

Fulvestrant for untreated locally advanced or metastatic oestrogen- receptor positive breast cancer

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

- 1.1 Fulvestrant is not recommended, within its marketing authorisation, for treating locally advanced or metastatic oestrogen-receptor positive breast cancer in postmenopausal women who have not had endocrine therapy before.
- 1.2 This recommendation is not intended to affect treatment with fulvestrant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made this recommendation

People with untreated disease are first offered an aromatase inhibitor, either anastrozole or letrozole. These drugs are considered to be similarly effective. Tamoxifen is used for women in whom an aromatase inhibitor is not tolerated or is contraindicated. Fulvestrant is a further treatment option that may have additional benefits for some women. However, the final results on overall survival from the FALCON trial are not available yet, so it is unclear whether fulvestrant will extend overall survival compared with aromatase inhibitors.

Because of the uncertainty in the clinical evidence, the cost effectiveness of fulvestrant compared with existing treatments is highly uncertain. However, it is likely to be above the range normally considered a cost-effective use of NHS resources, so fulvestrant cannot be recommended.

2 Information about fulvestrant

Information about fulvestrant

Marketing authorisation	<p>Fulvestrant (Faslodex, AstraZeneca) is indicated for 'the treatment of oestrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:</p> <ul style="list-style-type: none">• not previously treated with endocrine therapy (licence extension under appraisal) or• with disease relapse on or after adjuvant antioestrogen therapy, or disease progression on antioestrogen therapy' (appraised in NICE technology appraisal guidance on fulvestrant for the treatment of locally advanced or metastatic breast cancer).
Recommended dose and schedule	<p>The recommended dosage is 500 mg intramuscularly into the buttocks as 2×5-ml injections (1 in each buttock) on days 1, 15 and 29, and then once monthly (until disease progression).</p>
Price	<p>A pack of 2×5-ml (50 mg/ml) prefilled syringes costs £522.41 (NHS indicative price, British national formulary online, August 2017). Costs may vary in different settings because of negotiated procurement discounts.</p>

3 Committee discussion

The appraisal committee ([section 4](#)) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Current management

Aromatase inhibitors are standard care but further effective treatments are needed

3.1 The clinical expert explained that advanced or metastatic breast cancer without high-volume visceral disease or another indication for immediate chemotherapy is generally treated first-line with an aromatase inhibitor (anastrozole or letrozole). For a few people, tamoxifen may be more appropriate, for example, when aromatase inhibitors are not tolerated because of side effects such as arthralgia or gastrointestinal symptoms. The committee heard that current treatments are effective in providing a temporary improvement and delaying disease progression. However, more effective treatments that delay the need for chemotherapy and extend survival are needed. The committee concluded that aromatase inhibitors are the first-line treatment for endocrine-naïve advanced or metastatic oestrogen-receptor positive breast cancer, but that further effective treatments are needed.

Anastrozole and letrozole are considered to have a class effect

3.2 The committee was aware from past appraisals for advanced breast cancer that letrozole and anastrozole are considered to have a class effect. In addition, the clinical expert confirmed that multiple trials show that these agents are indistinguishable in terms of clinical effectiveness and toxicity. Therefore, the committee concluded that it is appropriate to consider anastrozole and letrozole as equivalent.

New treatment options

Fulvestrant is a further treatment option that may have additional benefits for some people

- 3.3 The committee heard from a patient expert who had previously had various treatments, including anastrozole, fulvestrant and chemotherapy. The patient expert explained that prolonging survival is of primary importance, but that quality of life is also important. Her experience was that quality of life and general wellbeing were very good while taking either fulvestrant or anastrozole. However, she found that chemotherapy was much harder to cope with and was much more detrimental to quality of life. She also explained that intramuscular injections with fulvestrant can be painful but this may be related to the competency of the person giving them, and a monthly injection may be preferable to daily tablets (such as aromatase inhibitors) for some people. For example, some people find swallowing tablets very difficult. The clinical expert noted that monthly injections may improve compliance, particularly for some vulnerable patients. The clinical expert explained that fulvestrant would ideally be used in place of an aromatase inhibitor for first-line treatment in patients within the licensed population, because of the progression-free survival gain seen in the trials. They explained that treatment would be started in hospital but it could then be delivered in primary care for convenience, although ongoing specialist supervision would be needed to monitor response. The committee acknowledged that fulvestrant provides a further treatment option that may have additional benefits for some people.

Direct comparison with anastrozole

Evidence from FALCON is more relevant than FIRST

- 3.4 The company presented direct head-to-head evidence comparing fulvestrant with anastrozole from 2 randomised-controlled trials:
- FIRST: an open-label non-inferiority study

- FALCON: a double-blind superiority study.

The committee noted that investigators and patients were not blinded to treatment allocation in FIRST, potentially leading to bias, whereas FALCON was a double-blind trial. There were also important differences in the baseline characteristics of the patients in FIRST compared with the licensed population, which called into question the generalisability of the trial population to clinical practice in England. The committee noted that the indication specified in the marketing authorisation is for postmenopausal women who have not previously had endocrine therapy, but around 25% of patients in FIRST had had endocrine therapy before (including aromatase inhibitors). Also, about 19% of patients in FIRST had human epidermal growth receptor 2 (HER2)-positive disease and 35% had an unknown HER2 status. The committee understood from the clinical expert that people with HER2-positive disease usually have HER2-targeted therapies such as trastuzumab. In contrast, the FALCON trial had no patients with HER2-positive disease and none had had endocrine therapy before. Therefore, the committee concluded that the FALCON data are more applicable to the evaluation of the clinical effectiveness of fulvestrant than the FIRST data because:

- the trial population directly reflects the licence (that is, postmenopausal women with endocrine-naive, oestrogen-receptor positive disease)
- the double-blind trial design reduces the likelihood of bias.

There is a gain in progression-free survival with fulvestrant but this is less in FALCON than in the FIRST trial

3.5 The FIRST trial collected data on time-to-progression rather than progression-free survival. However, the committee noted comments from the ERG that the definition of time-to-progression was very similar to that of progression-free survival so they can be considered comparable. It noted that the hazard ratio (HR) for progression or death was greater in FIRST than in FALCON (HR 0.66 in FIRST; HR 0.80 in FALCON). The difference between the fulvestrant and anastrozole arms in the median time to event was 10.3 months in FIRST compared with 2.8 months in FALCON. The committee accepted that the progression-free survival results from FALCON show modest improvement compared with anastrozole, but it stated that the results in FIRST should be interpreted

with caution because of concerns about the trial (see [section 3.4](#)).

Final overall-survival benefit with fulvestrant is uncertain

3.6 The overall-survival data from FALCON are immature (31% of events reached) and mature data are not expected until the end of 2019. An overall-survival benefit had been shown in FIRST (HR for death 0.70, 95% confidence interval [CI] 0.50 to 0.98, and a difference between the fulvestrant and anastrozole arms in median survival of 5.7 months). However, the committee noted that these results should be interpreted cautiously because they may not be generalisable to the licensed population (see [section 3.4](#)). In FIRST, the median overall-survival benefit was much shorter than the progression-free survival (5.7 months compared with 10.3 months). The committee was concerned that if an overall-survival benefit is shown in FALCON, it could be considerably lower than seen in FIRST, given that the progression-free survival was much shorter in FALCON than FIRST (2.8 months compared with 10.3 months; see [section 3.5](#)). The committee concluded that it is unclear whether, and by how much, fulvestrant would extend overall survival compared with anastrozole. It noted that mature data from FALCON, which is better matched to the licensed indication than FIRST, are needed.

Indirect treatment comparison with letrozole and tamoxifen

PO25 should be removed from the analysis and equal efficacy of anastrozole and letrozole should be assumed

3.7 The company carried out an indirect treatment comparison comparing fulvestrant with letrozole and tamoxifen. This included 3 studies in addition to FIRST and FALCON: NORTH AMERICAN and TARGET (anastrozole compared with tamoxifen); and PO25 (letrozole compared with tamoxifen). The committee noted comments from the ERG that it preferred to exclude PO25 from the network because it could not obtain patient-level data from it and the results were compromised by about a

50% crossover after progression. The committee therefore questioned whether the trial should be included in the analysis. It understood that PO25 was incorporated to allow a comparison between fulvestrant and letrozole. However, it recalled its earlier conclusion that letrozole and anastrozole have equivalent clinical effectiveness (see [section 3.2](#)) and so concluded that PO25 should be removed from the analysis.

The results of the indirect treatment comparison for overall survival are highly uncertain

3.8 The company applied the inclusion and exclusion criteria from FALCON to the included studies to 'match' the trial population in FALCON. This meant that the company derived a subgroup from the included studies to create a homogenous population. The ERG commented that this approach reduced the sample size of the comparator studies and broke randomisation in all the studies except for FALCON. Although FALCON excluded people with HER2-positive disease, it was unclear whether people with HER2-positive disease in the NORTH AMERICAN and TARGET studies (for a comparison with tamoxifen) had been excluded. The company commented that older trials would not necessarily have included HER2 testing because it was not routinely carried out at the time of enrolment. The committee considered whether the advantages of reducing heterogeneity outweighed the disadvantages of reducing the number of patients included in the analysis and breaking randomisation, but was not persuaded it was and so questioned the reliability of the results. Following consultation, the committee noted the company's view that the 'matched' analysis was a robust estimator of efficacy given the heterogeneity in the trial populations. The company stated that the analysis did not break randomisation, the relative treatment effects were consistent with published trial data and the baseline characteristics remained balanced in the matched subgroups. The ERG acknowledged that the baseline characteristics of the matched and whole trial populations were similar. However, it stated that stratification of the initial randomisation on the baseline characteristics used for matching would be the only way to avoid breaking randomisation. The company presented an updated indirect treatment comparison using intention-to-treat data from the included studies, instead of 'matching' the trial populations to FALCON. The committee agreed that the results of the

indirect comparison did not appear to have been distorted by the matching process. However, it remained concerned that the results for overall survival are highly uncertain, because mature data from FALCON were not available for inclusion in the analysis.

Survival extrapolations

Overall-survival projections are highly uncertain

3.9 The committee considered that the partitioned survival cost-effectiveness model presented by the company is acceptable for decision-making. It considered the parametric survival curves for extrapolating progression-free and overall survival, which were estimated from the indirect treatment comparison. It noted that the company chose generalised gamma distributions for progression-free survival and Weibull distributions for overall survival, based on clinical plausibility and statistical fit, and applied these to fulvestrant and all the comparators. The committee was satisfied with the choice of parametric survival curves because the projections seem consistent with clinical expert opinion. However, it was concerned that the data from FALCON were immature, and noted comments that much of the data used for the projection of overall survival were from FIRST. The committee recalled that the results from FIRST may not be generalisable to the licensed population (see [section 3.4](#)), and that the final overall-survival benefit from FALCON is highly uncertain (see [section 3.6](#)). Therefore, it concluded that the projections for overall survival are highly uncertain.

Utility values used in the model

The utility values are not in line with other appraisals, but are not critical to the cost-effectiveness analysis

3.10 The company derived utility values directly from FALCON using the EQ-5D questionnaire (progression-free survival 0.75; progressed disease 0.69). The ERG commented that using EQ-5D from the trial is consistent with the NICE reference case. The committee noted that the

value for progressed disease was higher than those used in past appraisals. The company acknowledged this and presented a scenario analysis using lower values. The committee noted that alternative utility values for progressed disease had little effect on the cost-effectiveness results, and did not pursue this issue further.

Cost-effectiveness estimate

The main area of uncertainty in the cost-effectiveness analysis is the projected overall-survival benefit

3.11 The committee noted that the initial incremental cost-effectiveness ratios (ICERs) presented by the company for fulvestrant compared with anastrozole and tamoxifen (based on the company's indirect treatment comparison that 'matched' the trial populations to FALCON) were about £34,100 and £22,500 per quality-adjusted life year (QALY) gained respectively. The ERG did an exploratory base-case analysis that changed the assumptions on resource use, setting for the administration for fulvestrant and use of subsequent therapies. The ERG also assumed equal efficacy for letrozole and anastrozole (excluding PO25 from the indirect comparison). The committee noted that these changes had very little impact on the ICERs for fulvestrant (about £33,500 and £23,700 per QALY gained, compared with anastrozole and tamoxifen respectively). However, it concluded that the main area of uncertainty in the cost-effectiveness analysis is the projected overall-survival benefit.

Fulvestrant is not a cost-effective use of NHS resources compared with aromatase inhibitors

3.12 The committee noted that the overall-survival projection for fulvestrant was mostly based on data from FIRST, which it had concluded was less relevant for its decision-making than FALCON (see [sections 3.4](#) and [3.9](#)). It also questioned the validity of the modelled results because the predicted difference in median survival between the fulvestrant and anastrozole arms was about 8.3 months in the model, whereas in FIRST it was 5.7 months (see [section 3.6](#)). It also noted the considerable uncertainty in the final cost-effectiveness estimates because of

immature overall-survival data from FALCON. It was uncertain whether, and by how much, fulvestrant would extend survival compared with anastrozole in the licensed population (see section 3.6). It therefore considered the ERG's scenario analyses that explored the effect of different predictions of overall survival on the ICERs. Lowering the estimate of the overall-survival gain for fulvestrant compared with anastrozole (to the equivalent of assuming an HR of 0.82 and 0.88, instead of 0.77 in the company's base case) increased the ICER to about £40,800 and £52,400 per QALY gained respectively. When the HR was assumed to be 1 (that is, fulvestrant was assumed to have no overall-survival benefit over anastrozole), the ICERs increased to above £200,000 per QALY gained. The committee concluded that the results are very sensitive to changes in the predicted overall-survival gain used for fulvestrant, and that the base-case results are highly uncertain. It considered that the base-case estimate is likely to be optimistic, being based on a projected median overall-survival benefit of 8.3 months, when the median difference in progression-free survival in FALCON was only 2.8 months and the overall-survival benefit is unknown. Following consultation, the company presented confidential ICERs based on a proposed alternative pricing assumption. However, the committee agreed that the revised base-case estimates remain highly uncertain and may substantially overestimate the cost effectiveness of fulvestrant. It concluded that further survival data from FALCON are needed in order to produce robust estimates of the cost effectiveness of fulvestrant. The committee appreciated that some patients would welcome this alternative treatment option, but at present it cannot recommend fulvestrant as a cost-effective use of NHS resources for postmenopausal women with untreated, locally advanced or metastatic oestrogen-receptor positive breast cancer.

Fulvestrant is not a cost-effective use of NHS resources for people in whom aromatase inhibitors are not tolerated or are contraindicated

3.13 The committee considered the ICERs for fulvestrant compared with tamoxifen. It noted that the ICERs estimated by both the company and the ERG were in the range of £20,000 to £30,000 per QALY gained. The committee referred to section 6.3.3 of [NICE's guide to the methods of](#)

technology appraisal. This states that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources take into account a number of factors including the degree of certainty around the ICER. The committee considered that the ICERs are highly uncertain because of the immaturity of the overall-survival data (the key driver of the results; see section 3.12). It noted that, in the ERG's scenario analysis that explored the effect of different predictions of overall-survival benefit, the ICERs vary from about £24,400 to £39,000 per QALY gained. The committee also noted the company's updated confidential ICERs, based on the proposed alternative pricing assumption. However, it concluded that the ICERs remain highly uncertain because of the immaturity of the overall-survival data used in the indirect comparison. Therefore, fulvestrant cannot be recommended as a cost-effective use of NHS resources for postmenopausal women who have untreated, locally advanced or metastatic oestrogen-receptor positive breast cancer.

Conclusion

It is unclear whether, and by how much, fulvestrant would extend overall survival compared with aromatase inhibitors

3.14 The committee concluded that the FALCON trial, which directly compared fulvestrant with anastrozole, was superior to the FIRST trial because the population is more relevant and it has less potential for bias. It noted that, for FALCON, the progression-free survival results are modest and the overall-survival data are immature. The committee was therefore unclear whether, and by how much, fulvestrant would extend overall survival compared with anastrozole.

Fulvestrant is not a cost-effective use of NHS resources compared with aromatase inhibitors or when aromatase inhibitors are not suitable

3.15 The overall-survival benefit for fulvestrant compared with existing treatments is highly uncertain, and could affect the estimates of cost effectiveness for fulvestrant compared with existing treatments. More

survival data from FALCON are needed in order to produce robust estimates of cost effectiveness. Therefore, fulvestrant cannot be recommended as a cost-effective use of NHS resources for postmenopausal women who have untreated, locally advanced or metastatic oestrogen-receptor positive breast cancer.

4 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Irina Voicechovskaja and Hamish Lunagaria

Technical Leads

Zoe Charles

Technical Adviser

Marcia Miller and Thomas Feist

Project Manager

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Accreditation

