CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Oncology (Injectable) – Fulvestrant Utilization Management Medical Policy
- Faslodex® (fulvestrant intramuscular injection – AstraZeneca; generic)

REVIEW DATE: 06/18/2025

OVERVIEW

Fulvestrant, an estrogen receptor antagonist, is indicated for **breast cancer** in the following situations:[1]

- As monotherapy:
  - Hormone receptor-positive (HR+) [i.e., estrogen receptor-positive (ER+) or progesterone receptor-positive (PR+)], human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
  - HR+ advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
- Combination therapy:
  - HR+, HER2-negative advanced or metastatic breast cancer in postmenopausal women, in combination with Kisqali® (ribociclib tablets), as initial endocrine based therapy or following disease progression on endocrine therapy.
  - HR+, HER2-negative advanced or metastatic breast cancer, in combination with Ibrance® (palbociclib capsules) or Verzenio® (abemaciclib tablets), in women with disease progression after endocrine therapy.

Fulvestrant binds to the estrogen receptor in a competitive manner.[1] Its affinity to the estrogen receptor is comparable to that of estradiol. By binding to the estrogen receptor, fulvestrant downregulates the estrogen receptor protein in human breast cancer cells.

The recommended dose of fulvestrant as monotherapy and for combination therapy is 500 mg administered intramuscularly (IM) as two 5 mL injections (one to two minutes per injection) on Days 1, 15, 29, and once monthly thereafter. Pre/perimenopausal women treated with the combination fulvestrant and cyclin dependent kinase 4/6 (CDK4/6) inhibitors (Ibrance, Kisqali, Verzenio) should be treated with gonadotropin-releasing hormone (GnRH) agonists for ovarian suppression. The modified dose for moderate hepatic impairment (Child-Pugh class B) for monotherapy and combination therapy is fulvestrant 250 mg IM as one 5 mL injection on Days 1, 15, 29, and once monthly thereafter. Fulvestrant is available as 5-mL prefilled syringes containing 250 mg/5 mL.

Guidelines

Fulvestrant is addressed in National Comprehensive Cancer Network (NCCN) guidelines:

- **Breast Cancer:** NCCN guidelines (version 4.2025 – April 17, 2025) recommend fulvestrant as monotherapy and in combination with other agents for the treatment of HR+ breast cancer in postmenopausal women or premenopausal women receiving ovarian ablation or suppression.[2] Fulvestrant is recommended for use as monotherapy or in combination with trastuzumab in women with HR+, HER2-positive breast cancer (category 2A). In women with HR+, HER2-negative breast cancer, fulvestrant is recommended as a "Preferred", first-line regimen with a CDK4/6 inhibitor (Kisqali, Verzenio) [both category 1]. It is a category 2A regimen for fulvestrant use in combination with Ibrance. Fulvestrant is recommended as one of the "Other Recommended Regimens" in combination with a non-steroidal aromatase inhibitor (anastrozole, letrozole). Fulvestrant monotherapy

is also recommended as first- and subsequent-line therapy as "Other Recommended Regimens" (category 2A). In these women, fulvestrant is recommended in the second- and subsequent-line setting in combination with CDK4/6 inhibitor (if a CDK4/6 inhibitor was not previously used) [category 1], everolimus (category 2A), or Piqray® (alpelisib tablets) [if the patient has a phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)-activating mutation] {category 1}. The guidelines recommend Itovebi® (inabolisib tablets) in combination with fulvestrant and Ibrance® (palbociclib tablets and capsules) under "Useful in Certain Circumstances" for HR+, HER2-negative tumors with *PIK3CA* activating mutations and disease progression on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion (category 1). Fulvestrant in combination with Truqap™ (capivasertib tablets) is a "Preferred Regimen" for second or subsequent-line therapy in patients with *PIK3CA/*serine/threonine protein kinase 1 *(AKT1)/*phosphatase and tensin homolog *(PTEN)*-alterations after progression or recurrence after one or more prior lines of endocrine therapy, including one line containing a CDK 4/6 inhibitor. Men with breast cancer should be treated similarly to postmenopausal women, except that the use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis. Fulvestrant with or without Nerlynx® (neratinib tablets) is listed as "Useful in Certain Circumstances" for patients with HER2-activating mutations in the following situations: patients with estrogen receptor-positive (ER+)/HER2-negative disease who have already received CDK4/6 inhibitor therapy (category 2B) or in triple-negative disease. Nerlynx + trastuzumab + fulvestrant is a category 2A recommended regimen and is also recommended in HR+/HER2- negative disease and triple-negative disease. HER2-activating mutations occur on the HER2 gene. HER2-activating mutations are clinically distinct from the classification of HER2-positive or HER2-negative disease. Examples of HER2 activating mutations include: L755S, D769H/Y, V777L, or exon 20 insertion.[5]

- **Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer:** NCCN guidelines (version 2.2025 – May 23, 2025) recommend single-agent fulvestrant as "Useful in Certain Circumstances" for the treatment of low-grade serous carcinoma for recurrence therapy in platinum-sensitive and platinum-resistant disease (category 2A).[3] Fulvestrant is also recommended under "Other Recommended Regimens" (category 2B) for primary therapy.
- **Uterine Neoplasms:** NCCN guidelines (version 3.2025 – March 7, 2025) recommend fulvestrant under "Other Recommended Regimens" for recurrent or metastatic endometrial carcinoma and for uterine sarcoma (low-grade endometrial stromal sarcoma, adenocarcinoma without sarcomatous overgrowth, or HR+ uterine sarcoma preferably in patients with small tumor volume or an indolent growth pace).[4] Both settings are category 2A recommendations.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of fulvestrant. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with fulvestrant, as well as the monitoring required for adverse events and long-term efficacy, approval requires fulvestrant to be prescribed by or in consultation with a physician who specializes in the condition being treated.

In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men/males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. Female/women are

defined as individuals with the biological traits of a woman, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of fulvestrant is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Breast Cancer – Fulvestrant Monotherapy**. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient has recurrent or metastatic hormone receptor (HR)-positive (i.e., estrogen receptor [ER]- or progesterone receptor [PR]-positive) disease; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient is a postmenopausal female* or a male*; OR
     - **ii.** Patient is pre/perimenopausal female* and meets ONE of the following (a or b):
       - **a)** Patient is receiving ovarian suppression/ovarian ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
         Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), or Zoladex (goserelin acetate subcutaneous implant).
       - **b)** Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist.

   * Refer to the Policy Statement.

   Dosing. 500 mg intramuscularly as two 5 mL injections, on Days 1, 15, 29 and once monthly thereafter.

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2. **Breast Cancer – Fulvestrant Combination Therapy**. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient has recurrent or metastatic hormone receptor (HR)-positive (i.e., estrogen receptor [ER]- or progesterone receptor [PR]-positive) disease; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient is a postmenopausal female* or a male*; OR
     - **ii.** Patient is pre/perimenopausal female* and meets ONE of the following (a or b):
       - **a)** Patient is receiving ovarian suppression/ovarian ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
         Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), or Zoladex (goserelin acetate subcutaneous implant).
       - **b)** Patient had had surgical bilateral oophorectomy or ovarian irradiation; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer and meets ONE of the following (a, b, or c):
       - **a)** Patient has progressed on or after at least one prior endocrine-based therapy and patient meets ONE of the following [(1), (2), or (3)]:

Note: Examples of endocrine therapy are tamoxifen, anastrozole, letrozole, exemestane.

(1) Patient has a phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha *(PIK3CA)*-mutated tumor and meets ONE of the following (i or ii):
- **i.** The medication is used in combination with Piqray (alpelisib tablets); OR
- **ii.** The medication is used in combination with Itovebi (inavolisib tablets) and Ibrance (palbociclib capsules and tablets); OR

(2) Patient meets ALL of the following [(i), (ii), and (iii)]:
- **(i)** Patient has at least ONE of *PIK3CA*, serine/threonine protein kinase (*AKT1*), or phosphatase and tensin homolog (*PTEN*)-alteration; AND
- **(ii)** The medication is used in combination with Truqap (capivasertib tablets); AND
- **(iii)** The patient has had disease progression on a cyclin dependent kinase (CDK)4/6 inhibitor; OR

(3) The medication will be used in combination with everolimus; OR

b) The medication will be used in combination with a CDK4/6 inhibitor or a non-steroidal aromatase inhibitor (i.e., anastrozole or letrozole); OR
Note: Examples of CDK4/6 inhibitors are Kisqali (ribociclib tablets), Ibrance (palbociclib capsules), Verzenio (abemaciclib tablets).

c) The tumor has a HER2-activating mutation and the patient meets BOTH of the following (i and ii):
Note: HER2-activating mutations are clinically distinct from the classification of HER2-positive or HER2-negative disease. Examples of HER2 activating mutations include: L755S, D769H/Y, V777L, or exon 20 insertion.
- **i.** The medication will be used in combination with Nerlynx (neratinib tablets); AND
- **ii.** Patient has tried at least one CDK4/6 inhibitor therapy; OR
  Note: Examples of CDK4/6 inhibitors are Kisqali (ribociclib tablets), Ibrance (palbociclib capsules and tablets), Verzenio (abemaciclib tablets).

ii. Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer and the medication is used in combination with a trastuzumab product; AND

D) The medication is prescribed by or in consultation with an oncologist.

* Refer to the Policy Statement.

Dosing. 500 mg intramuscularly as two 5 mL injections, on Days 1, 15, 29 and once monthly thereafter.

Other Uses with Supportive Evidence

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3. Breast Cancer – Triple Negative Disease. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient has recurrent or metastatic hormone receptor (HR)-negative (i.e., estrogen receptor [ER]- or progesterone receptor [PR]-negative) and human epidermal growth factor receptor 2 (HER2)-negative disease; AND

B) The tumor has a HER2-activating mutation; AND
Note: HER2-activating mutations are clinically distinct from the classification of HER2-positive or HER2-negative disease. Examples of HER2 activating mutations include: L755S, D769H/Y, V777L, or exon 20 insertion.

C) Patient meets ONE of the following (i or ii):
- **i.** Patient is a postmenopausal female* or a male*; OR
- **ii.** Patient is pre/perimenopausal female* and meets ONE of the following (a or b):

a) Patient is receiving ovarian suppression/ovarian ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), or Zoladex (goserelin acetate subcutaneous implant).
b) Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND

D) The medication will be used in combination with Nerlynx (neratinib tablets); AND
E) The medication will be prescribed by or in consultation with an oncologist.

* Refer to the Policy Statement.

Dosing. 500 mg intramuscularly as two 5 mL injections, on Days 1, 15, 29 and once monthly thereafter.

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4. Endometrial Carcinoma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Dosing. 500 mg intramuscularly as two 5 mL injections, on Days 1, 15, 29 and once monthly thereafter.

Limited dosing is available. The dose listed is recommended in the product labeling for approved uses.[1]

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5. Ovarian/Fallopian Tube/Primary Peritoneal Cancer. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient has recurrent low-grade serous carcinoma; AND
B) The medication is prescribed by or in consultation with an oncologist.

Dosing. 500 mg intramuscularly as two 5 mL injections, on Days 1, 15, 29 and once monthly thereafter.

Limited dosing is available. The dose listed is recommended in the product labeling for approved uses.[1]

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6. Uterine Sarcoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient meets ONE of the following criteria (i, ii, or iii):
i. Patient has low-grade endometrial stromal sarcoma; OR
ii. Patient has adenosarcoma without sarcomatous overgrowth; OR
iii. Patient has hormone receptor-positive uterine sarcoma; AND
B) The medication is prescribed by or in consultation with an oncologist.

Dosing. 500 mg intramuscularly as two 5 mL injections, on Days 1, 15, 29 and once monthly thereafter.

Limited dosing is available. The dose listed is recommended in the product labeling for approved uses.[1]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fulvestrant is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Faslodex® intramuscular injection [prescribing information]. Wilmington, DE: AstraZeneca; December 2023.
2. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2025 – April 17, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2025.
3. The NCCN Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (version 2.2025 – May 23, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2025.
4. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 3.2025 –March 7, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2025.
5. Bon G, Sofia Di Lisa F, Filomeno L, et al. HER2 mutation as an emerging target in advanced breast cancer. *Cancer Sci*. 2024; 115(7):2147-2158.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	05/24/2023
Annual Revision	**Breast Cancer – Fulvestrant Combination Therapy:** Added criteria for fulvestrant combination use with Truqap.	06/12/2024
Annual Revision	**Breast Cancer – Fulvestrant Combination Therapy:** Added criteria for fulvestrant combination use with Ibrance and Itovebi for *PIK3CA*-mutated breast cancer. Added criteria for fulvestrant use with Nerlynx in tumors with HER2 activating mutation and the patient has tried CDK4/6 inhibitor therapy. **Breast Cancer – Triple Negative Disease:** Condition of approval and criteria were added to "Other Uses with Supportive Evidence".	06/18/2025