TRUVEN HEALTH ANALYTICS
an IBM Company

COMPENDIA TRANSPARENCY TRACKING FORM

DATE: 9/26/2018

PACKET: 1793

DRUG: Bevacizumab

USE: Necrosis of central nervous system due to exposure to ionizing radiation

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, 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
Xu,Y.: Bevacizumab Monotherapy Reduces Radiation-induced Brain Necrosis in Nasopharyngeal Carcinoma Patients: A Randomized Controlled Trial. International Journal of Radiation Oncology Biology Physics Aug 01, 2018; Vol 101, Issue 5; pp. 1087-1095	Comments: This was a randomized, open-label, corticosteroid-controlled study. Overall, this study was at low risk of biases associated with poor random sequence generation, lack of blinding (for objective outcomes only), incomplete accounting of patients and outcome events, and selective outcome reporting. The risk of bias associated with poor allocation concealment was unclear and not discussed in the paper. For subjective outcomes, there was potentially high risk of bias for performance bias and detection bias due to the open-label design. Conversely, all of the MRI images were evaluated by a specified radiologist who was blinded to the treatment assignments.	S
Victor A. Levin, et al Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the CNS. Int J Radiat Oncol Biol Phys. 2011 April 1; 79(5): 1487–1495	Comments: This was a placebo-controlled randomized double-blind study. Overall, this study was at low risk of biases associated with lack of blinding, 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. A critical bias is the very small sample size.	S
Furuse M, et al. A prospective, multicentre, single-arm clinical trial of bevacizumab for patients with surgically untreatable, symptomatic brain radiation necrosis. Neuro-Oncology Practice 3(4), 272–280, 2016	Comments: This was a prospective, multicenter, single-arm trial. Of the 41 patients enrolled in this trial, 40 underwent three cycles of bevacizumab. One patient had an adverse event leading to the discontinuation of bevacizumab. Thirty-eight patients were followed up as the full analysis set. Thirty-six patients underwent six administrations of bevacizumab. Of the four patients who discontinued bevacizumab, two had AEs. The median follow-up period was 13.1 months for the full analysis set and 12.9 months for the safety analysis set. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively. The results should be interpreted with caution since the study lacked a control group.	S
Karen Tye, et al. An analysis of radiation necrosis of the central nervous system treated with bevacizumab. J Neurooncol (2014) 117:321–327		3

Yang Wang et al. Reversal of cerebral radiation necrosis with bevacizumab treatment in 17 Chinese patients. European Journal of Medical Research 2012, 17:25		3
Chung,C., Bryant,A., and Brown,P.: Interventions for the treatment of brain radionecrosis after radiotherapy or radiosurgery. Cochrane Database of Systematic Reviews Jul 09, 2018; Vol 2018, Issue 7; p. CD011492.		2

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 IIb: Recommended, in Some Cases	As no correlation between bevacizumab-induced imaging changes and improved clinical outcomes in radiation-induced brain necrosis has been demonstrated, primary endpoints for definitive studies should be clinical outcomes. No study to date conforms to this perspective. A randomized trial by Xu is suggestive of efficacy but compromised by an open label design; further, a reported much lower rate of serious adverse events than in other studies is suspicious and therefore a concern. A too small randomized trial by Fulse is compromised by on the basis of imaging changes rather than clinical changes, which may have led to premature and confounding cross-over.	N/A
Jeffrey Klein	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	The use of Bevacizumab to treat radiation induced necrosis of the central nervous system showed favorable results. The effectiveness was not seen until 6-8 weeks of continuous treatment. The studies were relatively small and adverse effects can be serious.	N/A
Richard LoCicero	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	Bevacizumab has been shown to reduce radiographic evidence of radionecrosis compared to placebo or steroids. Response was associated to improvement in performance status and symptoms control. Toxicity was consistent with that seen in routine use of bevacizumab.	N/A