hematol. 2019;94:812-827.
33. Derman BA, Zonder J, Reece D, et al. Phase 1/2 study of carfilzomib, pomalidomide, and dexamethasone with and without daratumumab in relapsed multiple myeloma. Blood Adv. 2023 Oct 10;7(19):5703-5712.
34. Lebel E, Kastritis E, Palladini G, et al. Venetoclax in relapse/refractory AL amyloidosis-a multicenter international retrospective real-world study. Cancers (Basel) 2023;15:1710. https://pubmed.ncbi.nlm.nih.gov/36980596/
35. Usmani, S.Z., Facon, T., Hungria, V. *et al.* Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nat Med* 31, 1195–1202 (2025). https://doi.org/10.1038/s41591-024-03485-7.
36. Meletios-Athanasios D, Voorhees PM, Schjesvold F, *et al.* Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients with High-Risk Smoldering Multiple Myeloma: Primary Results of the Aquila Study. *Blood* 2024; 144 (Supplement 1): 773. https://doi.org/10.1182/blood-2024-201057.

VIII. References (ENHANCED)

1e. Zonder JA, Crowley J, Hussein MA, et al. Superiority of Lenalidomide (Len) Plus High-Dose Dexamethasone (HD) Compared to HD Alone as Treatment of Newly-Diagnosed Multiple Myeloma (NDMM): Results of the Randomized, Double-Blinded, Placebo-Controlled SWOG Trial S0232. Blood, 110(11), 77.
2e. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2009;11(1):29-37.
3e. Zepeda VHJ, Duggan P, Neri PE, Bahlis NJ. Cyclophosphamide, Bortezomib and Dexamethasone (CyBORD) Is a Feasible and Active Regimen for Non-Transplant Eligible Multiple Myeloma Patients. Blood, 124(21), 5751.
4e. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood, 119(19), 4375-4382.
5e. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016; 374:1621-1634.
6e. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med 2015; 373:621-631.
7e. Lonial S, Richardson PG, Mateos MV, et al. ELOQUENT-2 update: Phase III study of elotuzumab plus lenalidomide/dexamethasone (ELd) vs Ld in relapsed/refractory multiple myeloma

(RRMM)—Identifying responders by subset analysis. Journal of Clinical Oncology 2016 34:15_suppl, 8037-8037.

8e. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. N Engl J Med 2015; 372:142-152.

9e. Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. Journal of Clinical Oncology 2018 36:8, 728-734.

10e. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016 Jan;17(1):27-38.

11e. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol. 2017 Oct;18(10):1327-1337.

12e. Zepeda VHJ, Duggan P, Neri PE, Bahlis NJ. Cyclophosphamide, Bortezomib and Dexamethasone (CyBORD) Is a Feasible and Active Regimen for Non-Transplant Eligible Multiple Myeloma Patients. Blood, 124(21), 5751.

13e. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389(10068):519–527. doi:10.1016/S0140-6736(16)31594-X.

14e. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012 Aug 20;30(24):2946-55. doi: 10.1200/JCO.2011.39.6820.

15e. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood. 2012;120(9):1801-1809. doi:10.1182/blood-2012-04-422683.

16e. Dytfeld D, Jasielec J, Griffith KA, et al. Carfilzomib, lenalidomide, and low-dose dexamethasone in elderly patients with newly diagnosed multiple myeloma. Haematologica. 2014;99(9):e162-e164. doi:10.3324/haematol.2014.110395.

17e. Kumar SK, Berdeja JG, Niesvizky R, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncol. 2014 Dec;15(13):1503-1512. doi: 10.1016/S1470-2045(14)71125-8.

18e. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020 Aug 20;136(8):936-945. doi: 10.1182/blood.2020005288.

19e. Kumar SK, Lacy MQ, Hayman SR, et al. Lenalidomide, cyclophosphamide and dexamethasone (CRd) for newly diagnosed multiple myeloma: results from a phase 2 trial. Am J Hematol. 2011;86(8):640-645. doi:10.1002/ajh.22053.

20e. Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 2016 May 26;127(21):2569-74. doi: 10.1182/blood-2016-01-693580.

21e. Dimopoulos MA, Grosicki S, Jędrzejczak WW, et al. All-oral ixazomib, cyclophosphamide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. Eur J Cancer. 2019 Jan;106:89-98. doi: 10.1016/j.ejca.2018.09.011.

22e. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol. 2007 Jul;138(2):176-85. doi: 10.1111/j.1365-2141.2007.06639.x.

23e. Sanchorawala V, Sarosiek S, Schulman A, et al. Safety, tolerability, and response rates of daratumumab in relapsed AL amyloidosis: results of a phase 2 study. Blood. 2020 Apr 30;135(18):1541-1547. doi: 10.1182/blood.2019004436.

24e. Roussel M, Merlini G, Chevret S, et al. A prospective phase 2 trial of daratumumab in patients with previously treated systemic light-chain amyloidosis. Blood. 2020 Apr 30;135(18):1531-1540. doi: 10.1182/blood.2019004369.

25e. Gasparetto C, Sanchorawala V, Snyder RM, et al. Use of melphalan (M)/dexamethasone (D)/bortezomib in AL amyloidosis. J Clin Oncol 2010; 28:Abstract 8024.

26e. Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood. 2011 Jul 28;118(4):865-73. doi: 10.1182/blood-2011-02-334227.

27e. Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis [published correction appears in Blood. 2020 Mar 26;135(13):1071]. Blood. 2017;130(5):597-605. doi:10.1182/blood-2017-03-771220.

28e. Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. Blood. 2012;119(23):5397-5404. doi:10.1182/blood-2012-02-413161.

29e. Richardson PG, Xie W, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. Blood. 2014 Mar 6;123(10):1461-9. doi: 10.1182/blood-2013-07-517276. Epub 2014 Jan 15. PMID: 24429336; PMCID: PMC4123434.

30e. Moreau P, Dimopoulos MA, Mikhael J, et al; IKEMA study group. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021 Jun 19;397(10292):2361-2371. doi: 10.1016/S0140-6736(21)00592-4. Epub 2021 Jun 4. PMID: 34097854.

31e. Krishnan A, Kapoor P, Palmer JM, et al. Phase I/II trial of the oral regimen ixazomib, pomalidomide, and dexamethasone in relapsed/refractory multiple myeloma. Leukemia. 2018;32(7):1567-1574. doi:10.1038/s41375-018-0038-8

32e. Richardson PG, Oriol A, Beksac M, et al; OPTIMISMM trial investigators. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019 Jun;20(6):781-794. doi: 10.1016/S1470-2045(19)30152-4. Epub 2019 May 13. PMID: 31097405.

33e. Attal M, Richardson PG, Rajkumar SV, et al; ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019 Dec 7;394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5. Epub 2019 Nov 14. Erratum in: Lancet. 2019 Dec 7;394(10214):2072. PMID: 31735560.

34e. Palladini G, Russo P, Milani P, et al. A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis. Haematologica. 2013 Mar;98(3):433-6. doi: 10.3324/haematol.2012.073593. Epub 2012 Sep 14.

35e. Sanchorawala V, Wright DG, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood. 2007 Jan 15;109(2):492-6. doi: 10.1182/blood-2006-07-030544.

36e. Joseph NS, Kaufman JL, Dhodapkar MV, et al. Long-Term Follow-Up Results of Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy and Risk-Adapted Maintenance Approach in Newly Diagnosed Multiple Myeloma. J Clin Oncol 2020;38:1928-1937. PMID: 32298201

37e. Facon T, Venner, CP. Bahlis, NJ. et al Ixazomib Plus LenalidomideDexamethasone (IRd) vs. PlaceboRd for Newly Diagnosed Multiple Myeloma (NDMM) Patients Not Eligible for Autologous Stem Cell Transplant: The Double-Blind, Placebo-Controlled, Phase 3 TOURMALINE-MM2 Trial [Abstract]. Abstract MM-347 presented at Society of Hema-to-logic Oncology (SOHO) Eighth Annual Meeting 2020. PMID: 33763699

38e. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024 Jan 25;390(4):301-313.

39e. Goldschmidt H, Mai EK, Bertsch U, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. Lancet Haematol. 2022 Nov;9(11):e810-e821.

40e. Sonneveld P, Zweegman S, Cavo M, et al. Carfilzomib, Pomalidomide, and Dexamethasone As Second-line Therapy for Lenalidomide-refractory Multiple Myeloma [published correction appears in Hemasphere. 2023 Feb 22;7(3):e856]. Hemasphere. 2022;6(10):e786. Published 2022 Sep 30. doi:10.1097/HS9.0000000000000786.

41e. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020;396(10262):1563-1573. doi:10.1016/S0140-6736(20)32292-3.

42e. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. N Engl J Med. 2018 Nov 8;379(19):1811-1822. doi: 10.1056/NEJMoa1805762.

43e. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012;119(19):4391-4394. doi:10.1182/blood-2011-11-390930.

44e. Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood 2007;110:787788.

45e. Muchtar E, Gertz MA, LaPlant BR, et al. Phase 2 trial of ixazomib, cyclophosphamide, and dexamethasone for previously untreated light chain amyloidosis. Blood Adv. 2022;6(18):5429-5435. Doi:10.1182/bloodadvances.2022007781.

46e. Facon T, Dimopoulos MA, Leleu XP, et al; IMROZ Study Group. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2024 Jun 3. doi: 10.1056/NEJMoa2400712. Epub ahead of print. PMID: 38832972.

47e. Derman BA, Zonder J, Reece D, et al. Phase 1/2 study of carfilzomib, pomalidomide, and dexamethasone with and without daratumumab in relapsed multiple myeloma. Blood Adv. 2023;7(19):5703-5712. doi:10.1182/bloodadvances.2022008866.

48e. Taenaka R, Shimokawa S, Katayama A, et al. Successful treatment with daratumumab, lenalidomide, and dexamethasone therapy followed by autologous stem cell transplantation for newly diagnosed polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes syndrome: a case report. J Med Case Rep. 2022;16(1):311. Published 2022 Aug 18. doi:10.1186/s13256-022-03552-y.

49e. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med. 2021;385(1):46-58. doi:10.1056/NEJMoa2028631.

50e. Milani P, Fazio F, Basset M, et al. High rate of profound clonal and renal responses with daratumumab treatment in heavily pre-treated patients with light chain (AL) amyloidosis and high bone marrow plasma cell infiltrate. Am J Hematol. 2020;95(8):900-905. doi:10.1002/ajh.25828.

51e. Khan, M., Stone, K., & van Rhee, F. (2018). Daratumumab for POEMS syndrome. Mayo Clinic Proceedings, 93(4), 542–544. https://doi.org/10.1016/j.mayocp.2018.02.001

52e. Landgren, CO, Ye JC, Hillengass J, et al. Randomized, multi-center study of carfilzomib, lenalidomide, and dexamethasone (KRd) with or without daratumumab (D) in patients with newly diagnosed multiple myeloma (NDMM): The ADVANCE clinical trial. J Clin Oncol. 2025;43:16_suppl, 7503-7503.

53e. Usmani SZ, Facon T, Hungria V, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. Nat Med. 2025 Apr;31(4):1195-1202.

54e. Leypoldt LB, Tichy D, Besemer B, et al. Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma. J Clin Oncol. 2024 Jan 1;42(1):26-37.

55e. Gay F, Roeloffzen W, Dimopoulos MA, et al. Results of the Phase III Randomized Iskia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone Vs Carfilzomib-Lenalidomide-Dexamethasone As Pre-Transplant Induction and Post-Transplant Consolidation in Newly Diagnosed Multiple Myeloma Patients (abstract 4). Blood (2023) 142 (Supplement 1): 4.

56e. Dimopoulos MA, Voorhees PM, Schjesvold F, et al; AQUILA Investigators. Daratumumab or Active Monitoring for High-Risk Smoldering Multiple Myeloma. N Engl J Med. 2025 May 8;392(18):1777-1788.

57e. Lebel E, Kastritis E, Palladini G, et al. Venetoclax in Relapse/Refractory AL Amyloidosis-A Multicenter International Retrospective Real-World Study. Cancers (Basel). 2023 Mar 10;15(6):1710.

58e. Prime Therapeutics Management. Darzalex IV Clinical Literature Review Analysis. Last updated July 2025. July 2025.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in 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
E85.3	Secondary systemic amyloidosis
E85.4	Organ-limited amyloidosis
E85.81	Light chain (AL) amyloidosis

ICD-10	ICD-10 Description
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)

The preceding information is intended for non-Medicare coverage determinations. 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 Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied 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
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
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