


MEDICAL / PHARMACY POLICY – 5.01.618

Selective Estrogen Receptor Modulators and Down Regulators

Effective Date:	Apr. 1, 2025	RELATED MEDICAL POLICIES:
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Replaces:	N/A	

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Introduction

Around two-thirds of breast cancers express the estrogen receptor (ER) alpha protein. These ER-positive tumors are dependent on the ER and its cognate ligand, estrogen, for their growth, survival, and progression. Selective estrogen receptor modulators (SERMs) and selective estrogen receptor down-regulators (SERDs) are two major classes of endocrine therapy drugs used for the treatment and/or prevention of ER-positive breast cancers. These therapies are all designed in one way or another to block ER function and signaling. Some SERMs also have estrogen activity in bone and, therefore, prevent bone loss, improve bone mineral density (BMD), and decrease the risk of vertebral fracture. This policy discusses when the use of brand SERMs and SERDs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Arimidex (anastrozole) oral	<p>Arimidex (anastrozole) may be considered medically necessary for:</p> <ul style="list-style-type: none"> • Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer <p>OR</p> <ul style="list-style-type: none"> • Treatment of postmenopausal women with hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer <p>OR</p> <ul style="list-style-type: none"> • Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy <p>OR</p> <ul style="list-style-type: none"> • Treatment of recurrent or metastatic endometrial or uterine cancer <p>OR</p> <ul style="list-style-type: none"> • Treatment of recurrent ovarian cancer <p>OR</p> <ul style="list-style-type: none"> • Risk reduction for breast cancer in postmenopausal women <p>AND</p> <ul style="list-style-type: none"> • The individual has tried generic anastrozole first and had an inadequate response or intolerance to generic anastrozole <p>AND</p> <ul style="list-style-type: none"> • Dose is ≤ 1 mg per day
Aromasin (exemestane) oral	<p>Aromasin (exemestane) may be considered medically necessary for:</p> <ul style="list-style-type: none"> • Adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two or three years of tamoxifen and are switched to Aromasin for completion of a total of five consecutive years of adjuvant hormonal therapy <p>OR</p> <ul style="list-style-type: none"> • Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy <p>OR</p> <ul style="list-style-type: none"> • Risk reduction for invasive breast cancer in postmenopausal women

Drug	Medical Necessity
	<p>AND</p> <ul style="list-style-type: none"> The individual has tried generic exemestane first and had an inadequate response or intolerance to generic exemestane <p>AND</p> <ul style="list-style-type: none"> Dose is ≤ 25 mg per day
Evista (raloxifene) oral	<p>Evista (raloxifene) may be considered medically necessary for:</p> <ul style="list-style-type: none"> Treatment and prevention of osteoporosis in postmenopausal women <p>OR</p> <ul style="list-style-type: none"> Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis <p>OR</p> <ul style="list-style-type: none"> Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer <p>AND</p> <ul style="list-style-type: none"> The individual has tried generic raloxifene first and had an inadequate response or intolerance to generic raloxifene <p>AND</p> <ul style="list-style-type: none"> Dose is ≤ 60 mg per day
Fareston (toremifene) oral	<p>Fareston (toremifene) may be considered medically necessary for:</p> <ul style="list-style-type: none"> Treatment of metastatic breast cancer in postmenopausal women with estrogen receptor positive or unknown tumors <p>AND</p> <ul style="list-style-type: none"> The individual has tried generic toremifene first and had an inadequate response or intolerance to generic toremifene <p>AND</p> <ul style="list-style-type: none"> Dose is ≤ 60 mg per day
Faslodex (fulvestrant) IM	<p>Faslodex (fulvestrant) may be considered medically necessary for:</p> <ul style="list-style-type: none"> Treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative* advanced breast cancer in postmenopausal women not previously treated with endocrine therapy <p>OR</p>

Drug	Medical Necessity
	<ul style="list-style-type: none"> • Treatment of hormone-receptor (HR)-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy <p>OR</p> <ul style="list-style-type: none"> • Treatment of HR-positive, HER2-negative* advanced or metastatic breast cancer in combination with ribociclib in postmenopausal women as initial endocrine-based therapy or following disease progression on endocrine therapy <p>OR</p> <ul style="list-style-type: none"> • Treatment of HR-positive, HER2-negative* advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression following endocrine therapy <p>OR</p> <ul style="list-style-type: none"> • Treatment in combination with Truqap (capivasertib) of adult individuals with HR-positive, HER2-negative* locally advanced or metastatic breast cancer with one or more <i>PIK3CA/AKT1/PTEN</i>-alterations and has progressed on at least one endocrine-based regimen in the metastatic setting or had recurrence on or within 12 months of completing adjuvant therapy <p>AND</p> <ul style="list-style-type: none"> • The individual has tried generic fulvestrant first and had an inadequate response or intolerance to generic fulvestrant <p>*Note: HER2-negative status is defined as 0 or 1+ intensity on immunohistochemical testing or 2+ intensity on immunohistochemical testing and no amplification on in situ hybridization.</p>
Femara (letrozole) oral	<p>Femara (letrozole) may be considered medically necessary for:</p> <ul style="list-style-type: none"> • Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer <p>OR</p> <ul style="list-style-type: none"> • Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy <p>OR</p>

Drug	Medical Necessity
	<ul style="list-style-type: none"> Treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer <p>OR</p> <ul style="list-style-type: none"> Treatment of recurrent ovarian cancer <p>AND</p> <ul style="list-style-type: none"> The individual has tried generic letrozole first and had an inadequate response or intolerance to generic letrozole <p>AND</p> <ul style="list-style-type: none"> Dose is ≤ 2.5 mg per day
Orserdu (elacestrant) oral	<p>Orserdu (elacestrant) may be considered medically necessary for:</p> <ul style="list-style-type: none"> Treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative*, <i>ESR1</i>-mutated advanced or metastatic breast cancer <p>AND</p> <ul style="list-style-type: none"> Experienced disease progression following at least one line of endocrine therapy <p>AND</p> <ul style="list-style-type: none"> Dose is 345 mg or less per day <p>*Note: HER2-negative status is defined as 0 or 1+ intensity on immunohistochemical testing or 2+ intensity on immunohistochemical testing and no amplification on in situ hybridization.</p>

Drug	Investigational
As listed	The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.

Length of Approval	
Approval	Criteria
Initial authorization	Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months.

Length of Approval

Approval	Criteria
Re-authorization criteria	Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
J9395	Injection, fulvestrant, (Faslodex), 25 mg

Related Information

Benefit Application

The drugs in this policy that are administered orally are managed through the pharmacy benefit. Drugs administered via IM injection are managed through the pharmacy and medical benefit.

Evidence Review

Background

Breast cancer is the second most commonly diagnosed cancer worldwide. It is also the leading cause of cancer death in women worldwide. In the United States, breast cancer accounts for over 260,000 cases each year and is responsible for over 40,000 deaths. The incidence rates decreased from 1999 to 2007 by 1.8% per year.

Breast cancer mortality rates have been decreasing since the 1970s. This decrease in mortality is due to improved breast cancer screening and improvements in adjuvant therapy. Therapy saves lives when breast cancers are treated earlier, as demonstrated in a landmark article in which women 40 to 69 who participated in organized mammography screening had a 60% lower risk of dying from breast cancer within 10 years after diagnosis and a 47% lower risk of dying from breast cancer within 20 years after diagnosis compared with women who did not participate in screening.

Once a diagnosis of breast cancer is established, it is important to accurately define the initial extent of disease since this information will affect treatment recommendations.

Summary of Evidence

Arimidex (anastrozole)

Efficacy

The first analysis of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial (median follow-up, 33 months) demonstrated that in adjuvant endocrine therapy for postmenopausal individuals with early-stage breast cancer, anastrozole was superior to tamoxifen in terms of disease-free survival (DFS), time to recurrence (TTR), and incidence of contralateral breast cancer (CLBC). DFS estimates at 4 years remained significantly more favorable (86.9% vs. 84.5%, respectively) for individuals receiving anastrozole compared with those receiving tamoxifen (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.76-0.99; $P = 0.03$). The benefit generated by anastrozole in terms of DFS was even greater in individuals with hormone receptor-positive tumors (HR, 0.82; 95% CI, 0.70-0.96; $P = 0.014$). The HR for TTR also indicated a significant benefit for individuals receiving anastrozole compared with those receiving tamoxifen (HR, 0.83; 95% CI, 0.71-0.96; $P = 0.015$), with additional benefit for individuals with hormone receptor-positive tumors (HR, 0.78; 95% CI, 0.65-0.93; $P = 0.007$). CLBC incidence data also continued to favor anastrozole (odds ratio [OR], 0.62; 95% CI, 0.38-1.02; $P = 0.062$), and statistical significance



was achieved in the hormone receptor-positive subgroup (OR, 0.56; 95% CI, 0.32-0.98; P = 0.042).

Two double-blind, controlled clinical studies of similar design (0030, a North American study and 0027, a predominately European study) were conducted to assess the efficacy of Arimidex compared with tamoxifen as first-line therapy for hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer in postmenopausal women. A total of 1021 individuals between the ages of 30 and 92 years old were randomized to receive trial treatment. Individuals were randomized to receive 1 mg of Arimidex once daily or 20 mg of tamoxifen once daily. The primary endpoints for both trials were time to tumor progression, objective tumor response rate, and safety. For the primary endpoints, trial 0030 showed that Arimidex had a statistically significant advantage over tamoxifen ($p=0.006$) for time to tumor progression; objective tumor response rates were similar for Arimidex and tamoxifen. Trial 0027 showed that Arimidex and tamoxifen had similar objective tumor response rates and time to tumor progression.

Anastrozole was studied in two controlled clinical trials (0004, a North American study; 0005, a predominately European study) in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy for either advanced or early breast cancer. In both studies there were no significant differences between treatment arms with respect to any of the efficacy parameters.

Safety/Tolerability

Adverse reaction data for adjuvant therapy are based on the ATAC trial. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for individuals receiving Arimidex 1 mg and tamoxifen 20 mg, respectively.

In women with pre-existing ischemic heart disease, an increased incidence of ischemic cardiovascular events was observed with Arimidex in the ATAC trial (17% of individuals on Arimidex and 10% of individuals on tamoxifen).

Results from the ATAC trial bone sub-study at 12 and 24 months demonstrated that individuals receiving Arimidex had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Individuals receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline.

During the ATAC trial, more individuals receiving Arimidex were reported to have elevated serum cholesterol compared to individuals receiving tamoxifen (9% versus 3.5%, respectively).

Based on findings from animal studies and its mechanism of action, Arimidex can cause fetal harm when administered to a pregnant woman. Anastrozole caused embryo-fetal toxicities in rats at maternal exposure that were 9 times the human clinical exposure, based on area under the curve (AUC). In rabbits, anastrozole caused pregnancy failure at doses equal to or greater than 16 times the recommended human dose on a mg/m² basis.

Aromasin (exemestane)

Efficacy

The Intergroup Exemestane Study 031 (IES) was a randomized, double-blind, multicenter, multinational study comparing exemestane (25 mg/day) vs. tamoxifen (20 or 30 mg/day) in postmenopausal women with early breast cancer. Individuals who remained disease-free after receiving adjuvant tamoxifen therapy for 2 to 3 years were randomized to receive an additional 3 or 2 years of Aromasin or tamoxifen to complete a total of 5 years of hormonal therapy. Disease-free survival in the intent-to-treat population was statistically significantly improved [Hazard Ratio (HR) = 0.69, 95% CI: 0.58, 0.82, P = 0.00003] in the Aromasin arm compared to the tamoxifen arm. In the hormone receptor-positive subpopulation representing about 85% of the trial individuals, disease-free survival was also statistically significantly improved (HR = 0.65, 95% CI: 0.53, 0.79, P = 0.00001) in the Aromasin arm compared to the tamoxifen arm. Consistent results were observed in the subgroups of individuals with node negative or positive disease, and individuals who had or had not received prior chemotherapy. An overall survival update at 119 months median follow-up showed no significant difference between the two groups, with 467 deaths (19.9%) occurring in the Aromasin group and 510 deaths (21.5%) in the tamoxifen group.

Exemestane 25 mg administered once daily was evaluated in a randomized double-blind, multicenter, multinational comparative study and in two multicenter single-arm studies of postmenopausal women with advanced breast cancer who had disease progression after treatment with tamoxifen for metastatic disease or as adjuvant therapy. In the comparative study, 769 individuals were randomized to receive Aromasin (exemestane tablets) 25 mg once daily (N = 366) or megestrol acetate 40 mg four times daily (N = 403). The objective response rates observed in the two treatment arms showed that Aromasin was not different from megestrol acetate. Response rates for Aromasin from the two single-arm trials were 23.4% and

28.1%. There were too few deaths occurring across treatment groups to draw conclusions on overall survival differences.

Safety/Tolerability

Aromasin tolerability in postmenopausal women with early breast cancer was evaluated in two well-controlled trials: the IES study and the 027 study (a randomized, placebo-controlled, double-blind, parallel group study specifically designed to assess the effects of exemestane on bone metabolism, hormones, lipids, and coagulation factors over 2 years of treatment).

The median duration of adjuvant treatment was 27.4 months and 27.3 months for individuals receiving Aromasin or tamoxifen, respectively, within the IES study and 23.9 months for individuals receiving Aromasin or placebo within the 027 study. Median duration of observation after randomization for Aromasin was 34.5 months and for tamoxifen was 34.6 months. Median duration of observation was 30 months for both groups in the 027 study.

Certain adverse reactions, which were expected based on the known pharmacological properties and side effect profiles of test drugs, were actively sought through a positive checklist. Signs and symptoms were graded for severity using CTC in both studies. Within the IES study, the presence of some illnesses/conditions was monitored through a positive checklist without assessment of severity. These included myocardial infarction, other cardiovascular disorders, gynecological disorders, osteoporosis, osteoporotic fractures, other primary cancer, and hospitalizations.

Within the IES study, discontinuations due to adverse reactions occurred in 6.3% and 5.1% of individuals receiving Aromasin and tamoxifen, respectively, and in 12.3% and 4.1% of individuals receiving exemestane or placebo respectively within study 027.

Evista (raloxifene)

Efficacy

The effects of Evista on fracture incidence and BMD in postmenopausal women with osteoporosis were examined at 3 years in a large randomized, placebo-controlled, double-blind, multinational osteoporosis treatment trial (MORE). All vertebral fractures were diagnosed radiographically; some of these fractures also were associated with symptoms (i.e., clinical fractures). The study population consisted of 7705 postmenopausal women with osteoporosis as defined by: a) low BMD (vertebral or hip BMD at least 2.5 standard deviations below the mean value for healthy young women) without baseline vertebral fractures or b) one or more baseline

vertebral fractures. Women enrolled in this study had a median age of 67 years (range 31 to 80) and a median time since menopause of 19 years. Evista, 60 mg administered once daily, increased spine and hip BMD by 2 to 3%. Evista decreased the incidence of the first vertebral fracture from 4.3% for placebo to 1.9% for Evista (relative risk reduction = 55%) and subsequent vertebral fractures from 20.2% for placebo to 14.1% for Evista (relative risk reduction = 30%). All women in the study received calcium (500 mg/day) and vitamin D (400 to 600 IU/day). Evista reduced the incidence of vertebral fractures whether or not individuals had a vertebral fracture upon study entry. The decrease in incidence of vertebral fracture was greater than could be accounted for by increase in BMD alone. The mean percentage change in BMD from baseline for Evista was statistically significantly greater than for placebo at each skeletal site. Bone biopsies for qualitative and quantitative histomorphometry were obtained at baseline and after 2 years of treatment. There were 56 paired biopsies evaluable for all indices. In Evista-treated individuals, there were statistically significant decreases in bone formation rate per tissue volume, consistent with a reduction in bone turnover. Normal bone quality was maintained; specifically, there was no evidence of osteomalacia, marrow fibrosis, cellular toxicity, or woven bone after 2 years of treatment. Endometrial thickness was evaluated annually in a subset of the study population (1781 individuals) for 3 years. Placebo-treated women had a 0.27 mm mean decrease from baseline in endometrial thickness over 3 years, whereas the Evista-treated women had a 0.06 mm mean increase. Individuals in the osteoporosis treatment study were not screened at baseline or excluded for pre-existing endometrial or uterine disease. This study was not specifically designed to detect endometrial polyps. Over the 36 months of the study, clinically or histologically benign endometrial polyps were reported in 17 of 1999 placebo-treated women, 37 of 1948 Evista-treated women, and in 31 of 2010 women treated with raloxifene HCl 120 mg/day. There was no difference between Evista- and placebo-treated women in the incidences of endometrial carcinoma, vaginal bleeding, or vaginal discharge.

The effects of Evista on BMD in postmenopausal women were examined in three randomized, placebo controlled, double-blind osteoporosis prevention trials: (1) a North American trial enrolled 544 women; (2) a European trial, 601 women; and (3) an international trial, 619 women who had undergone hysterectomy. In these trials, all women received calcium supplementation (400 to 600 mg/day). Women enrolled in these trials had a median age of 54 years and a median time since menopause of 5 years (less than 1 year up to 15 years postmenopause). The majority of the women were White (93.5%). Women were included if they had spine BMD between 2.5 standard deviations below and 2 standard deviations above the mean value for healthy young women. The mean T scores (number of standard deviations above or below the mean in healthy young women) for the three trials ranged from -1.01 to -0.74 for spine BMD and included women both with normal and low BMD. Evista, 60 mg administered once daily, produced increases in bone mass versus calcium supplementation alone, as reflected by dual-energy x-ray

absorptiometric (DXA) measurements of hip, spine, and total body BMD. Compared with placebo, the increases in BMD for each of the three studies were statistically significant at 12 months and were maintained at 24 months. The placebo groups lost approximately 1% of BMD over 24 months. Evista also increased BMD compared with placebo in the total body by 1.3% to 2.0% and in Ward's Triangle (hip) by 3.1% to 4.0%. The effects of EVISTA on forearm BMD were inconsistent between studies. In the European trial, Evista prevented bone loss at the ultradistal radius, whereas in the North American Trial it did not.

In placebo-controlled osteoporosis prevention trials, endometrial thickness was evaluated every 6 months (for 24 months) by transvaginal ultrasonography (TVU). A total of 2978 TVU measurements were collected from 831 women in all dose groups. Placebo-treated women had a 0.04 mm mean increase from baseline in endometrial thickness over 2 years, whereas the EVISTA-treated women had a 0.09 mm mean increase. Endometrial thickness measurements in raloxifene-treated women were indistinguishable from placebo. There were no differences between the raloxifene and placebo groups with respect to the incidence of reported vaginal bleeding. The effect of Evista on the incidence of breast cancer was assessed as a secondary safety endpoint in a randomized, placebo-controlled, double-blind, multinational osteoporosis treatment trial in postmenopausal women. After 4 years, Evista, 60 mg administered once daily, reduced the incidence of all breast cancers by 62%, compared with placebo (HR 0.38, 95% CI 0.22-0.67). Evista reduced the incidence of invasive breast cancer by 71%, compared with placebo (ARR 3.1 per 1000 women-years); this was primarily due to an 80% reduction in the incidence of ER-positive invasive breast cancer in the Evista group compared with placebo.

The effects of Evista 60 mg/day versus tamoxifen 20 mg/day over 5 years on reducing the incidence of invasive breast cancer were assessed in 19,747 postmenopausal women in a randomized, double-blind trial conducted in North America by the National Surgical Adjuvant Breast and Bowel Project and sponsored by the National Cancer Institute. Women in this study had a mean age of 58.5 years (range 35-83), a mean 5-year predicted invasive breast cancer risk of 4.03% (range 1.66-23.61%), and 9.1% had a history of lobular carcinoma in situ (LCIS). More than 93% of participants were White. As of 31 December 2005, the median time of follow-up was 4.3 years (range 0.07-6.50 years). Evista was not superior to tamoxifen in reducing the incidence of invasive breast cancer. The observed incidence rates of invasive breast cancer were Evista 4.4 and tamoxifen 4.3 per 1000 women per year. The results from a noninferiority analysis are consistent with Evista potentially losing up to 35% of the tamoxifen effect on reduction of invasive breast cancer. The effect of each treatment on invasive breast cancer was consistent when women were compared by baseline age, history of LCIS, history of atypical hyperplasia, 5-year predicted risk of breast cancer by the modified Gail model, or the number of relatives with a history of breast cancer. Fewer noninvasive breast cancers occurred in the tamoxifen group compared to the Evista group.



Safety/Tolerability

In clinical trials, Evista-treated women had an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism).

In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, an increased risk of death due to stroke was observed after treatment with Evista. During an average follow-up of 5.6 years, 59 (1.2%) Evista-treated women died due to a stroke compared to 39 (0.8%) placebo-treated women (22 versus 15 per 10,000 women-years; hazard ratio 1.49; 95% confidence interval, 1.00-2.24; $p=0.0499$). There was no statistically significant difference between treatment groups in the incidence of stroke (249 in Evista [4.9%] versus 224 placebo [4.4%]). Evista had no significant effect on all-cause mortality.

Limited clinical data suggest that some women with a history of marked hypertriglyceridemia (>5.6 mmol/L or >500 mg/dL) in response to treatment with oral estrogen or estrogen plus progestin may develop increased levels of triglycerides when treated with Evista.

Fareston (toremifene)

Efficacy

Three prospective, randomized, controlled clinical studies (North American, Eastern European, and Nordic) were conducted to evaluate the efficacy of Fareston for the treatment of breast cancer in postmenopausal women. The individuals were randomized to parallel groups receiving Fareston 60 mg (FAR60) or tamoxifen 20 mg (TAM20) in the North American Study or tamoxifen 40 mg (TAM40) in the Eastern European and Nordic studies. The North American and Eastern European studies also included high-dose toremifene arms of 200 and 240 mg daily, respectively. The studies included postmenopausal individuals with estrogen-receptor (ER) positive or estrogen-receptor (ER) unknown metastatic breast cancer. The individuals had at least one measurable or evaluable lesion. The primary efficacy variables were response rate (RR) and time to progression (TTP). Survival (S) was also determined. Ninety-five percent confidence intervals (95% CI) were calculated for the difference in RR between FAR60 and TAM groups and the hazard ratio (relative risk for an unfavorable event, such as disease progression or death) between TAM and FAR60 for TTP and S. Two of the 3 studies showed similar results for all effectiveness endpoints. However, the Nordic Study showed a longer time to progression for tamoxifen. The high-dose groups, toremifene 200 mg daily in the North American Study and 240 mg daily in the Eastern European Study, were not superior to the lower toremifene dose



groups, with response rates of 22.6% and 28.7%, median times to progression of 5.6 and 6.1 months, and median survivals of 30.1 and 23.8 months, respectively. The median treatment duration in the three pivotal studies was 5 months (range 4.2-6.3 months).

Safety/Tolerability

Toremifene has been shown to prolong the QTc interval in a dose-and concentration-related manner.

Hepatotoxicity, both increases in the serum concentration for grade 3 and 4 transaminitis and hyperbilirubinemia, including jaundice, hepatitis, and non-alcoholic fatty liver disease, have also been reported in clinical trials and postmarketing with Fareston.

Endometrial cancer, endometrial hypertrophy, hyperplasia, and uterine polyps have been reported in some individuals treated with Fareston. Endometrial hyperplasia of the uterus was observed in animals treated with toremifene.

Faslodex (fulvestrant)

Efficacy

Efficacy of Faslodex was established by comparison to the selective aromatase inhibitor anastrozole in two randomized, controlled clinical trials (one conducted in North America, Study 0021, NCT00635713; the other predominantly in Europe, Study 0020) in postmenopausal women with locally advanced or metastatic breast cancer. All individuals had progressed after previous therapy with an antiestrogen or progestin for breast cancer in the adjuvant or advanced disease setting. The effectiveness of Faslodex 250 mg was determined by comparing Objective Response Rate (ORR) and Time to Progression (TTP) results to anastrozole 1 mg, the active control. The two studies ruled out (by one-sided 97.7% confidence limit) inferiority of Faslodex to anastrozole of 6.3% and 1.4% in terms of ORR. There was no statistically significant difference in overall survival (OS) between the two treatment groups after a follow-up duration of 28.2 months in Study 0021 and 24.4 months in Study 0020.

The efficacy of Faslodex 500 mg in combination with palbociclib 125 mg was compared to Faslodex 500 mg plus placebo in PALOMA-3. PALOMA-3 (NCT-1942135) was an international, randomized, double-blind, parallel group, multi-center study of Faslodex plus palbociclib versus Faslodex plus placebo conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior



endocrine therapy. Consistent PFS results were observed across individual subgroups of disease site, sensitivity to prior hormonal therapy, and menopausal status. After a median follow-up time of 45 months, the final OS results were not statistically significant.

The efficacy of Faslodex in combination with ribociclib was compared to plus placebo in MONALEESA-3. MONALEESA-3 (NCT 02422615) was a randomized double-blind, placebo-controlled study of Faslodex plus ribociclib versus Faslodex plus placebo conducted in postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. Consistent results were observed in stratification factor subgroups of disease site and prior endocrine treatment for advanced disease.

The efficacy of Faslodex 500 mg in combination with abemaciclib 150 mg was compared to Faslodex 500 mg plus placebo in MONARCH 2. MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multi-center study conducted in women with HR-positive, HER2-negative metastatic breast cancer with disease progression following endocrine therapy treated with Faslodex plus abemaciclib versus Faslodex plus placebo. PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent results were observed across individual stratification subgroups of disease site and endocrine therapy resistance for PFS and OS.

MONALEESA-3 (NCT 02422615) was a randomized double-blind, placebo-controlled study of Faslodex plus ribociclib versus Faslodex plus placebo conducted in postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment. Consistent results were observed in stratification factor subgroups of disease site and prior endocrine treatment for advanced disease.

Safety/Tolerability

The most frequently reported adverse reactions in the Faslodex 500 mg group were injection site pain (11.6% of individuals), nausea (9.7% of individuals), and bone pain (9.4% of individuals); the most frequently reported adverse reactions in the Faslodex 250 mg group were nausea (13.6% of individuals), back pain (10.7% of individuals), and injection site pain (9.1% of individuals).



Femara (letrozole)

Efficacy

In a multicenter study (BIG 1-98, NCT00004205) enrolling over 8,000 postmenopausal women with resected, receptor positive early breast cancer, one of the following treatments was randomized in a double-blind manner: Option 1: A. tamoxifen for 5 years, or B. Femara for 5 years, or C. tamoxifen for 2 years followed by Femara for 3 years, or D. Femara for 2 years followed by tamoxifen for 3 years. Option 2: A. tamoxifen for 5 years, or B. Femara for 5 years. The study in the adjuvant setting, BIG 1-98 was designed to answer two primary questions: whether Femara for 5 years was superior to Tamoxifen for 5 years (Primary Core Analysis) and whether switching endocrine treatments at 2 years was superior to continuing the same agent for a total of 5 years. The medians of overall survival for both arms were not reached for the MAA. There was no statistically significant difference in overall survival. The hazard ratio for survival in the Femara arm compared to the tamoxifen arm was 0.87, with 95% CI (0.75, 1.02). There were no significant differences in DFS, OS, SDFS, and Distant DFS from switch in the Sequential Treatments Analysis with respect to either monotherapy (e.g., [tamoxifen 2 years followed by] Femara 3 years versus tamoxifen beyond 2 years, DFS HR 0.89; 97.5% CI 0.68, 1.15 and [Femara 2 years followed by] tamoxifen 3 years versus Femara beyond 2 years, DFS HR 0.93; 97.5% CI 0.71, 1.22). There were no significant differences in DFS, OS, SDFS, and Distant DFS from randomization in the Sequential Treatments Analyses.

A double-blind, randomized, placebo-controlled trial (MA-17, NCT00003140) of Femara was performed in over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who were disease free after 5 years of adjuvant treatment with tamoxifen. Disease-free survival was measured as the time from randomization to the earliest event of loco-regional or distant recurrence of the primary disease or development of contralateral breast cancer or death. DFS by hormone receptor status, nodal status and adjuvant chemotherapy were similar to the overall results. Data were premature for an analysis of survival.

Safety/Tolerability

Results of a safety study to evaluate safety in the adjuvant setting comparing the effect on lumbar spine (L2-L4) BMD of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) ($P < 0.0001$). Updated results from the BMD substudy (MA-17B) in the extended adjuvant setting demonstrated that at 2 years individuals receiving letrozole had a median decrease from baseline of 3.8% in hip BMD

compared to a median decrease of 2.0% in the placebo group. The changes from baseline in lumbar spine BMD in letrozole and placebo treated groups were not significantly different. In the adjuvant trial (BIG 1-98) the incidence of bone fractures at any time after randomization was 14.7% for letrozole and 11.4% for tamoxifen at a median follow-up of 96 months. The incidence of osteoporosis was 5.1% for letrozole and 2.7% for tamoxifen. In the extended adjuvant trial (MA-17), the incidence of bone fractures at any time after randomization was 13.3% for letrozole and 7.8% for placebo at a median follow-up of 62 months. The incidence of new osteoporosis was 14.5% for letrozole and 7.8% for placebo.

In the adjuvant trial (BIG 1-98), hypercholesterolemia was reported in 52.3% of letrozole individuals and 28.6% of tamoxifen individuals. Grade 3-4 hypercholesterolemia was reported in 0.4% of letrozole individuals and 0.1% of tamoxifen individuals. Also in the adjuvant setting, an increase of greater than or equal to 1.5 x upper limit of normal (ULN) in total cholesterol (generally nonfasting) was observed in individuals on monotherapy who had baseline total serum cholesterol within the normal range (i.e., less than =1.5 x ULN) in 155/1843 (8.4%) individuals on letrozole vs 71/1840 (3.9%) individuals on tamoxifen. Lipid lowering medications were required for 29% of individuals on letrozole and 20% on tamoxifen.

Based on post-marketing reports, findings from animal studies and the mechanism of action, Femara can cause fetal harm and is contraindicated for use in pregnant women. In post-marketing reports, use of letrozole during pregnancy resulted in cases of spontaneous abortions and congenital birth defects. Letrozole caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below the maximum recommended human dose (MHRD) on a mg/m² basis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during therapy with Femara and for at least 3 weeks after the last dose.

Orserdu (elacestrant)

Efficacy

In the subgroup of individuals whose tumors had ESR1 mutations, Orserdu reduced the risk of progression or death by 45% (PFS 3.8 months versus 1.9 months; hazard ratio [HR] = 0.55, 95% confidence interval [CI]: 0.39, 0.77) versus SOC. A statistically significant difference in PFS was also observed for all individuals in the intention-to-treat (ITT) population versus SOC (PFS 2.8 months versus 1.9 months; HR = 0.70; 95% CI, 0.55 to 0.88; P = 0.002). However, an exploratory analysis of PFS in the 250 (52%) individuals without ESR1 mutations showed an HR of 0.86 (95%



CI: 0.63, 1.19), indicating that the improvement in the ITT population was primarily attributed to the results seen in the ESR1-mutated population only.

Safety/Tolerability

Safety data were consistent with the other endocrine therapies. Most of the adverse events (AEs), including nausea and musculoskeletal pain, were Grade 1 and 2. No hematological safety signal was observed and none of the individuals in either of the two treatment arms had sinus bradycardia. The most common (>10%) AEs, including laboratory abnormalities, with Orserdu were musculoskeletal pain, nausea, increased cholesterol, increased aspartate transaminase, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased alanine transaminase, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.

US Preventive Services Task Force Recommendations

The USPSTF recommends offering risk-reducing medications to women at increased risk for breast cancer and at low risk for adverse medication effects (B recommendation) and recommends against routine use of risk-reducing medications in women not at increased risk (D recommendation). The current recommendation now includes aromatase inhibitors among medications that can reduce risk of breast cancer.

Various methods are available to identify women at increased risk for breast cancer, including formal clinical risk assessment tools or assessing breast cancer risk factors without using a formal tool. The USPSTF does not endorse any particular risk-prediction tool. The National Cancer Institute Breast Cancer Risk Assessment Tool and the Breast Cancer Surveillance Consortium Risk Calculator are based on models tested in US populations and are publicly available. There is no single cutoff for defining increased risk for all women.

Alternatively, clinicians may use combinations of risk factors to identify women at increased risk. Some examples of combinations of multiple risk factors in women at increased risk include (but are not limited to): age 65 years or older with 1 first-degree relative with breast cancer; age 45 years or older with more than 1 first-degree relative with breast cancer or 1 first-degree relative who developed breast cancer before age 50 years; age 40 years or older with a first-degree relative with bilateral breast cancer; presence of atypical ductal or lobular hyperplasia or lobular carcinoma in situ on a prior biopsy.

When considering prescribing breast cancer risk-reducing medications, the potential benefit of risk reduction of breast cancer must be balanced against the potential harms of adverse medication effects.

Tamoxifen, raloxifene, and aromatase inhibitors all reduce primary breast cancer risk in postmenopausal women. Use of raloxifene and aromatase inhibitors is indicated only in postmenopausal women; only tamoxifen is indicated for risk-reduction of primary breast cancer in premenopausal women.

2021 Update

Reviewed prescribing information for all drugs in policy. No new information was identified that would result in changes to policy statements.

2022 Update

Reviewed prescribing information for all drugs in policy. No new information was identified that would result in changes to policy statements.

2023 Update

Reviewed prescribing information for all drugs in policy. Added criteria for Orserdu (elacestrant) for the treatment of breast cancer.

2024 Update

Reviewed prescribing information for all drugs in policy. Updated Faslodex (fulvestrant) to include coverage criteria for the treatment of certain individuals with breast cancer in combination with Truqap (capivasertib).



2025 Update

Reviewed prescribing information for all drugs in policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

References

1. Arimidex (anastrozole) prescribing information. ANI Pharmaceuticals, Inc.; Baudette, MN. Revised December 2024.
2. Aromasin (exemestane) prescribing information. Pfizer Inc.; New York, NY. Revised December 2024.
3. Evista (raloxifene) prescribing information. Lilly USA, LLC.; Indianapolis, IN. Revised March 2023.
4. Fareston (toremifene) prescribing information. Kyowa Kirin, Inc.; Bedminster, NJ. Revised October 2024.
5. Faslodex (fulvestrant) prescribing information. AstraZeneca Pharmaceuticals, LP.; Wilmington, DE. Revised January 2021.
6. Femara (letrozole) prescribing information. Novartis Pharmaceuticals; East Hanover, NJ. Revised December 2024.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed March 9, 2025.
8. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Risk Reduction. Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast_risk.pdf. Accessed March 9, 2025.
9. Uspreventiveservicestaskforce.org. 2019. Breast Cancer: Medication Use To Reduce Risk. [online] Available at: <https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-medications-for-risk-reduction> Accessed March 9, 2025.
10. Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A, Sahmoud T; ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer*. 2003 Nov 1;98(9):1802-10. doi: 10.1002/cncr.11745. PMID: 14584060.
11. Orserdu (elacestrant) prescribing information. Stemline Therapeutics, Inc. New York, NY. Revised November 2023.
12. American Cancer Society. Breast cancer HER2 status. Last revised August 25, 2022. Accessed March 9, 2025. <https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html>
13. Bardia A, et al. EMERALD: Phase III trial of elacestrant (RAD1901) vs endocrine therapy for previously treated ER+ advanced breast cancer. *Future Oncol*. 2019(28):3209–3218. doi:10.2217/fon-2019-0370
14. Bidard FC, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized Phase III EMERALD trial. *J Clin Oncol*. 2022;40(28):3246–3256. doi:10.1200/JCO.22.00338
15. Brett JO, et al. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res*. 2021;23(1):85. doi:10.1186/s13058-021-01462-3
16. Centers for Disease Control and Prevention. Basic information about breast cancer. Last reviewed November 5, 2024. <https://www.cdc.gov/breast-cancer/about/index.html> Accessed March 9, 2025.



17. Ciruelos E, et al. The therapeutic role of fulvestrant in the management of patients with hormone receptor-positive breast cancer. *Breast*. 2014;23(3):201–8. doi:10.1016/j.breast. 2014.01.016
18. Dustin D, et al. ESR1 mutations in breast cancer. *Cancer*. 2019;125(21):3714–3728. doi:10.1002/cnrc.32345
19. O'Leary B, et al. The genetic landscape and clonal evolution of breast cancer resistance to palbociclib plus fulvestrant in the PALOMA-3 Trial. *Cancer Discov*. 2018;8(11):1390–1403. doi:10.1158/2159-8290.CD-18-0264

History

Date	Comments
11/01/20	New policy, approved October 13, 2020. Added criteria for Arimidex (anastrozole) for the treatment of breast, endometrial, ovarian, and uterine cancers. Added criteria for Aromasin (exemestane) for the treatment of breast cancer. Added criteria for Evista (raloxifene) for the treatment and prevention of osteoporosis and for the treatment of breast cancer. Added criteria for Fareston (toremifene) for the treatment of breast cancer. Added criteria for Faslodex (fulvestrant) for the treatment of breast cancer. Added criteria for Femara (letrozole) for the treatment of breast cancer and ovarian cancer.
01/01/22	Annual Review, approved December 2, 2021. No changes to policy statements.
11/01/22	Annual Review, approved October 24, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/23	Annual Review, approved March 14, 2023. Added criteria for Orserdu (elacestrant) for the treatment of breast cancer.
03/01/24	Annual Review, approved February 26, 2024. Updated Faslodex (fulvestrant) to include coverage criteria for the treatment of certain individuals with breast cancer in combination with Truqap (capivasertib).
11/01/24	Interim Review, approved October 21, 2024. Updated Faslodex (fulvestrant) coverage criteria to apply to the pharmacy and medical benefit. Added HCPCS code J9395 for Faslodex.
04/01/25	Annual Review, approved March 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit



booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

