

Arzerra® (ofatumumab) (Intravenous)



Document Number: MODA-0469

Last Review Date: 05/02/2022

Date of Origin: 06/2019

Dates Reviewed: 06/2019, 05/2020, 05/2021, 05/2022

I. Length of Authorization ^{1,10}

Coverage will be provided for 6 months with renewal subject to the following:

- CLL/SLL (first-line) may be renewed to allow for a total of 12 cycles
- CLL/SLL (relapsed) may not be renewed (unless the provisions for extended treatment have been met)
- CLL/SLL (single agent subsequent therapy) may not be renewed (unless the provisions for extended treatment have been met)
- CLL/SLL (extended treatment) may be renewed to provide for a total of 2 years of therapy
- Waldenström’s Macroglobulinemia/Lymphoplasmacytic lymphoma may be renewed to allow for up to a total of 3 cycles

II. Dosing Limits

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

- Arzerra 100 mg/5 mL single-use vial: 3 vials Day 1
- Arzerra 1000 mg/50 mL single-use vial: 2 vials weekly x 7 doses, then 2 vials every 4 weeks, then 1 vial every 8 weeks for up to 24 months

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

CLL/SLL	<p><u>First-Line</u></p> <ul style="list-style-type: none"> ▪ 30 billable units on day 1 and 100 billable units on day 8; then ▪ 100 billable units every 28 days for up to 11 doses <p><u>Single agent subsequent therapy</u></p> <ul style="list-style-type: none"> ▪ 30 billable units on day 1; then ▪ 200 billable units weekly x 7 doses; then ▪ 200 billable units every 28 days x 4 doses <p><u>Relapsed</u></p> <ul style="list-style-type: none"> ▪ 30 billable units on day 1 and 100 billable units on day 8; then ▪ 100 billable units every 28 days for up to 5 doses <p><u>Extended Treatment</u></p> <ul style="list-style-type: none"> ▪ 30 billable units on day 1 and 100 billable units on day 8; then
---------	--

	<ul style="list-style-type: none"> ▪ 100 billable units 7 weeks later and every 8 weeks thereafter
Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma	<ul style="list-style-type: none"> ▪ 30 billable units on day 1; then ▪ 200 billable units every 7 days x 4 doses

III. Initial Approval Criteria ¹

Coverage is provided in the following conditions:

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

Universal Criteria ¹

- Patient has been screened for the presence of hepatitis B (HBV) infection (i.e., HBsAg and anti-HBc) prior to initiating therapy and patients with evidence of current or prior HBV infection will be monitored for HBV reactivation during treatment; **AND**
- Must not be administered concurrently with live vaccines; **AND**

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) † ⊕ ^{1-3,6,12,22,27}

- Used as first-line therapy; **AND**
 - Used in combination with chlorambucil in patients considered inappropriate for fludarabine-based therapy (*Note: only applies to CLL*); **OR**
 - Used in combination with bendamustine ‡; **AND**
 - Patient does not have del(17p)/TP53 mutation (*patients ≥ 65 years, or younger patients with or without significant comorbidities; excluding use in frail patients [i.e., creatine clearance (CrCl) <70 mL/min]*); **OR**
- Used as subsequent therapy; **AND**
 - Used as a single agent; **AND**
 - Patient is refractory to both fludarabine- and alemtuzumab-containing regimens; **OR**
 - Patient is refractory to fludarabine and unable to receive treatment with alemtuzumab as a result of bulky (> 5 cm) lymphadenopathy; **OR**
 - Used in combination with fludarabine and cyclophosphamide (FC) for relapsed disease (*Note: only applies to CLL*); **OR**
- Used as extended treatment in patients with complete or partial response after at least 2 lines of therapy for recurrent or progressive disease (*Note: only applies to CLL*); **AND**
 - Used as a single agent

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma ‡ ^{2,4,81e}

- Used as a single agent; **AND**
- Patient is intolerant to rituximab; **AND**
 - Patient has previously failed primary therapy; **OR**
 - Patient has progressive or relapsed disease

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); ◊ Orphan Drug

IV. Renewal Criteria ¹

Coverage may be renewed based on 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 or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: Hepatitis B virus reactivation/infection, progressive multifocal leukoencephalopathy, severe infusion reactions, tumor lysis syndrome, cytopenias (neutropenia, anemia, and thrombocytopenia), etc.

V. Dosage/Administration ^{1,10}

Indication	Dose
CLL/SLL (First-line)	Administer 300 mg on Day 1, then 1,000 mg on Day 8, followed by 1,000 mg on Day 1 of subsequent 28-day cycles for a minimum of 3 cycles until best response or a maximum of 12 cycles
CLL/SLL (Single agent subsequent therapy)	Administer 300 mg on Day 1, followed 1 week later by 2,000 mg given weekly x 7 doses (infusions 2 through 8), followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses (infusions 9 through 12) for a total of 12 doses
CLL/SLL (Relapsed)	Administer 300 mg on Day 1, then 1,000 mg on Day 8, followed by 1,000 mg on Day 1 of subsequent 28-day cycles for a maximum of 6 cycles
CLL/SLL (Extended treatment)	Administer 300 mg on Day 1, then 1,000 mg on Day 8, followed by 1,000 mg 7 weeks later and every 8 weeks thereafter for up to a maximum of 2 years
Waldenström's/ Lymphoplasmacytic lymphoma	<p>Cycle 1:</p> <ul style="list-style-type: none"> • Administer 300 mg on day 1, then 1,000 mg weekly for weeks 2 through 4; OR • Administer 300 mg on day 1, then 2,000 mg weekly for weeks 2 through 5 <p>Cycle 2-3:</p> <ul style="list-style-type: none"> • Patients with stable disease or a minor response at week 16 of cycle 1 are eligible to receive a re-dosing cycle of 300 mg on day 1, then 2,000 mg for weeks 2 through 5.

- | | |
|--|---|
| | <ul style="list-style-type: none">• Patients responding to cycle 1 or the re-dosing cycle who developed disease progression within 36 months can receive treatment with 300 mg on day 1, then 2,000 mg for weeks 2 through 5. |
|--|---|

VI. Billing Code/Availability Information

HCPCS Code:

- J9302 – injection, ofatumumab, 10 mg; 1 billable unit = 10 mg

NDC:

- Arzerra 1000 mg/50 mL single-use vial: 00078-0690-xx
- Arzerra 100 mg/5 mL single-use vial: 00078-0669-xx

VII. References (STANDARD)

1. Arzerra [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation, August 2016. Accessed April 2022.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ofatumumab. National Comprehensive Cancer Network, 2022. 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 April 2022.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2022. National Comprehensive Cancer Network, 2022. 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 April 2022.
4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 2.2022. National Comprehensive Cancer Network, 2022. 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 April 2022.
5. Furman RR, Eradat H, DiRienzo CG, et al. A phase II trial of ofatumumab in subjects with Waldenstrom's macroglobulinemia. *Blood*. 2011;118:3701
6. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol* 2010;28:1749-1755

7. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) B-Cell Lymphomas. Version 1.2022. National Comprehensive Cancer Network, 2022. 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 April 2022.
8. Rosenbaum CA, Jung SH, Pitcher B, et al. Phase 2 multicentre study of single-agent ofatumumab in previously untreated follicular lymphoma: CALGB 50901 (Alliance). *Br J Haematol.* 2019 Feb 5.
9. Van Imhoff GW, McMillan A, Matasar MJ et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. *J Clin Oncol* 2017;35 (5):544-551.
10. Furman RR, Eradat HA, DiRienzo CG, et al. Once-weekly ofatumumab in untreated or relapsed Waldenström's macroglobulinaemia: an open-label, single-arm, phase 2 study. *Lancet Haematol.* 2017 Jan;4(1):e24-e34. doi: 10.1016/S2352-3026(16)30166-1. Epub 2016 Dec 1.
11. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet.* 2015 May 9;385(9980):1873-83. doi: 10.1016/S0140-6736(15)60027-7. Epub 2015 Apr 14.
12. Robak T, Warzocha K, Govind Babu K, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. *Leuk Lymphoma.* 2017 May;58(5):1084-1093. doi: 10.1080/10428194.2016.1233536. Epub 2016 Oct 12.
13. van Oers MH, Kuliczkowski K, Smolej L, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. *Lancet Oncol.* 2015 Oct;16(13):1370-9. doi: 10.1016/S1470-2045(15)00143-6. Epub 2015 Sep 13.
14. Lemery SJ, Zhang J, Rothmann MD, et al. U.S. Food and Drug Administration Approval: Ofatumumab for the Treatment of Patients with Chronic Lymphocytic Leukemia Refractory to Fludarabine and Alemtuzumab. 10.1158/1078-0432.CCR-10-0570 Published September 2010.
15. Chen L, Shah R, Cwynarski K. et al. Ofatumumab is a feasible alternative anti-CD20 therapy in patients intolerant of rituximab. *Br J Haematol.* 2019 Feb;184(3):462-465. doi: 10.1111/bjh.15110. Epub 2018 Jan 24.

VIII. References (ENHANCED)

- 1e. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma

- (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2016 Jun 23. pii: S1470-2045(16)30097-3.
- 2e. Cheson BD, Chua N, Mayer J, et al. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. *J Clin Oncol.* 2018 36:22, 2259-2266.
 - 3e. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. *N Engl J Med.* 2015;373(25):2425–2437.
 - 4e. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *N Engl J Med.* 2018 Dec 27;379(26):2517-2528.
 - 5e. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol.* 2012 Sep 10;30(26):3209-16.
 - 6e. Michallet AS, Aktan M, Hiddemann W, et al. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. *Haematologica.* 2018;103(4):698–706.
 - 7e. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med.* 2014 Mar 20;370(12):1101-10.
 - 8e. Shanafelt TD, Wang V, Kay NE, et al. A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912). *Blood.* 2018;132:LBA-4.
 - 9e. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood.* 2016 Jan 14;127(2):208-15.
 - 10e. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol.* 2016 Jul;17(7):928-942.
 - 11e. Woyach JA, Ruppert AS, Heerema NA, et al. Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: long-term follow-up of CALGB study 9712. *J Clin Oncol.* 2011;29(10):1349–1355.
 - 12e. Flinn IW, Panayiotidis P, Afanasyev B, et al. A phase 2, multicenter study investigating ofatumumab and bendamustine combination in patients with untreated or relapsed CLL. *Am J Hematol.* 2016 Sep;91(9):900-6.

- 13e. Sharman JP, Yimer HA, Boxer M, et al. Results of a phase II multicenter study of obinutuzumab plus bendamustine in pts with previously untreated chronic lymphocytic leukemia (CLL). *J Clin Oncol*. 2017;35(15_suppl):7523-7523.
- 14e. Ahn IE, Farooqui MZH, Tian X, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. *Blood*. 2018 May 24;131(21):2357-2366.
- 15e. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2007 Dec 10;25(35):5616-23.
- 16e. Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia [published correction appears in *Leukemia*. 2009 Dec;23(12):2326]. *Leukemia*. 2009;23(10):1779–1789.
- 17e. Byrd JC, Flynn JM, Kipps TJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. *Blood*. 2016;127(1):79–86.
- 18e. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med* 2018; 378:1107-1120.
- 19e. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213–223.
- 20e. Byrd JC, Hillmen P, O'Brien SM, et al. Long-term efficacy and safety with ibrutinib (ibr) in previously treated chronic lymphocytic leukemia (CLL): Up to four years follow-up of the RESONATE study. *J Clin Oncol*. 2017;35(15_suppl):7510-7510.
- 21e. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997–1007.
- 22e. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446–2455.
- 23e. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood*. 2002 May 15;99(10):3554-61.
- 24e. Faderl S, Ferrajoli A, Wierda W, O'Brien S, Lerner S, Keating MJ. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence [published correction appears in *Cancer*. 2010 Aug 15;116(16):3982. Dosage error in article text]. *Cancer*. 2010;116(10):2360–2365.
- 25e. Robak T, Dmoszynska A, Solal-Céligny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol*. 2010 Apr 1;28(10):1756-65.
- 26e. Castro JE, Sandoval-Sus JD, Bole J, Rassenti L, Kipps TJ. Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. *Leukemia*. 2008;22(11):2048–2053.

- 27e. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2012;31(5):584–591.
- 28e. Bühler A, Wendtner CM, Kipps TJ, et al. Lenalidomide treatment and prognostic markers in relapsed or refractory chronic lymphocytic leukemia: data from the prospective, multicenter phase-II CLL-009 trial. *Blood Cancer J*. 2016;6(3):e404. Published 2016 Mar 11.
- 29e. Byrd JC, Wierda WG, Schuh A, et al. Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Updated Results from the Phase 1/2 ACE-CL-001 Study. *Blood*. 2017;130:498.
- 30e. Gopal AK, Davies AJ, Flinn IW, et al. Idelalisib Monotherapy and Durable Responses in Patients with Relapsed or Refractory Small Lymphocytic Lymphoma (SLL). *Blood*. 2015;126:2743.
- 31e. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. *Blood*. 2014: 2196-2202.
- 32e. Österborg A, Jewell RC, Padmanabhan-Iyer S, et al. Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: final results from a pivotal study. *Haematologica*. 2015;100(8):e311–e314.
- 33e. Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. *J Clin Oncol*. 2006 Apr 1;24(10):1575-81.
- 34e. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2017;19(1):65–75.
- 35e. Zelenetz AD, Barrientos JC, Brown JR, et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2017;18(3):297–311.
- 36e. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol*. 2016 Feb;17(2):200-211.
- 37e. O'Brien S, Jones JA2, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. *Lancet Oncol*. 2016 Oct;17(10):1409-1418.
- 38e. Brown JR, Hillmen P, O'Brien S, et al. Extended follow-up and impact of high-risk prognostic factors from the phase 3 RESONATE study in patients with previously treated CLL/SLL. *Leukemia*. 2017;32(1):83–91.

- 39e. Sharman JP, Coutre SE, Furman RR, et al. Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors. *Blood*. 2014;124:330.
- 40e. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2016 Jun;17(6):768-778.
- 41e. Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2009 Aug 20;27(24):3994-4001.
- 42e. Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. *Leuk Lymphoma*. 2007 Dec;48(12):2412-7.
- 43e. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;123(22):3390–3397.
- 44e. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008 Oct 1;26(28):4579-86.
- 45e. Federico M, Luminari S, Dondi A, Tucci, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. *J Clin Oncol*. 2013 Apr 20;31(12):1506-13.
- 46e. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013 Apr 6;381(9873):1203-10.
- 47e. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *N Engl J Med* 2017; 377:1331-1344.
- 48e. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2007 May 2;99(9):706-14.
- 49e. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998 Aug;16(8):2825-33.
- 50e. Dreyling M, Santoro A, Mollica L, et al. Long-Term Efficacy and Safety from the Copanlisib CHRONOS-1 Study in Patients with Relapsed or Refractory Indolent B-Cell Lymphoma. *Blood*. 2018; 132:1595.

- 51e. Czuczman MS, Fayad L, Delwail V, et al. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. *Blood*. 2012 Apr 19;119(16):3698-704.
- 52e. Sehn LH, Goy A, Offner FC, et al. Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study. *J Clin Oncol*. 2015;33(30):3467–3474.
- 53e. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. 2011 Jan 1;377(9759):42-51.
- 54e. Martinelli G, Laszlo D, Ferreri AJ, et al. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. *J Clin Oncol*. 2005 Mar 20;23(9):1979-83.
- 55e. Conconi A, Martinelli G, Thiéblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. *Blood*. 2003 Oct 15;102(8):2741-5.
- 56e. Raderer M, Wohrer S, Streubel B, et al. Activity of rituximab plus cyclophosphamide, doxorubicin/mitoxantrone, vincristine and prednisone in patients with relapsed MALT lymphoma. *Oncology*. 2006;70(6):411-7.
- 57e. Salar A, Domingo-Domenech E, Estany C, et al. Combination therapy with rituximab and intravenous or oral fludarabine in the first-line, systemic treatment of patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type. *Cancer*. 2009 Nov 15;115(22):5210-7.
- 58e. Zucca E, Conconi A, Laszlo D, et al. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 Randomized Study. *J Clin Oncol*. 2013 Feb 10;31(5):565-72.
- 59e. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014;123(19):2944–2952.
- 60e. Salar A, Domingo-Domenech E, Panizo C, et al. Final Results of a Multicenter Phase II Trial with Bendamustine and Rituximab As First Line Treatment for Patients with MALT Lymphoma (MALT-2008–01). *Blood*. 2012;120:3691.
- 61e. Conconi A, Martinelli G, Thiéblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. *Blood*. 2003 Oct 15;102(8):2741-5.
- 62e. Kiesewetter B, Neuper O1, Mayerhoefer ME, et al. A pilot phase II study of ofatumumab monotherapy for extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) lymphoma. *Hematol Oncol*. 2018 Feb;36(1):49-55.
- 63e. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood*. 2017;129(16):2224–2232.

- 64e. Leonard JP, Trněný M, Izutsu K, et al. AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R2) Vs Rituximab/Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. *Blood*. 2018;132:445.
- 65e. Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. *Cancer*. 2006 Jul 1;107(1):125-35.
- 66e. Else M, Marín-Niebla A, de la Cruz F, et al. Rituximab, used alone or in combination, is superior to other treatment modalities in splenic marginal zone lymphoma. *Br J Haematol*. 2012 Nov;159(3):322-8.
- 67e. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010;116(12):2040–2045.
- 68e. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2011 Oct;12(11):1013-22.
- 69e. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol*. 2012;30(36):4462–4469.
- 70e. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2013 Jun 10;31(17):2103-9.
- 71e. Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. *Blood*. 2015 Feb 26;125(9):1394-402.
- 72e. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. *J Clin Oncol*. 2005 Oct 1;23(28):7013-23.
- 73e. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol*. 2005 Mar 20;23(9):1984-92.
- 74e. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2007 May 2;99(9):706-14.

- 75e. Casulo C, Iannotta A, Walkley J, et al. Ofatumumab-Bendamustine As First Line Treatment for Elderly Patients with Mantle Cell Lymphoma: A Phase II Risk Adapted Design with Comprehensive Geriatric Assessment. *Blood*. 2014;124:1751.
- 76e. Cavalli F, Rooney B, Pei L, et al. Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma (MCL) patients (pts) ineligible for bone marrow transplantation (BMT). *J Clin Oncol*. 2014;32(15_suppl):8500-8500.
- 77e. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. *Ann Oncol*. 2008;20(3):520–525.
- 78e. Furtado M, Dyer MJ, Johnson R, et al. Ofatumumab monotherapy in relapsed/refractory mantle cell lymphoma—a phase II trial. *Br J Haematol*. 2014 May;165(4):575-8.
- 79e. Dimopoulos MA, García-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). *Blood*. 2013 Nov 7;122(19):3276-82.
- 80e. Dimopoulos MA, Anagnostopoulos A, Kyrtsolis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol*. 2007 Aug 1;25(22):3344-9.
- 81e. Treon SP, Hanzis C, Tripsas C, et al. Bendamustine therapy in patients with relapsed or refractory Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2011 Feb;11(1):133-5.
- 82e. Paludo J, Abeykoon JP, Shreders A, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenström macroglobulinemia. *Ann Hematol*. 2018 Aug;97(8):1417-1425.
- 83e. Treon SP, Hunter ZR, Matous J, et al. Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: results of WMCTG Trial 03-248. *Clin Cancer Res*. 2007 Jun 1;13(11):3320-5.
- 84e. Ghobrial IM, Witzig TE, Gertz M, et al. Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom Macroglobulinemia. *Am J Hematol*. 2014 Mar;89(3):237-42.
- 85e. Österborg A, Jewell RC, Padmanabhan-Iyer S, et al. Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: final results from a pivotal study. *Haematologica*. 2015;100(8):e311–e314. doi:10.3324/haematol.2014.121459.
- 86e. Magellan Health, Magellan Rx Management. *Arzerra Clinical Literature Review Analysis*. Last updated April 2022. Accessed April 2022.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C83.00	Small cell B-cell lymphoma, unspecified site

ICD-10	ICD-10 Description
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	Small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C88.0	Waldenström macroglobulinemia
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse

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: <https://www.cms.gov/medicare-coverage-database/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.

Medicare Part B Administrative Contractor (MAC) Jurisdictions

Jurisdiction	Applicable State/US Territory	Contractor
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC