TRUVEN HEALTH ANALYTICS
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COMPENDIA TRANSPARENCY TRACKING FORM

DATE: 10/24/2018

PACKET: 1740

DRUG: Rituximab

USE: Chronic lymphoid leukemia, disease maintenance, following rituximab-containing chemotherapy

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, L, 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)]

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EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Dartigeas,C., Van Den,Neste E., Leger,J., et al: Rituximab maintenance versus observation following abbreviated induction with chemoimmunotherapy in elderly patients with previously untreated chronic lymphocytic leukaemia (CLL 2007 SA): an open-label, randomised phase 3 study. Lancet Haematol. Feb 2018; Vol 5, Issue 2; pp. e82-e94.	Comments: This was a multicenter, open-label, phase 3 randomized trial with 89 sites in France. Key bias criteria evaluated were (1) random sequence generation of randomization; (2) lack of allocation concealment, (3) lack of blinding, (4) incomplete accounting of patients and outcome events, and (5) selective outcome reporting bias. The study was at low risk of bias for these key criteria, and no additional biases were identified. Additional strengths included a power analysis, control for type 1 error rate, and analyses on potential confounding factors.	S
Greil,R., Obrtlikova,P., Smolej,L., et al: Rituximab maintenance versus observation alone in patients with chronic lymphocytic leukaemia who respond to first-line or second-line rituximab-containing chemoimmunotherapy: final results of the AGMT CLL-8a Mabtenance randomised trial. Lancet Haematol Jul 2016; Vol 3, Issue 7; pp. e317-e329.	Comments: This was the AGMT CLL-8a Mabtenance study which was an international, randomized, open-label, phase 3 clinical trial. The study included 29 centers in Austria, the Czech Republic, Slovakia, Bulgaria, and Romania recruited 263 patients. Key bias criteria evaluated were (1) random sequence generation of randomization; (2) lack of allocation concealment, (3) lack of blinding, (4) incomplete accounting of patients and outcome events, and (5) selective outcome reporting bias. The study was at low risk of bias for most of these key criteria. There was potential high risk of bias for the assessment of subjective outcomes. There was a similar proportion of patients who withdrew from the study prematurely, about 30% in each arm. In those patients, assessments for toxicity and progression were continued when feasible. Additional strengths included a power analysis and analyses on potential confounding factors.	S
Foa,R., Del,Giudice,I, Cuneo,A., et al: Chlorambucil plus rituximab with or without maintenance rituximab as first-line treatment for elderly chronic lymphocytic leukemia patients. Am J Hematol. May 2014; Vol 89, Issue 5; pp. 480-486.	Comments: This was a single-arm, phase II, open-label, multicenter study of CLB plus R (CLB-R) as induction, followed by a randomized maintenance with R or observation. Overall, this study was at low risk of biases associated with lack of blinding (for objective endpoints), incomplete accounting of patients and outcome events, and selective outcome reporting. The risk of bias associated with poor random sequence generation and allocation concealment was unclear and not discussed in the paper. There may be potential high risk of bias for subjective endpoints due to the open-label design. Additional strengths included a power analysis and analyses on potential confounding factors.	1

Robak,T.: Rituximab, cladribine, and cyclophosphamide (RCC) induction with rituximab maintenance in chronic lymphocytic leukemia: PALG - CLL4 (ML21283) trial. European Journal of Haematology May 01, 2018; Vol 100, Issue 5; pp. 465-474.	Comments: PALG CLL4 (ML21283) was an international, multicenter, open-label, randomized 2-arm phase IIIb study conducted in 6 centers, in 2 countries (Poland, Belarus). Key bias criteria evaluated were (1) random sequence generation of randomization; (2) lack of allocation concealment, (3) lack of blinding, (4) incomplete accounting of patients and outcome events, and (5) selective outcome reporting bias. The study was at low risk of bias for most of these key criteria. There was potential high risk of bias for the assessment of subjective outcomes. Additional strengths included a power analysis and analyses on potential confounding factors. A major caveat of the study was that it did not meet it's planned enrollment. The authors planned on recruiting 228 patients for induction therapy, 205 (90%) of them should be available for treatment assessment after induction therapy, 184 were expected to achieve CR/PR (90%), and 90% of these patients (165 patients) should have been eligible for randomization. If the dropout rate was not higher than 10% in the maintenance/observation period, at least 148 (90%) patients should have been available for final assessment after 2 years of the follow-up. 136 patients were enrolled in the study and 66 were randomized to a maintenance arm or observational arm. In the maintenance phase, there was a high rate of attrition.	3
Prica,A., Baldassarre,F., Hicks,L.K., et al: Rituximab in lymphoma and chronic lymphocytic leukaemia: a practice guideline. Clin Oncol (R Coll Radiol) Jan 2017; Vol 29, Issue 1; pp. e13-e28.		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
Felicia Gelsey, MS	None		
Stacy LaClaire, PharmD	None		
Catherine Sabatos, PharmD	None		
		John D Roberts	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
MICROMEDEX	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases		B
John D Roberts	Evidence is Inconclusive	Class III: Not Recommended	Two years of maintenance treatment with rituximab is associated with no demonstrated improvement in overall survival, a less than one year increase in progression free survival, and additional toxicities, some serious; in addition to additional inconvenience and cost.	N/A
Jeffrey Klein	Evidence Favors Efficacy	Class IIa: Recommended, in Most Cases	The use of Rituximab in CLL patients in the studies provided clearly demonstrated efficacy in the progression free survival category. Adverse effects do play a role and is to be considered by the prescriber, however to be able to offer a maintenance therapy with this type of benefit to the CLL patient is significant.	N/A

Richard LoCicero	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	Rituximab maintenance therapy has been shown to improve progression free survival (PFS) without effect on overall survival. Since PFS was the primary endpoint of both studies, efficacy was established. The value of prolonging PFS can be considered in the context of cost and toxicity.	N/A