TRUVEN HEALTH ANALYTICS

COMPENDIA TRANSPARENCY TRACKING FORM

DRUG: Bendamustine

INDICATION: Metastatic breast cancer

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, 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)]

TRUVEN HEALTH ANALYTICS

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Von,Minckwitz G., et al: Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC. Anti-Cancer Drugs Sep 2005; Vol 16, Issue 8; pp. 871-877.	Study methodology comments: This was a randomized, open-label, multicenter, comparative trial with many strengths. Strengths of the study included 1) defined primary and secondary outcomes and clinical response; 2) conducted a power analysis; 3) provided 95% confidence intervals for primary outcome; 4) presented inclusion criteria; 5) confirmed diagnosis; 6) responses were confirmed at 4 weeks; 7) randomized patients to treatment; 8) compared baseline characteristics; 9) controlled for the effect of potential confounds on outcomes; and 10) made statistical adjustments to preserve the type I error rate when analyzing the primary outcome. Weaknesses included 1) partial explanation of randomization procedure; 2) open-label design without the use of independent reviewers; 3) no discussion on power calculation; 4) no exclusion criteria; and 5) possible selection bias since subjects were not recruited in a random or consecutive manner.	S
Reichmann,U., et al: Salvage chemotherapy for metastatic breast cancer: results of a phase II study with bendamustine. Annals of Oncology Dec 2007; Vol 18, Issue 12; pp. 1981-1984.	Study methodology comments: This was an open-label time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for many potential confounds. Additional weaknesses included 1) absence of a power analysis; 2) open-label study without the use of independent assessors; 3) did not present 95% confidence intervals; and 4) possible selection bias since the patients were not recruited in a random or consecutive manner. Strengths of the study included 1) the use of a within-subject design to control for confounding effects of patient characteristics; 2) confirmed diagnosis; 3) had both inclusion and exclusion criteria; 4) defined response; 5) confirmed response at 4 weeks; 6) defined primary and secondary outcomes; and 7) examined the effect of some potential confounding factors on treatment outcome.	S
Hoffken,K., et al: Bendamustine as salvage treatment in patients with advanced progressive breast cancer: a phase II study. Journal of Cancer Research and Clinical Oncology 1998; Vol 124, Issue 11; pp. 627-632.	This was an open-label time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group. Additional weaknesses included 1) no exclusion criteria; 2) absence of a power analysis; 3) open-label design without the use of independent reviewers; and 4) possible selection bias since the patients were not recruited in a random or consecutive manner. Strengths included 1) the use of a within-subject design to control for confounding effects of patient characteristics; 2) defined response; 3) confirmed diagnosis; 4) responses were confirmed at 4 weeks; 5) had inclusion criteria; 6) presented 95% confidence intervals; and 7) assessed the effect of pretreatment with and without anthracyclines on outcomes.	S

Eichbaum M.H.R., et al: Weekly administration of bendamustine as salvage therapy in metastatic breast cancer: final results of a phase II study. Anti-Cancer Drugs Sep 2007; Vol 18, Issue 8; pp. 963-968.	Study methodology comments: This was an open-label time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group. Additional weaknesses included 1) did not present 95% confidence intervals; 2) open-label design without the use of independent reviewers; 3) did not discuss the details of the required sample size according to the Fleming design; and 4) possible selection bias since the patients were not recruited in a random or consecutive manner. Strengths included 1) the use of a within-subject design to control for confounding effects of patient characteristics; 2) defined response; 3) responses were confirmed at 4 weeks; 4) had inclusion and exclusion criteria; 5) defined primary and secondary outcomes; 6) analyzed the intent-to-treat population; and 7) examined the effect of some potential confounding factors on outcomes.	S
Steinbild,S, et al: Phase II Study with 3rd- or 4th-line bendamustine (flat dose) therapy in patients with metastatic breast cancer. Onkologie Sep 2009; Vol 32, Issue 8-9; pp. 488-492.	Study methodology comments: This was an open-label time-series trial conducted with a two-stage design. The results should be interpreted with caution. A major weakness of the study was the absence of a control group. Additional weaknesses included 1) no exclusion criteria; 2) small sample size; 3) open-label design without the use of independent reviewers; and 4) possible selection bias since the patients were not recruited in a random or consecutive manner. Strengths included 1) the use of a within-subject design to control for confounding effects of patient characteristics; 2) defined response; 3) defined primary and secondary outcomes; 4) responses were confirmed at 4 weeks; 5) had inclusion criteria; 6) presented 95% confidence intervals; and 7) assessed the effect of pretreatment with anthracycline- or taxane-containing therapy on response.	S
Klippstein,A., et al: Pneumocystis carinii pneumonia as a complication of bendamustine monotherapy in a patient with advanced progressive breast cancer. Journal of Cancer Research and Clinical Oncology May 2003; Vol 129, Issue 5; pp. 316-319.		3
Von,Minckwitz G., et al: A phase III randomized trial of bendamustine hydrochloride , methotrexate, and 5-FU (BMF) versus CMF as first-line treatment of patients with metastatic breast cancer. EJC Supplements Sep 2003; Vol 1, Issue 5; p. S201.		3

Loibl,S., et al: A Multicentre Phase I Dose Finding Study to Investigate the Combination of Bendamustine with Weekly Paclitaxel As First Or Second Line Therapy in Patients with Anthracycline Pretreated Metastatic Breast Cancer - the Rita Trial. Annals of Oncology Sep 2008; Vol 19, Issue 8; pp.69-69.		3
Loibl,S, et al: Phase I dose finding study evaluating the combination of bendamustine with weekly paclitaxel in patients with pre-treated metastatic breast cancer: RiTa trial. Cancer Chemotherapy and Pharmacology Apr 2009; Vol 63, Issue 5; pp. 953-958.		1
Von,Minckwitz G., et al: Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC. Anti-Cancer Drugs Sep 2005; Vol 16, Issue 8; pp. 871-877.		1
Pirvulescu,C.: Bendamustine in metastatic breast cancer: An old drug in new design. Breast Care Nov 01, 2008; Vol 3, Issue 5; pp. 333-339.		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
Amy Hemstreet	None	Edward P. Balaban, DO	None
Stacy LaClaire, PharmD	None	Susan Goodin, PharmD	None
Felicia Gelsey, MS	None	James E. Liebmann, MD	None
		Keith A. Thompson, MD	None
		John M. Valgus, PharmD	None

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	---	---	Indication discussion	B
Edward P. Balaban, DO	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	Believe more Phase III studies are warranted- testing against CMF resulted in borderline results + equivocal overall efficacy finding	N/A
Susan Goodin, PharmD	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	Small studies monotherapy with responses seen, it is just unclear in which patients responses occurred (2nd, 3rd, 4th or > in therapy). Phase III combination study revealed improved outcome with Bendamustine compared to cyclophosphamide based therapy.	N/A

James E. Liebmann, MD	Evidence is Inconclusive	Class IIb: Recommended, In Some Cases	Bendamustine has modest activity in breast cancer. As a single agent in previously treated patients, the objective response rate is ~20%. In the randomized trial in untreated patients, BMF was practically identical to CMF. Toxicity is acceptable. There are no data in previously treated patients comparing bendamustine with other agents (E.G., Capecitabine, Vinorelbine, Gemcitabine, platinum, etc.) Hence, use of the drug in this disease is defensible, but it is probably wiser to use more established compounds.	N/A
Keith A. Thompson, MD	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	None	N/A
John M. Valgus, PharmD	Evidence is Inconclusive	Class IIb: Recommended, In Some Cases	Although several trials show activity in refractory setting, noncomparative and almost all from same country. Phase III trial would need to be replicated.	N/A