TRUVEN HEALTH ANALYTICS™
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COMPENDIA TRANSPARENCY TRACKING FORM

DATE: 05/23/16

PACKET: 1133

DRUG: Everolimus

USE: Malignant tumor of breast, advanced, hormone receptor-negative, HER2 positive, in trastuzumab-containing regimens

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, R, 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
Andre, F., O'Regan,R., Ozguroglu,M., et al: Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncology May 2014; Vol 15, Issue 6; pp. 580-591.	Comments: This study was an international, randomised, double-blind, placebo-controlled, phase 3 trial done at 149 centres in 21 countries. 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.	S
Hurvitz,S.A., Andre,F., Jiang,Z., et al: Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial. Lancet Oncology Jul 2015; Vol 16, Issue 7; pp. 816-829	Comments: This study was an international, randomised, double-blind, placebo-controlled, phase 3 trial done at 141 sites in 28 countries. 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.	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
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.

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ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	Evidence is Inconclusive	Class IIb: Recommended, In Some Cases		A
John D Roberts	Evidence is Inconclusive	Class III: Not Recommended	Addition of everolimus to trastuzumab-containing chemotherapy in advanced, hormone-receptor negative, HER2 positive breast cancer has been assessed in two clinical trials that involve somewhat different patient populations and for which only progression free survival and toxicity data are available. It is uncertain that there is an improvement in progression free survival, and, if there is, the magnitude may be quite modest. There is an important increase in toxicity. The risk benefit ratio probably is unfavorable. These results were obtained in a carefully monitored context. In a practice setting benefits are likely to be less and toxicities greater. Choice of an appropriate everolimus dose is problematic: a low dose is less toxic but may be much less effective; administration of a high dose commonly requires dose adjustments in order to avoid more severe toxicities. If these studies subsequently demonstrate an overall survival benefit, the risk-benefit ratio would require re-assessment.	N/A
Jeffrey Klein	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	The addition of everolimus to trastuzumab regimens showed some benefits in progression free survival versus placebo. Everolimus appears to reverse trastuzumab resistance, but the subtype of HR negative and HER2 positive category of patient has to be met to achieve the best results. This "category" of breast cancer patient might limit everolimus use. The adverse effects that everolimus can cause needs to be managed prophylactically and diligently.	N/A
Richard LoCicero	Evidence is Inconclusive	Class IIb: Recommended, In Some Cases	The addition of everolimus to trastuzumab and vinorelbine improved PFS. The addition of everolimus to trastuzumab and paclitaxel did not reach the predetermined PFS endpoint. The efficacy of everolimus added to trastuzumab-containing regimens is not unequivocally established and may only be considered in the context of treatment toxicity given limited clinical benefit.	N/A