TRUVEN HEALTH ANALYTICS

COMPENDIA TRANSPARENCY TRACKING FORM

DRUG: Exemestane

INDICATION: Breast cancer, Neoadjuvant therapy for hormone receptor-positive disease in postmenopausal women

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

	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Semiglazov,V.F., et al: Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer Jul 15, 2007; Vol 110, Issue 2; pp. 244-254.	Study methodology comments: This was a randomized, open-label, comparative trial. Strengths of the study included 1) randomized patients to groups; 2) explained method of randomization; 3) had both inclusion and exclusion criteria; 4) defined primary and secondary outcomes; 5) defined outcomes and response; 6) conducted a power analysis; and 7) controlled for the effect of confounding factors on outcomes. Weaknesses included 1) open-label design without the use of independent reviewers; 2) did not present 95% confidence intervals; and 3) possible selection bias since subjects were not recruited in a random or consecutive manner. Clinical comments: No stratification of results between exemestane and anastrozole.	3
Toi M, et al. Ki67 index changes, pathological response and clinical benefits in primary breast cancer patients treated with 24weeks of aromatase inhibition. Cancer Sci. 2011 Apr;102(4):858-865.	Study methodology comments: This was an open-label time-series trial. 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) open-label design without the use of independent reviewers; 2) no exclusion criteria; 3) partial explanation of power; 4) did not present 95% confidence intervals; and 5) possible selection bias since 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) defined primary and secondary outcomes and response; 4) had inclusion criteria; 5) responses were confirmed at four weeks; 6) examined the effect of many potential confounding factors on treatment outcome; 7) conducted a power analysis; 8) immunostained slides were independently evaluated by an assessor blinded to clinical outcome; and 9) assessed the intent-to-treat population. Clinical comments: No stratification of results between exemestane and anastrozole	S

Barnadas,A., et al: Exemestane as primary treatment of oestrogen receptor-positive breast cancer in postmenopausal women: a phase II trial. Br J Cancer Feb 10, 2009; Vol 100, Issue 3; pp. 442-449.	Study methodology comments: This was an open-label time-series trial. 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) open-label design without the use of independent reviewers; and 2) possible selection bias since 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) defined primary and secondary outcomes and response; 4) had inclusion and exclusion criteria; 5) responses were confirmed at four weeks; 6) examined the effect of many potential confounding factors on treatment outcomes; 7) conducted a power analysis; 8) provided 95% confidence intervals; 9) used a single blinded assessor to review immunochemistry and histological data; and 10) used the same assessor at each research site to assess tumor response.	S
Mlineritsch,B., et al: Exemestane as primary systemic treatment for hormone receptor positive post-menopausal breast cancer patients: a phase II trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-17). Breast Cancer Res Treat Nov 2008; Vol 112, Issue 1; pp. 203-213.	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) open-label design without the use of independent reviewers; 2) absence of a power analysis; 3) did not present 95% confidence intervals; and 4) possible selection bias since 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) defined primary and secondary outcomes and response; 4) had inclusion and exclusion criteria; 5) responses were confirmed at four weeks; and 6) examined the effect of some potential confounding factors on treatment outcome.	3
Tubiana-Hulin,M., et al: Exemestane as neoadjuvant hormonotherapy for locally advanced breast cancer: results of a phase II trial. Anticancer Res Jul 2007; Vol 27, Issue 4C; pp. 2689-2696.	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) open-label design without the use of independent reviewers; and 2) possible selection bias since patients were not recruited in a random or consecutive manner. A major strength of the study was the use of blinded reviewers to assess tumor response. Other strengths included: 1) the use of a within-subject design to control for confounding effects of patient characteristics; 2) presented 95% confidence intervals; 3) defined primary and secondary outcomes and response; 4) had inclusion criteria; 5) conducted power analysis; 6) confirmed response at 4 weeks; and 7) examined the effect of some potential confounding factors on treatment outcome	S

Takei,H., et al: Multicenter phase II trial of neoadjuvant exemestane for postmenopausal patients with hormone receptor-positive, operable breast cancer: Saitama Breast Cancer Clinical Study Group (SBCCSG-03). Breast Cancer Res Treat Jan 2008; Vol 107, Issue 1; pp. 87-94.	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) open-label design without the use of independent reviewers; 2) did not present 95% confidence intervals; and 3) possible selection bias since patients were not recruited in a random or consecutive manner. A major strength of the study was the use of a central review board to assess tumor response. Other strengths included: 1) the use of a within-subject design to control for confounding effects of patient characteristics; 2) confirmed diagnosis; 3) defined primary and secondary outcomes and response; 4) had inclusion and exclusion criteria; 5) conducted power analysis; 6) confirmed estrogen receptor and PgR status; and 7) examined the effect of some potential confounding factors on treatment outcome.	3
Freedman,O.C., et al: A randomized trial exploring the biomarker effects of neoadjuvant sequential treatment with exemestane and anastrozole in post-menopausal women with hormone receptor-positive breast cancer. Breast Cancer Research and Treatment Jan 2010; Vol 119, Issue 1; pp. 155-161.		2
Olson, JA, et al. ACOSOG Z1031: A randomized phase II trial comparing exemestane, letrozole, and anastrozole in postmenopausal women with clinical stage II/III estrogen receptor-positive breast cancer. Abstract. 2010 Breast Cancer Symposium.	Study methodology comments: Abstract	3
N. Sato, et al. Neoadjuvant exemestane for 24 weeks in postmenopausal women with hormone receptor positive stage II or IIIA breast cancer (JFMC34-0601). 2009 ASCO Annual Meeting	Study methodology comments: Abstract	3

Semiglazov,V., et al: Exemestane (E) vs tamoxifen (T) as neoadjuvant endocrine therapy for postmenopausal women with ER plus breast cancer (T2N 1-2, T3NO-1, T4NOMO). Journal of Clinical Oncology Jun 01, 2005; Vol 23, Issue N16,1,S; pp. 11S-11S.	Study methodology comments: Abstract	3
Wolf,C.J., et al: An open label, randomized phase II trial of primary systemic therapy with exemestane (EXE 25 mg/d) plus epirubicin (EPI, 20 vs 30 mg/m(2) q1w x 8-12) in breast cancer: An interim analysis of the German Neoadjuvant Aromasin Initiative (GENARI-3). Journal of Clinical Oncology Jul 15, 2004; Vol 22, Issue N14,S; pp. 82S-82S.	Study methodology comments: Abstract	3
Sancho,B., et al: Exemestane in primary breast cancer patients who are eligible to receive neoadjuvant hormonal therapy. EJC Supplements Jan 2010; Vol 8, Issue N3; pp. 75-75.	Study methodology comments: Abstract	3
Krainick,U., et al: Phase II study to define safety and efficacy of exemestane as preoperative therapy for postmenopausal patients with primary breast cancer - final results of the German Neoadjuvant Aromasin Initiative (GENARI). Breast cancer research and treatment 2003; Vol 82, Issue 1; pp. S55-S55.		3

Freedman,O., et al: A randomized, phase III trial exploring the effects of neoadjuvant sequential treatment with steroidal (exemestane) and non-steroidal (anastrozole) aromatase inhibitors on biomarkers in post-menopausal women with hormone receptor positive locally advanced breast cancer (LABC). EJC Supplements Sep 2009; Vol 7, Issue N2; pp. 269-269.	Study methodology comments: Abstract	3
Gil,m., et al: Exemestane as neoadjuvant treatment in patients >65 years with T>3 cm; preliminary results of a multicenter Spanish phase II trial. Breast Cancer Research and Treatment Dec 2002; Vol 76, Issue Supplement 1; p. S77.	Study methodology comments: Abstract	3
Dehart,J.R., et al: Decreased estrogen receptor and progesterone receptor expression associated with neoadjuvant therapy of exemestane in combination with celecoxib in postmenopausal women with breast cancer. Modern Pathology Mar 2007; Vol 20, Issue 2; pp. 28A-28A.	Study methodology comments: Abstract	3
Semiglazov,V.F., et al: Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer Jul 15, 2007; Vol 110, Issue 2; pp. 244-254.	Study methodology comments: Abstract	3

Semiglazov,V., et al: Direct comparison of primary (neoadjuvant) endocrine therapy vs primary chemotherapy in postmenopausal women with ER-positive breast cancer. Breast Feb 2005; Vol 14, Issue Suppl. 1; p. S39.	Study methodology comments: Abstract	3
Sato,N., et al: Neoadjuvant exemestane for 24 weeks in postmenopausal women with hormone receptor positive stage II or IIIA breast cancer (JFMC34-0601). Journal of Clinical Oncology May 20, 2009; Vol 27, Issue N15,S; p. 1.	Study methodology comments: Abstract	3
Chow,L.W.C. and Toi,m.: Prospective randomized celecoxib+anti-aromatase neoadjuvant Phase II trial on postmenopausal hormone receptor positive primary breast cancer. Breast cancer research and treatment Dec 2002; Vol 76, Issue Supplement 1; p. S77.	Study methodology comments: Abstract	3
Dixon,J.M., et al: Exemestane as neoadjuvant treatment for locally advanced breast cancer: Endocrinologic and clinical endpoints. Breast Cancer Research and Treatment Nov 2000; Vol 64, Issue 1; p. 53.	Study methodology comments: Abstract	3
Dalenc,F., et al: Tamoxifen and exemestane (E) in combination as neoadjuvant treatment of hormone sensitive post-menopausal breast cancer women: Clinical efficacy and effects an tumor pathology and immunopathology. Journal of Clinical Oncology Jul 15, 2004; Vol 22, Issue N14,S; pp. 876S-876S.	Study methodology comments: Abstract	3

Wolf,C., et al: Neoadjuvant exemestan alone or combined with metronomic chemotherapy (epirubicine; paclitaxel; docetaxel): efficacy plus tolerability. Final results of a multicenter phase I/II study (GENARI: German neoadjuvant arornasin initiative). Breast Cancer Research and Treatment 2006; Vol 100, Issue Suppl. 1; p. S151.	Study methodology comments: Abstract	3
Gibson,Lorna, et al: Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database of Systematic Reviews (Online) 2009; Issue 4; p. CD003370.		4
Thomssen,C.: Update 2010 of the German AGO recommendations for the diagnosis and treatment of early and metastatic breast cancer - Chapter a: Surgery, pathology and prognostic factors, adjuvant and neoadjuvant therapy, adjuvant radiotherapy. Breast Care Aug 01, 2010; Vol 5, Issue 4; pp. 259-265.		4
Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol. 2007 Dec;18(12):1927-34. Epub 2007 Nov 12. Review.		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
Margi Schiefelbein, PA	None	Edward P. Balaban, DO	None
Stacy LaClaire, PharmD	None	James E. Liebmann, MD	None
Felicia Gelsey, MS	None	Keith A. Thompson, MD	None
		John M. Valgus, PharmD	None
		Jeffrey A. Bubis,DO	Other payments: Dendreon

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	---	---		B
Edward P. Balaban, DO	Evidence Favors Efficacy	Class IIa: Recommended, in Most Cases	Lack of control group limits 'Effective' rating: Otherwise this drug and this approach leans very heavily from 'Favors Efficacy' to 'Effective.'	N/A
James E. Liebmann, MD	Effective	Class IIb: Recommended, In Some Cases	Pre-operative hormonal therapy with Tamoxifen or an AI is safe and effective in post-menopausal women with ER(+) tumors. Its use, however, should be limited to those patients who are candidates for breast conservation surgery, but who have tumors that preclude such surgery without pre-operative tumor shrinkage. Another, smaller group who would be candidates for initial treatment with an AI is composed of patients who are too frail to tolerate surgery.	N/A

Keith A. Thompson, MD	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	None	N/A
John M. Valgus, PharmD	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	In this selective pt population Exemestane demonstrates efficacy however it was not compared to alternative therapies (ie; tam or chemo) so limited strength of evidence.	N/A
Jeffrey A. Bubis,DO	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	The only reason to use this agent in this setting is that it may increase the likelihood of breast conserving surgery being successful when the patient refuses or is not a candidate for cytotoxic therapy and is post menopausal with an ER(+) tumor. It does not alter survival and there are no randomized trials supporting its efficacy with regard to other outcome measures.	N/A