National PBM Drug Monograph
Fulvestrant (Faslodex®)
January 2004

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Introduction

Hormone sensitive breast cancer in postmenopausal women has been successfully treated with the anti-estrogen tamoxifen for over 20 years. Despite success with tamoxifen, there are limitations to its use. It has partial agonist activity in some tissues, leading to an increased incidence of endometrial cancer, thrombosis, and may be implicated in the development of resistance.

The purpose of this monograph is to review the medical data for the estrogen receptor antagonist fulvestrant, a steroidal analogue of estradiol, in the treatment of patients with hormone sensitive breast cancer that has progressed while on anti-estrogen therapy. The FDA approved fulvestrant in May of 2002.

Synonyms: ICI 182,780

Pharmacology/Pharmacokinetics[1, 2,3]

The estrogen receptor (ER) is a transcription factor that binds to DNA. Normally, estradiol binds to ER causing receptor dimerization and ER binding to specific DNA sites known as estrogen response elements (EREs). Then transcription of estrogen dependent genes is initiated. The ER contains 2 domains involved in transcription activation: activation function 1 (AF-1) and activation function 2 (AF-2). AF-1 is hormone independent and AF-2 requires hormone binding for activity. Although maximum transcription activity requires both Af-1 and AF-2, transcription can occur with only one activation function.

Fulvestrant binds to the ER, blocking both the hormone dependent and hormone independent activation functions and preventing transcription of AF-1 and AF-2 genes. In addition, fulvestrant disrupts ER dimerization, causing the ER to be less stable and resulting in degradation of the receptor. In contrast, tamoxifen blocks activation of AF-2, but not AF-1, allowing dimerization and transcription activity at the AF-1 site resulting in partial agonist activity.

The pharmacologic effects of fulvestrant on the postmenopausal endometrium were assessed in 20 normal volunteers. Each patient was screened for an appropriate endometrial response to oral ethinyloestradiol for 14 days. A washout period of 2-6 weeks followed to allow for endometrial thickness to return to postmenopausal levels. Fulvestrant 125mg, 250mg, or placebo was given as an intramuscular injection. 14 days later oral ethinyloestradiol was again administered. There was a statistically significant difference in endometrial thickening response in the fulvestrant 250mg group (mean 4.2 mm) versus the placebo group (mean 11.22 mm)($p=0.0001$).[4] Fulvestrant was able to block the uterine stimulatory effects of ethinyloestradiol.

Pharmacokinetic Parameters	Fulvestrant
Metabolism	Similar to endogenous steroids: oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate. Identified metabolites are less active or similar to the parent. CYP3A4 is the only isoenzyme involved in oxidation; the relative contribution is unknown
Elimination	Rapidly cleared by hepatobiliary route; 90% excreted in feces; renal elimination negligible
Half-life	40 days
Protein Binding	99%PPB

With monthly administration, AUC increases by 2.5 fold versus single dose AUC, and steady state plasma concentrations are reached in 3-6 doses. Intramuscular administration maintains plasma concentrations over a 28 ±3 day period.

A pharmacokinetic evaluation following a single dose of 250mg or 2 125mg doses given intramuscularly in postmenopausal women found that plasma concentrations were measurable up to 28 days after both dosing methods, the Cmax was similar for both methods, and the AUC was similar in both groups (the ratio of AUC (0-28) of the single injection to that of the double injections was 1.01; 95% CI 0.68-1.51).[5]

Special populations:
Geriatric – No difference in pharmacokinetic profile related to age
Gender – No difference in pharmacokinetic profile following a single intravenous dose between men and women or between premenopausal women and postmenopausal women. No pharmacokinetic differences after a single intramuscular dose between men and postmenopausal women.
Race – No difference observed in clinical trials, although 87.4% were Caucasian, with only 7.8% Black and 4.4% Hispanic. In another trial, no difference between postmenopausal Japanese women and non-Japanese women.

FDA Approved Indication(s) and Off-label Uses

Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

Off-label uses: first-line therapy in hormone sensitive breast cancer, following disease progression while on an aromatase inhibitor, neoadjuvant therapy in breast cancer, in premenopausal women with breast cancer, endometriosis, dysfunctional uterine bleeding, uterine fibroids

Dosage and Administration

Fulvestrant is available in pre-filled syringes either as a single 250mg/5ml (50mg/ml) injection or 2 125mg/2.5ml (50mg/ml) injections. The product should be stored in the refrigerator at 2-8°C (36-46°F).

The recommended dose is 250mg administered intramuscularly in the buttock monthly (every 28 days ± 3 days), either as a single 5ml injection or two concurrent 250mg injections given slowly.

Patients with hepatic impairment: use of fulvestrant has not been studied in patients with moderate or severe hepatic compromise. No dosage adjustment is needed with mild hepatic impairment.

Adverse Effects (Safety Data)

Combined Adverse Events ≥5%

Body system and adverse event	Fulvestrant (N=423) (%)	Anastrozole (N=423) (%)
Whole body	68.3	67.6
Asthenia	22.7	27.0
Pain	18.9	20.3
Headache	15.4	16.8
Back pain	14.4	13.2
Abdominal pain	11.8	11.6
Injection site pain*	10.9	6.6
Pelvic pain	9.9	9.0
Chest pain	7.1	5.0
Flu syndrome	7.1	6.4
Fever	6.4	6.4
Accidental injury	4.5	5.7
Cardiovascular	30.3	27.9
Vasodilatation	17.7	17.3
Digestive	51.5	48.0
Nausea	26.0	25.3
Vomiting	13.0	11.8
Constipation	12.5	10.6
Diarrhea	12.3	12.8
Anorexia	9.0	10.9
Hematologic/lymphatic	13.7	13.5
Anemia	4.5	5.0

Metabolic/Nutritional	18.2	17.7
Peripheral edema	9.0	10.2
Musculoskeletal	25.5	27.9
Bone pain	15.8	13.7
Arthritis	2.8	6.1
Nervous system	34.3	33.8
Dizziness	6.9	6.6
Insomnia	6.9	8.5
Paresthesia	6.4	7.6
Depression	5.7	6.9
Anxiety	5.0	3.8
Respiratory	38.5	33.6
Pharyngitis	16.1	11.6
Dyspnea	14.9	12.3
Increased cough	10.4	10.4
Skin	22.2	23.4
Rash	7.3	8.0
Sweating	5.0	5.2
Urogenital	18.2	14.9
UTI	6.1	3.5

* Only those anastrozole patients in the North American trial also received placebo injections

During the first six weeks of therapy when changing from existing hormonal therapy to fulvestrant, <1% reported vaginal bleeding.

Precautions/Contraindications

Contraindications: Fulvestrant is contraindicated in pregnant women and in patients with a known hypersensitivity to the drug or its components.

Precautions:
Hepatic impairment
Safety and efficacy have not been evaluated in patients with moderate or severe hepatic impairment.

Impairment of fertility
In animal studies, fulvestrant doses approximately 1-5 fold the exposure achieved in women caused an increased incidence of benign ovarian granulosa cell tumors in female rats. At doses 1/100 of those in humans based on BSA, fulvestrant caused a reduction in female fertility and embryonic survival in female rats.
In male rats, doses 1.3-1.6 fold the systemic exposure in women caused testicular Leydig cell tumors. In doses of 10-15mg/kg in male rats, fulvestrant caused a loss of spermatozoa, seminiferous tubular atrophy, and degenerative changes in the epididymides; changes in the testes and epididymides did not recover 20 weeks after cessation.

Drug Interactions

There are no known drug interactions. Co-administration with midazolam, a CYP3A4 substrate showed no inhibitory effects by fulvestrant. When given with rifampin, a CYP3A4 inducer, there were no changes in the fulvestrant pharmacokinetics. There are no clinical studies on the concomitant use of strong CYP3A4 inhibitors with fulvestrant.

Efficacy Measures

Primary Endpoint: Time to Progression (TTP) (# of days from randomization until progression or death from any cause, whichever comes first)

Secondary Endpoints: Objective Response (OR)
Duration of response (DOR) (# of days from randomization to progression)
Tolerability
Time to Treatment Failure (TTF) (# of days from randomization to progression, death, or withdrawal from treatment, whichever comes first)

Clinical Trials

Two randomized phase III trials with similar designs were conducted to test for efficacy and safety of fulvestrant compared to oral anastrazole. Both trials initially included an arm using a fulvestrant dose of 125mg monthly, but a planned interim analysis of the data in the first 30 patients found no objective response and this arm was discontinued.

Trial 021- The North American Trial[6]
Patients were postmenopausal women with locally advanced or metastatic breast cancer who had progressed on adjuvant therapy with an antiestrogen or who progressed after first-line endocrine therapy for advanced disease. This was a randomized, multicenter, double blinded, double-dummy trial. Evidence of tumors with hormone sensitivity included known estrogen receptor positivity, known progesterone receptor positivity, or prior sensitivity to hormonal therapy.

Prior treatment with tamoxifen occurred in 95% of the fulvestrant group and 96% of the anastrozole group. A total of 400 patients were enrolled from 83 centers. Fulvestrant was administered as 2 x 2.5ml IM injections once a month. At a median follow-up of 16.8 months, 84% of the fulvestrant patients and 86% of the anastrozole patients had progressed.

Efficacy Data- Trial 021

Outcome	Fulvestrant (N=206)	Anastrozole (N=194)	P-value
Median TTP (months)	5.4	3.4	P=0.43
Median TTF (months)	4.6	3.3	P=0.69
OR (CR+PR)(%)	17.5	17.5	P=0.96
Clinical Benefit (CR+PR+SD ≥24 weeks)(%)	42.2	36.1	---
Median DOR (months) (in responders only)	19.0 (n=36)	10.8 (n=34)	---

At the time of this analysis 35.4% of fulvestrant patients and 33.5% of anastrozole patients had died.
When the duration of response (DOR) for all patients (responders and nonresponders) was analyzed, the ratio of average durations for fulvestrant vs anastrozole was 1.35, 95% CI, 1.10-1.67 ($p<0.01$).

Five patients in each group withdrew due to an adverse event. Most adverse events were mild, and the incidence and severity were generally similar between the groups. Although animal studies showed fulvestrant did not cross the blood-brain barrier, the incidence of hot flashes was similar between the groups in clinical trials. Since both groups received monthly injections (placebo in the anastrozole group), it is of interest to compare injection site reactions in this trial. 27% of fulvestrant patients and 23.3% of anastrozole patients reported injection site reactions; none were serious (site pain, reaction, or inflammation). One patient in the fulvestrant group withdrew due to severe injection site reactions.

Trial 020- The European Trial[7]
The European trial had a similar patient population. It was an open-label, randomized, multicenter trial. The fulvestrant was given as a single 250mg/5ml intramuscular injection. 97% of patients in the fulvestrant group and 98% of patients in the anastrozole group had previously received tamoxifen.

Efficacy Data-The European Trial

Outcome	Fulvestrant (N=222)	Anastrozole (N=229)	P-value
Median TTP (months)	5.5	5.1	P=0.84
Median TTF (months)	4.6	4.1	P=0.81
OR(CR+PR)(%)	20.7	15.7	P=0.20
Clinical Benefit (CR+PR+SD≥24 weeks)(%)	44.6	45	---
Median DOR (months) (In responders only)	15 (n=48)	14.5 (n=39)	---

At the time of the analysis, 82.4% of the fulvestrant patients and 83.4% of the anastrozole patients had progressed at a median follow-up of 14.4 months. The ratio of the average duration of response for fulvestrant and anastrozole in all patients was 1.27; 95% CI 1.05-1.55; P=0.01.

Both treatments were well tolerated. 3.2% of fulvestrant patients and 1.3% of anastrozole patients withdrew because of adverse events. The majority of side effects were mild or moderate. The incidence of endocrine therapy related side effects (weight gain, thromboembolic events, and vaginitis) were low in both groups. Injection site reactions in the fulvestrant group occurred in 7.3%, were mild and non-serious, and one patient withdrew due to an injection site event.

Combined analysis[8]
A prospectively designed combined analysis was planned for the two phase III trials.

Outcome	Fulvestrant (N=428)	Anastrozole (N=423)	P-value
Median TTP (months)	5.5	4.1	HR 0.95; 95.14% CI, 0.82-1.10; p=0.48
Median TTF (months)	4.6	3.6	HR 0.96, 95% CI, 0.83-1.11; p=0.61
OR (CR+PR) (%)	19.2	16.5	---
DOR (months) (In responders)	16.7 (n=84)	13.7 (n=73)	---

Median follow-up was 15.1 months.
The majority of treatment failures were due to disease progression: 93.4% of treatment failures in the fulvestrant group and 95.6% of treatment failures in the anastrozole group. Other reasons for treatment failure included AEs (1.4% fulvestrant failures, 1.2% anastrozole failures), protocol non-compliance (1.4% fulvestrant, 1.2% anastrozole), and withdrawal of informed consent (1.2% fulvestrant and 0.5% anastrozole).
The DOR in all randomized patients was longer in the fulvestrant group when comparing the ratio of average response duration to anastrozole: 1.3 (95% CI, 1.13-1.5; P<0.01).
Adverse Events occurred in 90.1% of fulvestrant patients and 89.1% of anastrozole patients. The majority were mild or moderate. The most common AEs were nausea (26% vs 25.3%), asthenia (22.7% vs. 27%), pain (18.9% vs. 20.3%), vasodilatation (17.7% vs. 17.3%) and headache 15.4% vs. 16.8%) for fulvestrant and anastrozole, respectively.
Withdrawals due to AEs were low. Serious AEs considered at least possibly related to study medication occurred in 1.7% of fulvestrant patients and 1.2% of anastrozole patients.
Eight fulvestrant patients and 6 anastrozole patients died as the result of an adverse event. Only one patient in the anastrozole group was considered a drug-related death (CVA and thrombophlebitis). The only AE category that differed between the groups was joint disorders, which occurred more frequently in the anastrozole group (p=0.0036). Local injection site reactions were mostly mild or moderate, and the frequency depended on the method and volume administered: 1.1% in the single fulvestrant 250mg injection group, 4.6% in the 2x2.5ml fulvestrant group, and 4.4% in the 2x2.5ml placebo group.

A recent update on survival analysis for the two trials found that at an extended median follow-up of 27.2 months, the median duration of survival was 27.4 months in the fulvestrant group and 27.7 months in the anastrozole group (San Antonio Breast Cancer Symposium, December 5, 2003).

Acquisition Costs

Drug	Dose	Cost/Month/patient ($)
Fulvestrant	250mg/month	547.92
Anastrozole	1mg	32.93
Tamoxifen	20mg	71.30

Conclusions

Efficacy
In two large comparative trials fulvestrant was effective as anastrozole in treating locally advanced or metastatic breast cancer following progression of disease while on tamoxifen or other endocrine therapies with respect to time to progression of disease, time to treatment failure, objective response, duration of response, and duration of survival. Patients in the fulvestrant group had a longer duration of response numerically, but it was not statistically significant. Use in men has been restricted to a pharmacokinetic study in healthy volunteers.

Safety
The adverse event profile between fulvestrant and anastrozole was similar. Adverse events were typically mild or moderate and did not cause a large number of withdrawals. Local injection site reactions were variable and rarely caused withdrawal from the study. Although short term exposure did not show agonist activity with regard to the endometrium, longer term studies are needed to evaluate potential long-term risks seen with other endocrine therapies.

Cost of therapy is a consideration, especially since alternative oral therapies are relatively less expensive.

Recommendations

The gold standard first-line endocrine therapy has been tamoxifen. Following progression of disease, second-line therapy with a non-steroidal aromatase inhibitor (anastrozole, letrozole) or a steroidal aromatase inhibitor (exemestane) has been shown to produce superior survival versus megestrol acetate. It is in this population (tamoxifen failures) that fulvestrant has shown equivalency with anastrozole.

However, the aromatase inhibitors anastrozole and letrozole now have approval for use in first-line therapy. Both drugs have demonstrated an increased TTP when compared to tamoxifen in phase III trials, and have a better side effect profile. Fulvestrant has been investigated in the first-line treatment setting, but the appropriate population for this use has not been defined.

Finally, anastrozole has been evaluated in the adjuvant setting in a randomized trial versus tamoxifen. Anastrozole had a longer disease free survival than tamoxifen and a slightly better side effect profile. Because the data has not yet reached the 5+ years of exposure like the historical tamoxifen data, expert professional organizations do not recommend anastrozole in the adjuvant setting at this time, unless a patient has some contraindications to tamoxifen.[9]

Fulvestrant is a viable option for treatment of locally advanced or metastatic breast cancer in postmenopausal women who have progressed following therapy with tamoxifen. Consideration should be given to patient convenience, compliance, safety, and cost in comparing other available endocrine therapies. Given this information, an aromatase inhibitor is recommended for patients who progress during adjuvant antiestrogen therapy or during first-line endocrine therapy with an antiestrogen unless contraindicated.

What if the aromatase inhibitors become more commonplace as first-line therapy? Currently there is no data on the use of fulvestrant following progression of disease after aromatase inhibitor therapy. There is an on-going trial comparing fulvestrant vs. exemestane following disease progression on a non-steroidal aromatase inhibitor.

Are hormone therapies effective when fulvestrant fails? A small number of fulvestrant patients from the phase III clinical trials received further endocrine therapy following progression on fulvestrant. The majority received an aromatase inhibitor. About half of the patients who initially had a CR, PR, or SD on fulvestrant had a PR or SD on subsequent endocrine therapy. About one-third of patients who did not have a CR, PR or SD on fulvestrant had a PR or SD on subsequent endocrine therapy.[10] More studies are needed to confirm these results.

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Reviewed by:
Date: January 2004

Appendix

<table>
<tr><th>Study</th><th>Inclusion</th><th>Results</th><th>Safety</th></tr>
<tr>
<td>Osborne et al.
0021 North American
N=400
R, MC, DB, DD
Fulvestrant 2x125mg IM
Plus oral placebo
Versus
Placebo 2x2.5ml IM
Plus oral anastrozole 1mg

Supported by AstraZeneca</td>
<td>Postmenopausal women
-locally advanced or metastatic breast cancer
-progressed on adjuvant antiestrogen OR progressed after 1st line endocrine therapy
-measurable or assessable disease</td>
<td>
<table>
<tr><th>Demographic</th><th>Fulv (n=206)</th><th>Anast (n=194)</th></tr>
<tr><td>Age</td><td>63</td><td>62</td></tr>
<tr><td>Prior Tx
Chemo
Endo adv dis
Endo adjuv</td><td>
62.6
53.4
59.2</td><td>
62.9
50
59.8</td></tr>
<tr><td>Hormone Receptor
ER a/o PR +
ER/PR UK
ER/PR -ve</td><td>
86.9
6.3
6.8</td><td>
87.1
7.7
5.2</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Fulv</th><th>Anast</th></tr>
<tr><td>TTP (mos)</td><td>5.4</td><td>3.4 NSS</td></tr>
<tr><td>TTF (mos)</td><td>4.6</td><td>3.3 NSS</td></tr>
<tr><td>OR (%)</td><td>17.5</td><td>17.5</td></tr>
<tr><td>DOR (mos) (responders)</td><td>19</td><td>10.8</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Event</th><th>Fulv</th><th>Anast</th></tr>
<tr><td>Withdraw due to AE</td><td>2.5%</td><td>2.6%</td></tr>
<tr><td>Hot flashes</td><td>23.5</td><td>24.9</td></tr>
<tr><td>Weight gain</td><td>1.5</td><td>1.6</td></tr>
<tr><td>Vaginitis</td><td>3.4</td><td>2.6</td></tr>
<tr><td>Thromboembolism</td><td>3.4</td><td>6.7</td></tr>
<tr><td>Joint disorders</td><td>9.3</td><td>13.5</td></tr>
<tr><td>Inj site reactions</td><td>27</td><td>23.3</td></tr>
</table>
</td>
</tr>
<tr>
<td>Howell, et al.
0020 European
N=451
R, OL, MC
Fulvestrant 250mg IM
VS
Anastrozole 1mg PO

Supported by AstraZeneca</td>
<td>Postmenopausal women
-locally advanced or metastatic breast cancer
-progressed on adjuvant antiestrogen OR progressed after 1st line endocrine therapy
-measurable or assessable disease</td>
<td>
<table>
<tr><th>Demographic</th><th>Fulv</th><th>Anast</th></tr>
<tr><td>Age</td><td>63</td><td>64</td></tr>
<tr><td>Prior Tx
Chemo
Endo adv dis
Endo adjuv</td><td>
42.3
56.8
54.5</td><td>
42.8
56.3
52.0</td></tr>
<tr><td>Hormone Receptor
ER a/o PR +
ER/PR UK
ER/PR –ve</td><td>
73.4
23.0
3.6</td><td>
79.9
16.2
3.9</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Fulv</th><th>Anast</th></tr>
<tr><td>TTP (mos)</td><td>5.5</td><td>5.1 NSS</td></tr>
<tr><td>TTF (mos)</td><td>4.6</td><td>4.1 NSS</td></tr>
<tr><td>OR (%)</td><td>20.7</td><td>15.7 NSS</td></tr>
<tr><td>DOR (mos) (responders)</td><td>15</td><td>14.5</td></tr>
</table>
</td>
<td>
<table>
<tr><th>Event</th><th>Fulv</th><th>Anast</th></tr>
<tr><td>Withdrawal due to AE</td><td>3.2</td><td>1.3</td></tr>
<tr><td>Thromboembolic</td><td>3.7</td><td>1.7</td></tr>
<tr><td>Vaginitis</td><td>1.8</td><td>1.3</td></tr>
<tr><td>Weight gain</td><td>0.5</td><td>1.7</td></tr>
<tr><td>Joint Disorders</td><td>1.4</td><td>8.3</td></tr>
<tr><td>Inj Site reaction</td><td>7.3</td><td>---</td></tr>
</table>
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</tr>
</table>

R=randomized, DB=double-blind, DD=double dummy, MC=multicenter, Fulv=fulvestrant, Anast=anastrozole, Endo=endocrine, adv dis=advanced disease, adjuv=adjuvant, ER=estrogen receptor, PR=progesterone receptor, UK=unknown, TTP=time to progression, TTF=time to treatment failure, OR=objective response, DOR= duration of response, NSS=not statistically significant, AE= adverse event

References

[1] Howell A, Osborne CK, Morris C, Wakeling AE. ICI 182,780 (Faslodex™): Development of a novel, "pure" antiestrogen. Cancer 2000;89:817-825.
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[7] Howell A, Robertson JFR, Albano JQ, Aschermannova A, Mauriac L, Kleeberg UR, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Onc 2002;20:3396-3403.
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