NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using fulvestrant in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: [August 2017]

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using fulvestrant in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 25 September 2017

Second appraisal committee meeting: 4 October 2017

Details of membership of the appraisal committee are given in section 5.

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 that has not previously been treated with endocrine therapy.

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 these recommendations

Current first-line management is with 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.

The estimated cost effectiveness for fulvestrant compared with aromatase inhibitors is above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per quality-adjusted life year gained), and is associated with considerable uncertainty. The estimate of cost effectiveness for fulvestrant compared with tamoxifen is also highly uncertain because of a lack of data and because the results of the indirect treatment comparison may not be reliable.

2 The technology

Fulvestrant (Faslodex), AstraZeneca	
Marketing authorisation	Fulvestrant is indicated for 'the treatment of oestrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women: • 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	The recommended dosage is 500 mg intramuscularly into the buttocks as 2 x 5 ml injections (1 in each buttock) on days 1, 15 and 29, and then once monthly (until disease progression).
Price	A pack of 2 x 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.

3 Committee discussion

The appraisal committee (section 5) 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-naive 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 well-being 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. The patient expert also explained that intramuscular injections with fulvestrant can sometimes be painful, but that having a monthly injection may be preferable to daily tablets (such as aromatase inhibitors) for some people. The committee heard from the clinical expert that fulvestrant would ideally be used in place of an aromatase inhibitor for the first-line treatment of patients within the licensed population because of the

progression-free survival gain seen in the trials. The clinical expert explained that treatment would be started in hospital, but that treatment could 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 neither the investigators nor the patients were 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 was for postmenopausal women who have not previously been treated with endocrine therapy but around 25% of patients in FIRST had prior endocrine therapy (which includes the aromatase inhibitors). In addition, about 19% of patients in FIRST had HER2-positive disease and 35% had an unknown HER2 status in the trial and 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 only included patients that reflected the licensed indication (that is, endocrine-naive). Therefore, the committee concluded that the FALCON

data were more applicable to the evaluation of the clinical effectiveness of fulvestrant than the FIRST data because:

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

There is a modest gain in progression-free survival with fulvestrant

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 in FIRST was greater than that for 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 showed modest improvement versus anastrozole but stated that the results in FIRST should be interpreted with caution because of the concerns set out in section 3.4 and a high dropout rate (37% of patients in the fulvestrant arm and 49% in the anastrozole arm).

Final overall survival benefit with fulvestrant is uncertain

3.6 The overall survival data from FALCON are immature, so overall survival outcomes are not yet available. The committee noted that 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) but that these results should be interpreted cautiously for the reasons set out in section 3.4. The clinical expert stated that the results for progression-

free survival in FALCON were disappointing (see section 3.5) but expected that an overall survival benefit would be seen, agreeing that this was uncertain. The committee concluded that it remained unclear whether, and to what extent, fulvestrant extends overall survival compared with anastrozole.

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 may not be reliable

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. It would have liked to have compared the results using the 'matched' population with those for the full 'unmatched' population to assess the robustness of the results. The committee concluded that the 'matching' approach adopted by the company may not have been appropriate and so it was not confident that the results of the indirect treatment comparison were reliable.

Survival extrapolations

Overall survival projections are highly uncertain

3.9 The committee considered the partitioned survival cost-effectiveness model presented by the company to be acceptable. It then considered the parametric survival curves for extrapolating progression-free and overall survival that 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 seemed consistent with clinical expert opinion. However, it was concerned that the data from FALCON were immature and noted comments that much of the data that drove the projection for overall survival were from FIRST. The committee was aware of the limitations of FIRST (low generalisability and potential bias because of the open-label study design; 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 were 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 incremental cost-effectiveness ratios (ICERs) presented by the company for fulvestrant compared with anastrozole and tamoxifen were approximately £34,100 and £22,500 per quality-adjusted life year (QALY) gained respectively. It understood that the ERG had changed some assumptions around resource use, setting for the administration for fulvestrant and use of subsequent therapies in an exploratory base-case analysis. Also, the ERG had 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 (approximately £33,500 and £23,700 per QALY gained compared with anastrozole and tamoxifen respectively). The committee considered that the ICERs presented for fulvestrant

compared with anastrozole were above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to 30,000 per QALY gained). However, it concluded that the main area of uncertainty in the cost-effectiveness analysis was the projected overall survival benefit, and gave this further consideration.

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

3.12 The committee was concerned that much of the overall survival projection for fulvestrant was driven by data from FIRST, which the committee had already concluded was less relevant than FALCON (see section 3.4 and 3.9), and about the validity of the modelled results because the predicted difference between the fulvestrant and anastrozole arms in median survival from the model was about 8 months, whereas in FIRST it was 5.7 months (see section 3.6). It was also aware that there was considerable uncertainty in the final cost-effectiveness estimates because the overall survival data from FALCON were immature. The committee recalled that it was uncertain whether, and to what extent, 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 impact of different predictions of overall survival on the ICERs. Lowering the estimate of the overall survival gain for fulvestrant compared with anastrozole, that is, to the equivalent of assuming a hazard ratio of 0.82 and 0.88 (instead of 0.77 in the company's base case) increased the ICER to approximately £40,800 and £52,400 per QALY gained respectively. When the equivalent of the hazard ratio 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. Therefore, the committee considered that the results were very sensitive to changes in the predictions about the overall survival gain associated with fulvestrant and that the base-case results were highly uncertain. It concluded that it could not 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 (see section 3.12). 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 there was considerable uncertainty around the results because there were concerns about the methods used to indirectly compare fulvestrant with tamoxifen (see section 3.8). In addition, the ICERs were associated with considerable uncertainty because of the immaturity of the overall survival data (the key driver of the results; see section 3.12). The committee noted that, in the ERG's scenario analysis that explored the impact of different predictions of overall survival benefit, the ICERs varied from approximately £24,400 to £39,000 per QALY gained. The committee concluded that the ICERs were highly uncertain because of the immaturity of the overall survival data and because it was not confident that the results of the indirect treatment comparison were reliable. Therefore, the committee concluded that fulvestrant could not 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 in whom aromatase inhibitors are not tolerated or are contraindicated.

Conclusion

It is unclear whether, and to what extent, fulvestrant extends overall survival compared with the 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 was more relevant and it had less potential for bias. It noted that, for FALCON, the progression-free survival results were modest and that the overall survival data were immature. The committee was therefore unclear whether, and to what extent, fulvestrant would extend overall survival compared with anastrozole.

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

3.15 The company's and ERG's base-case ICERs for fulvestrant compared with anastrozole (approximately £34,100 and £33,500 per QALY gained respectively) were above the range normally considered to be a cost-effective use of NHS resources (that is, £20,000 to 30,000 per QALY gained). In addition, there was substantial uncertainty about the final overall survival benefit for fulvestrant compared with anastrozole, which could have raised the ICER even higher. Therefore, fulvestrant could not 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 compared with aromatase inhibitors.

Fulvestrant is not recommended when aromatase inhibitors are not suitable

3.16 The company's ICER for fulvestrant compared with tamoxifen was approximately £22,500. However, there was substantial uncertainty in the final overall survival benefit for fulvestrant and in the indirect comparison with tamoxifen. Therefore, the committee could not recommend tamoxifen for postmenopausal women who have untreated locally advanced or

metastatic oestrogen-receptor positive breast cancer when aromatase inhibitors are not suitable.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Jane Adam
Chair, appraisal committee
August 2017

5 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.

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.

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.

Hamish Lunagaria
Technical Lead

Zoe Charles
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Marcia Miller and Thomas Feist
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