**COMPENDIA TRANSPARENCY TRACKING FORM**

**DATE:** June 20, 2022

**OFF-LABEL ID #:** 2395

**DRUG NAME:** Venetoclax

**OFF-LABEL USE:** Multiple myeloma; Relapsed or refractory, t(11;14) positive, combination therapy

| COMPENDIA TRANSPARENCY REQUIREMENTS | |
|---|---|
| 1 | Provide criteria used to evaluate/prioritize the request (therapy) |
| 2 | Disclose evidentiary materials reviewed or considered |
| 3 | Provide names of individuals who have substantively participated in the review or disposition of the request and disclose their potential direct or indirect conflicts of interest |
| 4 | Provide meeting minutes and records of votes for disposition of the request (therapy) |

**EVALUATION/PRIORITIZATION CRITERIA: C,** *to meet requirement 1

| CODE | EVALUATION/PRIORITIZATION CRITERIA |
|---|---|
| **A** | Treatment represents an established standard of care or significant **advance** over current therapies |
| **C** | **Cancer** or cancer-related condition |
| **E** | Quantity and robustness of **evidence** for use support consideration |
| **L** | **Limited** alternative therapies exist for condition of interest |
| **P** | **Pediatric** condition |
| **R** | **Rare** disease |
| **S** | **Serious**, life-threatening condition |

**Note: a combination of codes may be applied to fully reflect points of consideration [eg, therapy may represent an advance in the treatment of a life-threatening condition with limited treatment alternatives (ASL)]**

**EVIDENCE CONSIDERED:**

*to meet requirements 2 and 4

| CITATION | STUDY-SPECIFIC COMMENTS | LITERATURE CODE |
|---|---|---|
| Kumar, SK, Harrison, SJ, Cavo, M, et al: Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol Dec 2020; Vol 21, Issue 12; pp. 1630-1642. | This was a double-blind, placebo-controlled randomized clinical trial that investigated the combination of bortezomib with either venetoclax or placebo in adult patients with relapsed or refractory multiple myeloma. The risk of bias associated with randomization, allocation concealment, performance, detection, and selective reporting were deemed low risk. The risk of bias associated with attrition was deemed moderate risk due to fairly uneven attrition between groups. | S |
| Kaufman, JL, Gasparetto, C, Schjesvold, FH, et al: Targeting BCL-2 with venetoclax and dexamethasone in patients with relapsed/refractory t(11;14) multiple myeloma. Am J Hematol Apr 01, 2021; Vol 96, Issue 4; pp. 418-427. | This was a prospective open-label phase I/II clinical trial that investigated venetoclax in patients with relapsed or refractory multiple myeloma. The risk of bias due to confounding, selection of participants, classification of and deviation from intervention, and selective reporting were deemed low risk. The risk of attrition bias was deemed serious risk due to high attrition relative to sample size. The risk of bias associated with measurement of outcome was deemed moderate risk due to the outcome being investigator-assessed. A major caveat of the study is the lack of a control group. | S |
| Costa, LJ, Davies, FE, Monohan, GP, et al: Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma. Blood Adv Oct 12, 2021; Vol 5, Issue 19; pp. 3748-3759. | | 2 |
| Szita, VR, Mikala, G, Kozma, A, et al: Targeted venetoclax therapy in t(11;14) multiple myeloma: real world data from seven Hungarian centers. Pathol Oncol Res Feb 28, 2022; Vol 28, p. 1610276. | | 3 |

| | | |
|---|---|---|
| Sidiqi, MH, Al Saleh, AS, Kumar, SK, et al: Venetoclax for the treatment of multiple myeloma: outcomes outside of clinical trials. Am J Hematol Sep 01, 2021; Vol 96, Issue 9; pp. 1131-1136. | | 3 |
| Nahi, H, Kashif, M, Klimkowska, M, et al: Low dose venetoclax as a single agent treatment of plasma cell malignancies harboring t(11;14). Am J Hematol Aug 01, 2021; Vol 96, Issue 8; pp. 925-933. | | 2 |
| Regidor, B, Goldwater, MS, Wang, J, et al: Low dose venetoclax in combination with bortezomib, daratumumab, and dexamethasone for the treatment of relapsed/refractory multiple myeloma patients-a single-center retrospective study. Ann Hematol Aug 2021; Vol 100, Issue 8; pp. 2061-2070. | | 3 |
| Basali, D, Chakraborty, R, Rybicki, L, et al: Real-world data on safety and efficacy of venetoclax-based regimens in relapsed/refractory t(11;14) multiple myeloma. Br J Haematol Jun 2020; Vol 189, Issue 6; pp. 1136-1140. | | 3 |

| | | |
|---|---|---|
| US Food & Drug Administration (FDA): FDA warns about the risks associated with the investigational use of Venclexta in multiple myeloma. US Food & Drug Administration (FDA). Silver Spring, MD. Mar 21, 2019. Available from URL: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-associated-investigational-use-venclexta-multiple-myeloma. | | 4 |
| Dimopoulos, Meletios A.1; Moreau, Philippe2; Terpos, Evangelos1; Mateos, María-Victoria3; Zweegman, Sonja4; Cook, Gordon5; Delforge, Michel6; Hájek, Roman7; Schjesvold, Fredrik8,,9; Cavo, Michele10; Goldschmidt, Hartmut11; Facon, Thierry12; Einsele, Hermann13; Boccadoro, Mario14; San-Miguel, Jesús15; Sonneveld, Pieter16; Mey, Ulrich17 Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up, HemaSphere: February 2021 - Volume 5 - Issue 2 - p e528 doi: 10.1097/HS9.0000000000000528 | | S |

**Literature evaluation codes: S = Literature selected; 1 = Literature rejected = Topic not suitable for scope of content; 2 = Literature rejected = Does not add clinically significant new information; 3 = Literature rejected = Methodology flawed/Methodology limited and unacceptable; 4 = Other (review article, letter, commentary, or editorial)**

## CONTRIBUTORS:

*to meet requirement 3

| PACKET PREPARATION | DISCLOSURES | EXPERT REVIEW | DISCLOSURES |
|---|---|---|---|
| Megan Smith | None | | |
| Stacy LaClaire, PharmD | None | | |
| Catherine Sabatos, PharmD | None | | |
| | | John D Roberts | None |
| | | Todd Gersten | None |
| | | Richard LoCicero | Incyte Corporation<br><br>Local PI for REVEAL. Study is a multicenter, non-interventional, non-randomized, prospective, observational study in an adult population for patients who have been diagnosed with clinically overt PV and are being followed in either community or academic medical centers in the US who will be enrolled over a 12-month period and observed for 36 months. |

## ASSIGNMENT OF RATINGS:

*to meet requirement 4

| | EFFICACY | STRENGTH OF RECOMMENDATION | COMMENTS | STRENGTH OF EVIDENCE |
|---|---|---|---|---|
| **IBM MICROMEDEX** | Evidence Favors Efficacy | Class IIb: Recommended, in Some Cases | | B |

| | | | | |
|---|---|---|---|---|
| John Roberts | Evidence Favors Efficacy | Class IIb: Recommended, in Some Cases | Addition of venetoclax to the combination of bortezomib and dexamethasone has been shown in a single, small randomized trial to improve progression free survival but not overall survival in patients with t(11;14)-positive, relapsed or refractory myeloma who were proteasome inhibitor sensitive or naive. Although there was no increase in infection related mortality in these patients, in t(11;14)-negative patients addition of venetoclax was associated with increased mortality, primarily due to infection. Concurrent treatment with prophylactic antibiotics is recommended. Guidelines typically recommend that most or all patients with relapsed or refractory myeloma receive an immunomodulatory agent such as lenamidolide as second or subsequent line therapy; yet, in this study more than 30% of patients had not received such treatment. Thus, it is unclear whether prior immunomodulatory agent therapy is preferred. | |
| Richard LoCIcero | Evidence Favors Efficacy | Class IIb: Recommended, in Some Cases | Two clinical trials, and ESMO clinical practice guidelines support the use of venetoclax in the treatment of relapsed or refractory, t(11;14)+ multiple myeloma. While unexpected toxicity was not observed, death due to infection occurred in patients treated with venetoclax. | |
| Todd Gersten | Evidence Favors Efficacy | Class IIb: Recommended, in Some Cases | Venetoclax has activity in relapsed, refractory myeloma harboring t(11;14). | |