NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA239; Fulvestrant for the treatment of locally advanced or metastatic breast cancer

Final recommendation post consultation
The guidance should be transferred to the 'static guidance list'.

1. Background

This guidance was issued in December 2011.

At the GE meeting of 29 July 2014 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

The guidance should be transferred to the 'static guidance list'.

3. Rationale for selecting this proposal

No new relevant clinical evidence has emerged that is expected to affect the recommendations in TA239. Fulvestrant is not expected to receive an extension to its marketing authorisation. The NHS list price of fulvestrant has not changed since the original appraisal. TA239 did not include any specific recommendations for further research. In view of the above information, an update is not considered necessary.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Novartis Pharmaceuticals	**Response to proposal:** No comment	**Comment from Technology Appraisals**
Please note that Novartis Pharmaceuticals UK has no comments.		Response noted.

Respondent: Pfizer	**Response to proposal:** Agree	**Comment from Technology Appraisals**
We are not aware of any new evidence that would lead to a change in the existing recommendations in TA239.		Response noted.

Respondent: Royal College of Nursing	**Response to proposal:** No comment	**Comment from Technology Appraisals**
Nurses working caring for people with Breast cancer were invited to submit comments to inform on the draft scope of the above health technology appraisal. The Royal College of Nursing does not have any comments to make on this draft scope at this stage.		Response noted.

Respondent: Royal College of Pathologists	**Response to proposal:** No comment	**Comment from Technology Appraisals**
We have no comment to make on this review.		Response noted.

Respondent: Royal College of Physicians, National Cancer Research Institute, Royal College of Radiologists, Association of Cancer Physicians	**Response to proposal:** Disagree
Fulvestrant has always had limited availability within England and Wales and is relatively costly in comparison to other endocrine therapies and requires intramuscular administration. Our experts recognise the difficulties in interpretation of the data for high dose fulvestrant as an alternative to aromatase inhibitors within the marketing authorisation and would not at this stage advocate a widespread adoption of high dose fulvestrant as an alternative to second line aromatase inhibitor therapy for locally advanced or metastatic breast cancer. We do however recognise that in some patients compliance with oral medication is very challenging and there are groups who are for a variety of reasons unable to comply with regular oral medication many of whom are not receiving nasogastric feeding. We would therefore recommend review of the guidance in relation to the often very vulnerable group of patients where there are genuine problems with oral compliance (not always related to swallowing ability) and amended to recognise that Fulvestrant should be made available in these limited circumstances. Our Understanding is that the majority of patients prescribed Fulvestrant within the NHS have in fact been prescribed outside the direct marketing authorisation. This agent has been mainly used as after progression on one or two aromatase inhibitors and or antioestrogen in women where there has been a demonstrable benefit to endocrine therapy either as a documented clinical response or prolonged period of disease stabilisation and where alternative options such as cytotoxic chemotherapy or evorolimus and exemestance are either fully contraindicated or anticipated to produce problematic and potentially life threatening toxicity. While use in these circumstances is outside the scope of the appraisal the existence of the guidance has been influential in commissioners decisions in withdrawing	**Comment from Technology Appraisals** Response noted. For any technology there may be clinical circumstances that prohibit a patient from receiving the technology, for example medical contraindications. During the course of an appraisal, the Committee can explore if there are additional recommendations or adjustments that can be made to accommodate the needs of specific groups of patients. The purpose of this review proposal is to look at, among other things, the available evidence for the technology and when ongoing research will be completed to determine whether an update of the guidance is necessary. In its appraisals of health technologies, NICE is bound by the marketing authorisation of the technology under appraisal. For TA239, the marketing authorisation places fulvestrant as an alternative to aromatase inhibitors after anti-oestrogen treatment (that is, as a second-line treatment). Therefore, NICE cannot make recommendations on the use of fluvestrant in other clinical settings.

access to fulvestrant for patients in these circumstances which we regard as unfortunate as this has prevented access to a small group of patients where this drug has a clinically recognised role.	

Respondent: AstraZeneca	**Response to proposal:** Disagree
AstraZeneca is now able to share the results of the Mixed Treatment Comparison (MTC) conducted of fulvestrant for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen (AO) therapy, or disease progression on therapy with an AO. This analysis is based on the mature (75%) analysis of the CONFIRM trial. You can find this analysis in attachment to this email. We would kindly ask you to consider the attached document as a draft which is still subject to further internal review. In this analysis, the concerns raised by the Evidence Review Group (ERG) during the original STA process of fulvestrant have been taken into consideration and been addressed. Please refer to sections 5.2 (p13) – 5.5 (p22) for the analysis of the post-AO subgroup data which we believe will be of most interest. AstraZeneca believes this new evidence support a review of TA-239 and furthermore plans to modify the Cost-effectiveness Model that was used for the 2010 STA Submission as follows: • Faslodex 500 mg versus AIs as 2nd Line treatment after relapse on or after adjuvant anti-estrogen therapy or disease progression on therapy with an anti-estrogen • Use the prior anti-estrogen subgroup from CONFIRM • Use the updated MTC in attachment	**Comment from Technology Appraisals** Response noted. The results of the updated analysis are similar to those considered by the Committee in TA239, and so are unlikely to change the Committee's view on the relative effectiveness of fulvestrant. In addition, the Committee agreed that only data from the subgroup in the CONFIRM trial who had received an anti-oestrogen as their last treatment before fulvestrant should be included in the network meta-analysis. The results of the updated analysis for this subgroup therefore did not provide substantial new evidence that warrants an appraisal review, and incorporating those results within the model is unlikely to change the Committee's conclusion about the cost effectiveness of fulvestrant. The Committee identified the choice of the parametric survival models used to project time to progression (TTP) and overall survival as a source of uncertainty (see section 4.7 in TA239). Although the updated analysis used alternative methods for the survival analysis of TTP and overall survival, no justification was given for the modeling approach taken (parametric or proportional hazards modeling) or the parametric distributions chosen. It is therefore not clear whether the

	new evidence is robust. The Committee concluded that the studies selected for inclusion in the original network meta-analysis were heterogeneous, which in its consideration, introduced high uncertainty about the validity of the results of the analysis (see section 4.9 in TA239). As these same studies were included in the updated analysis, the validity of the results remains uncertain. In addition, the updated analysis included 3 new studies. However, an assessment of heterogeneity between studies, qualitative that being or quantitative, was not presented. Therefore, the extent of bias in the analysis is unknown. In summary, the new evidence was not considered to be of substantial nature to warrant an appraisal review. Furthermore, the main concerns of the Committee about the clinical-effectiveness evidence for fulvestrant remain largely unaddressed. It is therefore recommended that TA239 be transferred to the static list.

Paper signed off by: Elisabeth George, 20 October 2014

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