COMPENDIA TRANSPARENCY TRACKING FORM

DATE: May 1, 2023

OFF-LABEL ID #: 2503

DRUG NAME: Ibrutinib

OFF-LABEL USE: Diffuse non-Hodgkin's lymphoma, large cell (clinical)

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, E, R, S *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
Atallah-Yunes SA, et al. Novel Immune-Based treatments for Diffuse Large B-Cell Lymphoma: The Post-CAR T Cell Era. Front. Immunol. 2022; 13:901365.		4
Hou K, et al. Efficacy and safety of ibrutinib in diffuse large B-cell lymphoma: A single-arm meta-analysis. Critical Reviews in Oncology / Hematology 152 (2020) 103010		3
Younes A, Sehn LH, Johnson P, et al. Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2019 May 20;37(15):1285-1295.	This was a randomized placebo controlled clinical trial that investigated ibrutinib in patients with diffuse large B-cell lymphoma. The risk of bias due to randomization, allocation concealment, performance, detection, and selective reporting were deemed low risk. The risk of bias associated with attrition was deemed moderate risk because drop-out rate due to adverse events was much higher in the ibrutinib group than the placebo group.	S
Ramchandren 2022. The iR2 regimen (ibrutinib plus lenalidomide and rituximab) for relapsed/refractory DLBCL: A multicentre, non-randomised, open-label phase 2 study	This was a prospective single-arm phase 1b/2 clinical trial that investigated combination therapy with ibrutinib, lenalidomide, and rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma. The risk of bias due to confounding, selection, classification of and deviation from intervention, attrition, selective reporting, and measurement of outcome were deemed low risk. A major caveat of the study is the lack of a control group.	S
Wilson 2015. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma		2

Westin 2022. Smart Start: Rituximab, Lenalidomide, and Ibrutinib in Patients With Newly Diagnosed Large B-Cell Lymphoma	This was a prospective single-arm phase 2 clinical trial that investigated combination therapy with ibrutinib, lenalidomide, and rituximab in patients with newly diagnosed diffuse large B-cell lymphoma. The risk of bias due to confounding, selection, classification of and deviation from intervention, selective reporting, and measurement of outcome were deemed low risk. A major caveat of the study is the lack of a control group.	S
Xu, P, et al. Ibrutinib, rituximab, and lenalidomide in unfit or frail patients aged 75 years or older with de novo diffuse large B-cell lymphoma: a phase 2, single-arm study. Lancet Healthy Longev 2022; 3: e481–90	This was a prospective single-arm phase 2 clinical trial that investigated induction therapy with ibrutinib in elderly patients with diffuse large B-cell lymphoma. The risk of bias due to confounding, selection, classification of and deviation from intervention, selective reporting, and measurement of outcome were deemed low risk. The risk of bias associated with attrition was deemed serious risk because drop-out rate was higher than the prespecified sample size analysis. A major caveat of the study is the lack of a control group.	S
Wilson 2021. Phase 1b/2 study of ibrutinib and lenalidomide with dose-adjusted EPOCH-R in patients with relapsed/refractory diffuse large B-cell lymphoma		3
Johnson 2023. Clinical impact of ibrutinib plus R-CHOP in untreated DLBCL co-expressing BCL2 and MYC in the phase 3 PHOENIX trial		3
Zhu et al. Rituximab, lenalidomide and BTK inhibitor as frontline treatment for elderly or unfit patients with diffuse large B-cell lymphoma: a real-world analysis of single center. Experimental Hematology & Oncology (2022) 11:57		3
Búa BR, et al. Updated Results of a Phase 2 Study from GELTAMO Investigating the Combination of Ibrutinib with R-GEMOX in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Clinical Lymphoma, Myeloma & Leukemia September 2021; S381		4

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		
		Todd Gersten	None
		Jeffrey Klein	None
		Richard LoCicero	Incyte Corporation 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
Jeffrey Klein	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	The use of Ibrutinib in 3 smaller studies (4 studies in total) demonstrated various degrees of good survival rates, good progression free survival, and a durable response. The high degree of serious adverse events in all studies is seen. One larger study it was clear that ages > 60 had a significant higher rate of toxicity with Ibrutinib, as well as an insignificant benefit profile. The ages < 60 had better overall medical results, yet the degree of adverse effects was prevalent.	

Todd Gersten	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	The prevailing body of evidence reflects activity of ibrutinib when part of a multidrug regimen in both newly diagnosed and relapsed patients. The strongest evidence is suggested in those < 60yo, when added to R-CHOP, where an OS benefit was seen in a randomized placebo controlled trial. In that same trial, however, a benefit in EFS was not seen in those > 60yo.	
Richard LoCicero	Effective	Class IIb: Recommended, in Some Cases	While ibrutinib does not replace or show efficacy in combination with standard therapy for Diffuse large cell Non-Hodgkin lymphoma, it has been shown to have efficacy in some populations. In combination with lenalidomide and rituximab, ibrutinib has activity and a toxicity profile to be used in patients not eligible for cytotoxic chemotherapy. It has also been shown to have efficacy in relapsed and refractory disease.	