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Medication Policy Manual | **Policy No:** dru462

Topic: Venclexta™, venetoclax | **Date of Origin:** July 15, 2016

Committee Approval Date: January 13, 2017 | **Next Review Date:** January 2018

Effective Date: February 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Venetoclax (Venclexta) is an oral medication used in the management of chronic lymphocytic leukemia (CLL) with 17p deletion when the disease is resistant to, or relapses after, at least one prior CLL therapy. CLL with 17p deletion is associated with poor clinical outcomes and poor response to chemotherapy relative to other CLL variants.

Policy/Criteria

I. Most contracts require prior authorization approval of venetoclax (Venclexta) prior to coverage. Venetoclax (Venclexta) may be considered medically necessary when criteria A through D below are met.

A. A diagnosis of chronic lymphocytic leukemia (CLL).

AND

B. Confirmation of 17p deletion [del(17p)/TP53 mutation].

AND

C. The disease has relapsed after, or was refractory to, at least one prior CLL therapy.

AND

D. Venetoclax (Venclexta) is used as monotherapy.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers venetoclax (Venclexta) to be a self-administered medication.

B. When prior authorization is approved, one Starting Pack may be authorized for the initial 28-day ramp-up dosing schedule.

C. After the initial ramp-up dosing schedule, venetoclax (Venclexta) may be authorized in quantities of up to 120 tablets per month.

D. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Venetoclax (Venclexta) is considered investigational when administered concomitantly with other CLL therapies.

IV. Venetoclax (Venclexta) is considered investigational when used for all other conditions, including but not limited to:

A. CLL without 17p deletion [del(17p)/TP53 mutation]

B. Mantle cell lymphoma

C. Multiple myeloma

Position Statement

- Venetoclax (Venclexta) is an orally administered medication approved for the treatment of chronic lymphocytic leukemia (CLL) when 17p deletion [del(17p)/TP53 mutation] is present and prior therapy for CLL has not been effective.
- To date, there is no evidence demonstrating that venetoclax (Venclexta) has a beneficial effect on any clinically meaningful outcome (e.g. improved survival or quality of life).
    * Venetoclax (Venclexta) was approved via the FDA Accelerated approval pathway based on improvement in overall response rate (ORR), a surrogate marker that has not been shown to accurately predict benefit for any clinically relevant outcome.
    * Venetoclax (Venclexta) has not been compared with placebo or any active comparator.
- The National Comprehensive Cancer Network (NCCN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guideline lists venetoclax (Venclexta) among several category 2A recommendations for the treatment of relapsed or refractory CLL with or without del (17p)/TP53 mutation; however, only preliminary data is available for the use of venetoclax (Venclexta) in patients without a confirmed 17p deletion [del(17p)/TP53 mutation].
- There is a high risk of tumor lysis syndrome when initiating venetoclax (Venclexta). The dose is slowly ramped up over the first four weeks of therapy to minimize the impact of this adverse effect (AE).
- Following the initial dose ramp up, the usual maintenance dose of venetoclax (Venclexta) is 400 mg (4 x 100 mg tablets) orally once per day until progression of disease.
- Common AEs observed with venetoclax (Venclexta) include gastrointestinal side effects, fatigue, and bone marrow suppression (e.g. neutropenia, anemia, and thrombocytopenia).
- Although there is interest in using venetoclax (Venclexta) in the front-line treatment setting, and in combination with other CLL therapies, current evidence is limited to its use as a monotherapy when other therapies have not been effective.
- There is interest in studying venetoclax (Venclexta) in several other cancers and disease settings; however, evidence outside of the relapsed or refractory CLL setting is limited at this time.

Clinical Efficacy

- Venetoclax (Venclexta) received FDA Accelerated approval based on a single-arm trial that reported overall response rates (ORR) in a small number of subjects with chronic lymphocytic leukemia (CLL). There is currently no evidence that it has a beneficial effect on any clinically relevant outcome (e.g. overall survival or quality of life). [1,2]
    * Subjects in the study had confirmation of CLL with 17p deletion [del(17p)/TP53 mutation] and had a median of two prior therapies for their CLL.
    * Venetoclax (Venclexta) was initiated at 20 mg orally daily, and was then slowly ramped up over a four week period to minimize the risk of significant tumor lysis syndrome. The target maintenance dose was 400 mg orally daily. It was given until progression of disease.
    * The trial reported an ORR of 79.4%. The majority were partial responses (69.2%).

- There is no evidence directly comparing venetoclax (Venclexta) with placebo or any active comparator. Additionally, there is no evidence demonstrating its safety and effectiveness in the first-line setting, or when used concomitantly with any other CLL therapy.
- The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guideline lists venetoclax (Venclexta) monotherapy among several category 2A recommendations for relapsed or refractory CLL with del(17p). However, there is a preference for ibrutinib (Imbruvica) over venetoclax (Venclexta) due to increased tolerability and preliminary overall survival data. [3]

Investigational Uses

- Based on Phase I trials and the www.clinicaltrials.gov website, several studies of venetoclax (Venclexta) are planned in other CLL settings as well as in other cancers. A clinical benefit of venetoclax (Venclexta) has not been established in these settings.
    * A Phase I, open-label, dose-escalation study included CLL and small lymphocytic lymphoma (SLL) subjects without 17p deletion. The trial reported an ORR of 80% based on doses ranging from 150 mg to 1,200 mg per day; the majority were partial responses (88%). [4] Although NCCN guidelines lists venetoclax (Venclexta) as a category 2A recommendation for relapsed or refractory CLL without del(17p), many category 1 recommendations are available. [3]
    * A Phase III study of venetoclax (Venclexta) in multiple myeloma is currently recruiting subjects.
    * The NCCN B-cell Lymphomas guideline lists several category 2A recommendations as second-line therapy in mantle cell lymphoma, including venetoclax (Venclexta). This recommendation was based on an unpublished Phase I, open-label study that included 28 patients with mantle cell lymphoma. [5]
- There is currently limited evidence evaluating the safety and efficacy of venetoclax (Venclexta) in settings outside of relapsed or refractory CLL with del(17p).

Regence Pharmacy Services performs independent analyses of oncology medications. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN clinical practice guidelines.

Safety [1]

- The safety information for venetoclax (Venclexta) is based on a single-arm observational trial. Its safety relative to other therapies is unknown.
- Because venetoclax (Venclexta) belongs to a new medication class (BCL-2 inhibitors), it likely has a different safety profile than other CLL therapies.
- Warnings and precautions include significant tumor lysis syndrome, neutropenia, and embryo-fetal toxicity.
- Live vaccinations should not be administered during therapy with venetoclax (Venclexta).
- Venetoclax (Venclexta) may interact with strong or moderate CYP3A4 inhibitors and P-gp inhibitors.

Dosing [1]

- Venetoclax (Venclexta) is available as 10 mg, 50 mg, and 100 mg tablets.
- The dose of venetoclax (Venclexta) should be slowly ramped up to avoid severe tumor lysis syndrome. There is a Starting Pack available that provides the first four weeks of medication packaged according to the recommended ramp-up schedule.
- The target maintenance dose is 400 mg (4 x 100 mg tablets) orally once per day.

Cross References
Arzerra®, ofatumumab, Medication Policy Manual, Policy No. 196
Gazyva®, obinutuzumab, Medication Policy Manual, Policy No. 327
Imbruvica®, ibrutinib, Medication Policy Manual, Policy No. 326
Rituxan®, rituximab, Medication Policy Manual, Policy No. 214
Zydelig®, idelalisib, Medication Policy Manual, Policy No. 363

Codes	Number	Description
HCPCS	J8999	Oral chemotherapeutic drug, not otherwise classified
ICD-10	C91.10, C91.12	Small lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)

References

1. Venclexta™ (venetoclax) [package insert]. North Chicago, IL: AbbVie, Inc.; April 2016.
2. 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. *The Lancet Oncology*. 2016 May 10. PMID: 27178240
3. NCCN Clinical Practice Guidelines in Oncology™. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v.1.2017. [cited 12/22/2016]; Available from: www.nccn.org/professionals/physician_gls/pdf/cll.pdf
4. Roberts, AW, Davids, MS, Pagel, JM, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. *The New England journal of medicine*. 2016 Jan 28;374(4):311-22. PMID: 26639348
5. NCCN Clinical Practice Guidelines in Oncology™. B-cell Lymphomas v.1.2017. [cited 12/22/2016]; Available from: www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

Revision History

Revision Date	Revision Summary
01/13/2017	Updated investigational uses.
7/15/2016	New policy