

# Fulvestrant

Concise evaluated information to support the managed entry of new medicines in the NHS

## Summary

- Fulvestrant is the first of a new class of drugs known as selective oestrogen receptor down-regulators (SERDs). It is a 'pure' oestrogen-receptor antagonist with no oestrogenic agonist activity.
- Fulvestrant has been licensed for the treatment of postmenopausal women with oestrogen-receptor positive, locally advanced or metastatic breast cancer whose disease has progressed or relapsed on or after previous anti-oestrogen therapy.
- Data from two pivotal phase III trials involving over 850 women found fulvestrant, in monthly intramuscular (IM) doses of 250mg, to be at least as effective as the aromatase inhibitor, anastrozole 1mg daily. The primary endpoint, time to disease progression, was 5.5 and 4.1 months, respectively, in a combined analysis of the studies.
- Limited data indicate that women whose disease progresses during fulvestrant treatment remain sensitive to further endocrine therapy.
- Adverse effects of fulvestrant appear to be similar in type and frequency to those of anastrozole. Data on long-term adverse effects of fulvestrant are not yet available.
- Fulvestrant is approximately four times the cost of third-generation aromatase inhibitors, which are the current agents of choice for recurrent treatment of breast cancer. The service impact of monthly IM administration also needs to be considered.

## Introduction

Fulvestrant, a 7 $\alpha$ -alkyl analogue of oestradiol, is the first of a new class of drugs known as selective oestrogen receptor down-regulators (SERDs). It has recently been licensed in the UK for the treatment of postmenopausal women with oestrogen-receptor positive, locally advanced or metastatic breast cancer whose disease has progressed or relapsed on or after previous anti-oestrogen therapy.

Other anti-oestrogen therapies marketed for breast cancer include tamoxifen (current first-line treatment) and the aromatase inhibitors. Both tamoxifen and fulvestrant interfere with the binding of oestrogen at tumour oestrogen receptors (ER); fulvestrant has greater affinity for receptors and also degrades ER protein. Unlike tamoxifen, fulvestrant has no partial agonist activity. It has been hypothesised that this may increase its duration of effect and reduce the likelihood of some side effects. Aromatase inhibitors reduce circulating oestrogen levels.<sup>1,2</sup>

## Evidence

Evidence for clinical efficacy rests on the results of two large phase III studies in which patients were randomised to fulvestrant 250mg IM monthly or anastrozole 1mg daily. The trials were conducted in North America (n=400) and internationally (Europe, South Africa and Australia, n=451).<sup>3,4</sup> Both trials were of similar design and had the same inclusion and exclusion criteria. However, the North American study was double-blind and the international study was open-label. All patients had a life expectancy of more than 3 months and had locally advanced or metastatic disease that had progressed during adjuvant or first-line endocrine therapy. None had received previous treatment with an aromatase inhibitor. Most had hormone sensitive tumours. Patients were followed-up for 16.8 months in the North American trial and 14.4 months in the international study.

**Brand Name, (Manufacturer):** Faslodex (AstraZeneca)

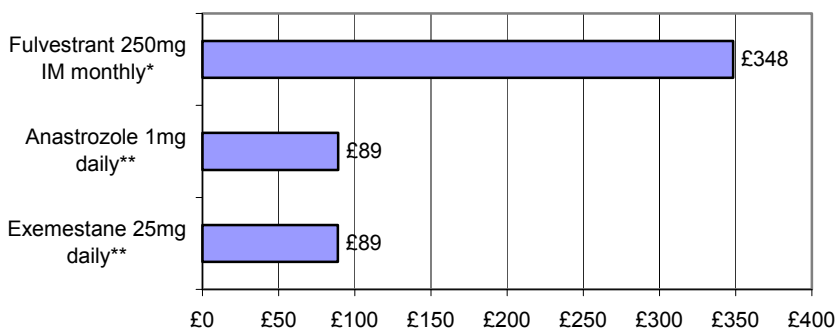
**BNF Therapeutic Class:** 8.3.4.1 Hormone antagonists, breast cancer

**Licensed Indications:** Treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy or disease progression on therapy with an anti-oestrogen.

**Dosage and Administration:** 250 mg at intervals of 1 month by intramuscular (IM) injection. Faslodex is presented as a pre-filled syringe containing 250mg fulvestrant in 5ml solution. A safety needle for connection to the barrel is provided.

**Marketed:** May 2004

**Cost Comparisons:** Cost for 30 days' treatment:



Cost: \*AstraZeneca promotional material Fas 04/13912; \*\*MIMS June 2004  
N.B. Doses shown for general comparison and do not imply therapeutic equivalence

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The primary endpoint in each trial was time to disease progression (TTP), which was measured from the time of randomisation until objective disease progression or death from any cause. Secondary endpoints included the objective response rate (OR), the duration of response (DOR), time to death (TTD), time to treatment failure (TTF), tolerability and quality of life (QoL) measures. Both trials were originally designed to detect superior efficacy of fulvestrant over anastrozole but the results did not reach statistical significance. Retrospective comparisons for non-inferiority, which were not described in the trial protocols, but were validated by an independent panel, were performed for TTP, TTF and OR. Confidence intervals [CI] were adjusted to account for this.

Fulvestrant was as effective as anastrozole for the primary endpoint of TTP, and there was no statistically significant difference for the majority of secondary endpoints between the two treatments. In the North American trial, the median TTP for fulvestrant was 5.4 months and for anastrozole 3.4 months (hazard ratio [HR] 0.92; 95.14% CI, 0.74 to 1.14; P=0.43). At analysis 83.5% and 86.1% of patients, respectively, had experienced disease progression. In the international study, the median TTPs for fulvestrant and anastrozole were 5.5 and 5.1 months (HR 0.98; 95.14% CI, 0.80 to 1.21; P=0.84); corresponding disease progression rates were 82.4% and 83.4%. QoL was similar for both treatment groups in each trial. Detailed results are given in appendix II.

In a combined analysis of both trials, TTP values for fulvestrant and anastrozole were 5.5 and 4.1 months, respectively.<sup>5</sup> No statistically significant differences were recorded for any of the clinical outcomes. At an extended median follow-up of 27.2 months, 74.5% and 76.1% of patients in the fulvestrant and anastrozole groups had died, and the median TTD was 27.4 and 27.2 months, respectively.<sup>6</sup>

A retrospective analysis of the combined data evaluated the effects

of further endocrine therapies in patients whose tumours became resistant to fulvestrant.<sup>7</sup> Of 54 patients who had initially derived clinical benefit from fulvestrant, subsequent endocrine therapy resulted in a partial response in four, and stable disease lasting for  $\geq 24$  weeks in 21; one partial response and 17 stable disease outcomes were noted among 51 patients who had not previously responded to fulvestrant.

## Safety

A range of adverse effects associated with fulvestrant and anastrozole were noted in the two key studies. Among the most common were vasodilation, asthenia (weakness) and headache, which are consistent with oestrogen deprivation. The percentage of patients experiencing these and other adverse effects was similar in both groups, with the exception of joint disorders which were more frequent in patients receiving anastrozole. Injection site pain occurred in 16.7% of the fulvestrant treated group. Few patients (0.9%) withdrew from fulvestrant treatment because of adverse effects.<sup>1-4</sup>

Safety data for fulvestrant are limited and long-term effects on oestrogen-responsive tissues remain uncertain. This is important given that fulvestrant is the first of a new class of drugs. Such data are also required to confirm whether a lack of partial agonist activity reduces the risk of oestrogen associated adverse effects, such as thromboembolic events and endometrial cancer, and increases the likelihood of adverse effects on bone density.

## Place in Therapy

Based on 1999 figures, there are around 36,000 new cases of breast cancer a year in England and Wales (70 cases per 100,000 population). Approximately 10 to 20 patients per 100,000 population will relapse or progress on first-line treatment with tamoxifen.<sup>1,2</sup>

Third generation aromatase inhibitors such as anastrozole are the current agents of choice for second-line treatment. Fulvestrant is no more effective than anastrozole, has similar tolerability and is four times more expensive. The service impact of once monthly IM injections also has to be taken into account. Although it has been suggested that monthly IM administration will increase compliance over a daily oral regimen, this has not been demonstrated. Current evidence does not support the routine use of fulvestrant in preference to aromatase inhibitors.

Studies of the efficacy of fulvestrant following aromatase inhibitor use are underway. Such trials will help clarify the optimum sequence of hormonal therapy for postmenopausal women with advanced breast cancer.<sup>8</sup>

## Key Papers

3. Osborne CK, Pippen J, Jones SE et al. *J Clin Oncol* 2002; **20**: 3386-95
4. Howell A, Robertson JFR, Quaresma Albano J et al. *J Clin Oncol* 2002; **20**: 3396-403

## Appendix I: Bibliography Appendix II: Table of Clinical Trials

## Risk Management Issues:

Faslodex should be stored in a fridge at 2° to 8°C and be protected from light.

The safety needle (SafetyGlide) must be fitted to the syringe before administration. Once used, the protection device must be activated before the needle is discarded in a sharps collector. Activation of the protective mechanism may cause minimal splatter of fluid that remains on the needle after injection. It is recommended that activation is carried out away from others.<sup>8</sup>

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## Appendix I

### Bibliography

#### References

1. UKMi/NPC. Fulvestrant. New Drugs in Clinical Development. Sep 2003 (3/03/03)
2. London New Drugs Group. Update on fulvestrant (Faslodex) for advanced breast cancer. APC/DTC Briefing May 2003
3. Osborne CK, Pippin J, Jones SE et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy. Results of a North American trial. *J Clin Oncol* 2002; **20**: 3386-95.
4. Howell A, Robertson JFR, Quaresma Albano J 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 Oncol* 2002; **20**: 3396-403
5. Robertson JFR, Osborne CK, Howell A et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women. A prospective combined analysis of two multicenter trials. *Cancer* 2003; **98**: 229-38
6. Pippin J, Osborne CK, Howell A et al. Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: a prospective combined survival analysis of two multicenter trials. 26<sup>th</sup> Annual San Antonio Breast Cancer Symposium. December 2003. Poster 426
7. Vergote I, Robertson JFR, Kleeberg U et al. Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy. *Breast Canc Res Treat* 2003; **79**: 207-11
8. McKeage K, Curran MP and Plosker GL. Fulvestrant. A review of its use in hormone-receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. *Drugs* 2004; **64**: 633-48
9. AstraZeneca UK Ltd. Faslodex. Summary of Product Characteristics. Mar 2004

## Fulvestrant

### Appendix II

**Table: Summary of trial data in the second-line treatment of advanced, postmenopausal breast cancer**

	North American study <sup>3</sup>		International study <sup>4</sup>		Combined analysis <sup>5</sup>	
	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
Number of patients	206	194	222	229	428	423
ER and/or PgR positive tumours	86.9%	87.1%	73.4%	79.9%	79.9%	83.2%
<b>Primary endpoint</b>						
Median time to disease progression (TTP)	5.4 months	3.4 months	5.5 months	5.1 months	5.5 months	4.1 months
Hazard ratio	0.92 [95.14% CI, 0.74 to 1.14] P=0.43		0.98 [95.14%CI, 0.80 to 1.21] P=0.84		0.95 [95.14%CI, 0.82 to 1.10] P=0.48	
% who had progression at analysis	83.5%	86.1%	82.4%	83.4%	82.1%	84.6%
<b>Secondary endpoints</b>						
Objective response rate (OR)	17.5%	17.5%	20.7%	15.7%	19.2%	16.5%
Clinical benefit (complete response + partial response + stable disease ≥24 weeks)	42.2%	36.1%	44.6%	45%	43.5%	40.9%
Median duration of response (DOR) in responders	19.0 months (n=36)	10.8 months (n=34)	15.0 months (n=48)	14.5 months (n=39)	16.7 months (n=84)	13.7 months (n=73)
Median duration of clinical benefit in all patients	12.9 months (n=87)	10.9 months (n=70)	11.7 months (n=100)	11.4 months (n=104)	11.8 months (n=187)	11.2 months (n=174)
Ratio of average response duration	1.35 [95%CI, 1.10 to 1.67] P<0.01		1.27 [95%CI, 1.05 to 1.55] P=0.01		1.30 [95%CI, 1.13 to 1.50] P<0.01	
Median time to treatment failure (TTF)	4.6 months	3.3 months	4.6 months	4.1 months	4.6 months	3.6 months
Treatment failures	79.6%	84.0%	84% (n=188)	85.6% (n=196)		
Number who had died at time of analysis	35.4% (n=73)	33.5% (n=65)	36.9% (n=82)	36.2% (n=83)	36.2%	35.0%