

Venclexta™ (venetoclax) (Oral)

Document Number: IC-0276

Last Review Date: 05/01/2020

Date of Origin: 05/31/2016

Dates Reviewed: 05/2016, 04/2017, 04/2018, 12/2018, 05/2019, 06/2019, 05/2020

I. Length of Authorization

Coverage will be provided for six months and may be renewed.

- When used for CLL/SLL in combination with rituximab, coverage may be renewed up to a total 24 months of therapy (*from day 1 of cycle 1 of rituximab*).
- When used for CLL/SLL in combination with obinutuzumab, coverage may be renewed up until the end of 12 cycles of obinutuzumab therapy (*Venetoclax therapy begins on day 22 of cycle 1 of obinutuzumab*).

II. Dosing Limits

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

- Venclexta Starting Pack: 1 pack per 28 days
- Venclexta 10 mg tablet: 2 tablets per day
- Venclexta 50 mg tablet: 1 tablet per day
- Venclexta 100 mg tablet: 8 tablets per day

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

- AML: 600 mg daily
- Mantle Cell Lymphoma and BPDCN: 800 mg daily
- All other indications: 400 mg daily

III. Initial Approval Criteria

Coverage is provided for treatment of the following conditions:

- Patient is at least 18 years old unless otherwise specified; **AND**

Universal Criteria

- Patient must not have a concurrent diagnosis of multiple myeloma; **AND**
- Patient must not receive live attenuated vaccines prior to, during, or after venetoclax treatment until B-cell recovery occurs; **AND**
- Patient will not be on concomitant therapy with moderate or strong CYP3A-inducers (e.g., rifampin, carbamazepine, phenytoin, St. john's wort, etc.); **AND**

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) †/Φ 1,2,8-12

- Patient must not be on strong CYP3A-inhibitors (e.g., posaconazole, nefazadone, ritonavir, grapefruit juice, etc.) during initiation and ramp-up phase

Acute Myeloid Leukemia (AML) †/Φ 1-3, 13,14

- Patient is at least 60 years old or is unable to receive intensive induction therapy due to comorbidities (e.g., PS \geq 2, moderate hepatic impairment, severe cardiac or pulmonary disease, CL_{CR} < 45 mL/min, etc.); **AND**
 - Used in combination with azacitidine, decitabine, or low-dose cytarabine; **AND**
 - Patient has newly-diagnosed disease; **OR**
 - Used as post-induction therapy following response to previous lower intensity therapy with the same regimen; **OR**
- Patient has relapsed/refractory disease; **AND**
 - Used in combination with the initial successful induction regimen in patients with late relapse (\geq 12 months) if not administered continuously and not stopped due to development of clinical resistance; **OR**
 - Used in combination with azacitidine, decitabine, or low-dose cytarabine

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) ‡ 2-5

- Patient has relapsed/refractory disease; **AND**
- Used in combination with azacitidine, decitabine, or low-dose cytarabine

Mantle Cell Lymphoma ‡ 2,6,7

- Used as second line therapy; **AND**
- Used as a single agent

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

IV. Renewal Criteria 1,2,4-7

Coverage can be renewed based on the following criteria:

- Patients continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: tumor lysis syndrome, severe neutropenia, severe infection, etc.; **AND**

Acute Myeloid Leukemia (AML)

- Disease stabilization or improvement as evidenced by a complete response [CR] (i.e. morphologic, cytogenetic or molecular complete response CR), complete hematologic response or a partial response by CBC, bone marrow cytogenetic analysis, QPCR, or FISH

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

- Venetoclax/rituximab regimen: Patient has not received more than 24 months of therapy;
OR
- Venetoclax/obinutuzumab regimen: Patient has not received more than 12 cycles of therapy

All other indications

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread

V. Dosage/Administration ^{1,3-7}

Indication	Dose
CLL/SLL	<p><u>Dose titration schedule:</u></p> <ul style="list-style-type: none"> • Week 1: 20 mg daily • Week 2: 50 mg daily • Week 3: 100 mg daily • Week 4: 200 mg daily • Week 5 and thereafter: 400 mg daily <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> • 400 mg once daily after completing the 5-week dose ramp-up schedule. • Continue until disease progression or unacceptable toxicity <p><u>Rituximab combination therapy</u></p> <ul style="list-style-type: none"> • Start rituximab administration after the patient has completed the 5-week dose ramp-up schedule with venetoclax and has received the 400 mg dose of venetoclax for 7 days. • Continue venetoclax 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab <p><u>Obinutuzumab combination therapy</u></p> <ul style="list-style-type: none"> • Start obinutuzumab administration at 100 mg on Cycle 1 Day 1, followed by 900 mg on Cycle 1 Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28 day cycle, for a total of 6 cycles. • On Cycle 1 Day 22, start venetoclax therapy according to the 5-week ramp-up schedule. After completing the ramp-up schedule on Cycle 2 Day 28, patients should continue Venclexta 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12.
AML	<p><u>Dose titration schedule:</u></p> <ul style="list-style-type: none"> • Day 1: 100 mg daily • Day 2: 200 mg daily • Day 3: 400 mg daily • Days 4 and beyond: 400 mg daily (when used in combination with azacitidine or decitabine) or 600 mg daily (when used in combination with low-dose cytarabine) • Continue until disease progression or unacceptable toxicity
BPDCN	200 mg daily (NOTE: dosing can range from 100 mg to 800 mg daily)
Mantle Cell Lymphoma	<p><u>Dose titration schedule:</u></p> <ul style="list-style-type: none"> • Week 1: 20 mg daily • Week 2: 50 mg daily • Week 3: 100 mg daily

Indication	Dose
	<ul style="list-style-type: none"> • Week 4: 200 mg daily • Week 5 and thereafter: 400 mg daily • Dose may be escalated up to 800 mg daily at week 6 or later for patients with an insufficient response • Continue until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS code:

- J8999 - Prescription drug, oral, chemotherapeutic, Not Otherwise Specified

NDC:

- Venclexta Starting Pack: 00074-0579-xx
- Venclexta 10mg tablet: 00074-0561-xx
- Venclexta 50mg tablet: 00074-0566-xx
- Venclexta 100mg tablet: 00074-0576-xx

VII. References

1. Venclexta [package insert]. North Chicago, IL; Abbvie, Inc. July 2019. Accessed April 2020.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) venetoclax. National Comprehensive Cancer Network, 2020. 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 2020.
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia 3.2020. National Comprehensive Cancer Network, 2019. 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 April 2020.
4. Rausch CR, Dinardo CD, Kadia TM, et al. Results of Off-Label Venetoclax Use in Combination with Low-Intensity Chemotherapy in Patients with Relapsed and Refractory Myeloid Malignancies. *Medicine* 2017.
5. Montero J, Stephansky J, Cai T, et al. Blastic Plasmacytoid Dendritic Cell Neoplasm Is Dependent on BCL2 and Sensitive to Venetoclax. DOI: 10.1158/2159-8290.CD-16-0999 Published February 2017.
6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas 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 Guidelines, go online to NCCN.org. Accessed April 2020.

7. Davids MS, von Keudell G, Portell CA, et al. Revised Dose Ramp-Up to Mitigate the Risk of Tumor Lysis Syndrome When Initiating Venetoclax in Patients With Mantle Cell Lymphoma. *J Clin Oncol*, JCO1800359; 2018 Oct 25. PMID: 30359156. DOI: 10.1200/JCO.18.00359
8. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients With CLL and Coexisting Conditions. *N Engl J Med*, 380 (23), 2225-2236; Jun 6. PMID: 31166681. DOI: 10.1056/NEJMoa1815281
9. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med*, 378 (12), 1107-1120; 2018 Mar 22. PMID: 29562156. DOI: 10.1056/NEJMoa1713976
10. 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*, 17 (6), 768-778; Jun 2016. PMID: 27178240. DOI: 10.1016/S1470-2045(16)30019-5
11. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 With Venetoclax in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med*, 374 (4), 311-22; 2016 Jan 28. PMID: 26639348. PMID: PMC7107002 DOI: 10.1056/NEJMoa1513257
12. 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*, 19 (1), 65-75; Jan 2018. PMID: 29246803. PMID: PMC6027999 DOI: 10.1016/S1470-2045(17)30909-9
13. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax Combined With Decitabine or Azacitidine in Treatment-Naive, Elderly Patients With Acute Myeloid Leukemia. *Blood*, 133 (1), 7-17; 2019 Jan 3. PMID: 30361262. PMID: PMC6318429 DOI: 10.1182/blood-2018-08-868752
14. Wei AH, Strickland Jr SA, Hou JZ, et al. Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study. *J Clin Oncol*, 37 (15), 1277-1284; 2019 May 20. PMID: 30892988. DOI: 10.1200/JCO.18.01600

Appendix 1 – Covered Diagnosis Codes

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

ICD-10	ICD-10 Description
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
C83.10	Mantle cell lymphoma, unspecified site
C83.11	Mantle cell lymphoma, lymph nodes of head, face, and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C86.4	Blastic NK-cell lymphoma
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C92.00	Acute myeloblastic leukemia not having achieved remission
C92.01	Acute myeloblastic leukemia, in remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.50	Acute myelomonocytic leukemia not having achieved remission
C92.51	Acute myelomonocytic leukemia, in remission
C92.52	Acute myelomonocytic leukemia, in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia, in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia, in relapse
C93.00	Acute monoblastic/monocytic leukemia not having achieved remission
C93.01	Acute monoblastic/monocytic leukemia, in remission
C93.02	Acute monoblastic/monocytic leukemia, in relapse
C94.00	Acute erythroid leukemia not having achieved remission
C94.01	Acute erythroid leukemia, in remission
C94.02	Acute erythroid leukemia, in relapse
C94.20	Acute megakaryoblastic leukemia not having achieved remission
C94.21	Acute megakaryoblastic leukemia, in remission
C94.22	Acute megakaryoblastic leukemia, 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: <http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx>. Additional indications may be covered at the discretion of the health plan.

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

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