National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: 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.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Association of Breast Surgery	It would be appropriate to refer this topic to NICE for appraisal.	Comments noted. No action required.
	AstraZeneca	It is appropriate to refer this topic to NICE for appraisal.	
	Breast Cancer Now	It is appropriate to refer this topic to NICE for appraisal.	
	Novartis	Yes this topic is appropriate for a NICE appraisal.	
Wording	Association of Breast Surgery	In clinical practice a very small percentage of patients have metastatic disease at initial diagnosis. Patients with ER positive breast cancer who then develop metastatic disease will all have received adjuvant endocrine therapy either Tamoxifen or an Aromatase Inhibitor. The wording	Comments noted. The population in the scope reflects the population in the clinical trials of fulvestrant, which excluded patients who had received any prior hormonal treatment for breast cancer. The committee will appraise the technology within the boundaries of its marketing

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		of the remit is for patients who have not received endocrine treatment so the majority of metastatic ER positive patients would not be able to receive this drug.	authorisation; the marketing authorisation has not yet been received.
	AstraZeneca	The current wording of the remit should be amended to 'locally advanced (not considered amenable to surgery or radiotherapy of curative intent) or metastatic breast cancer'.	Comment noted. Until the marketing authorisation is received, it is preferable to keep the population in the scope broad. The committee will appraise the technology within the boundaries of its marketing authorisation. The company can make a case in its submission, with clear justification, for targeting a subgroup of the scoped population.
	Breast Cancer Now	The wording appears to be appropriate. It is however worth noting that fulvestrant does not currently have a marketing authorisation for this indication.	Comments noted. NICE appraises technologies within their marketing authorisations in the UK and aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted (sooner for technologies that are eligible for consideration in the Cancer Drugs Fund). The technology section of the scope provides details of the current marketing authorisation and ongoing clinical trials for fulvestrant.
	Novartis	Yes	Noted. No action required.
Timing Issues	Association of Breast Surgery	It would be helpful in clinical practice to have another treatment option for women with ER positive metastatic breast cancer	Comments noted. No action required.

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	Breast Cancer Now	Metastatic breast cancer is breast cancer that has spread outside of the breast to another part of the body. At this stage of disease, breast cancer can be controlled but not cured – metastatic breast cancer is a terminal diagnosis. It is essential that women with metastatic breast cancer have access to the best available treatments and that new advances in treatments are approved for routine use as quickly as possible.	Comments noted. No action required. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted (sooner for technologies that are eligible for consideration in the Cancer Drugs Fund).

Comment 2: the draft scope

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Background information	Association of Breast Surgery	Locally advanced breast cancer is defined as tumours greater then 5cm OR (not and) fixed to the skin or chest wall	Comments noted. The background section of the scope has been updated.
	AstraZeneca	The key issue in the background information section relates to the appropriate use and interpretation of 'locally advanced' breast cancer. Fulvestrant is not expected to be considered an option for patients with locally advanced disease which is considered amenable to surgery or radiotherapy of curative intent. Therefore the estimate of the size of the potentially eligible population, as well as the description of current treatment options should be reviewed.	Comments noted. The background section is intended to provide a brief summary of the disease, on a broad level, to provide context for the positioning of the technology in the pathway. The epidemiology data were not intended to reflect the population for whom fulvestrant will be considered. The population in which fulvestrant will be appraised, within its marketing authorisation, is specified in the population section of the scope. No action required.

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	Breast Cancer Now	The background information states that the endocrine therapies used in clinical practice includes aromatase inhibitors and specifically names anastrozole and letrozole. Exemestane is also an aromastase inhibitor used in clinical practice and should be included in this list.	Comments noted. The treatments listed in the background section focus on the population who will be eligible for fulvestrant. Fulvestrant has been studied in clinical trials in people who have not received any prior endocrine therapy. The marketing authorisation for exemestane positions it after 2-3 years of adjuvant tamoxifen therapy, or for disease that has progressed following anti-oestrogen therapy. The background section has been updated to specify that the treatments are relevant to untreated disease.
The technology/ intervention	AstraZeneca	Please amend the final paragraph to make it clear that this refers to the current licencing status and marketing authorisation wording.	Comment noted. The wording has been updated to make it clearer that this reflects the current marketing authorisation.
	Breast Cancer Now	As far as we are aware, the description of the technology appears to be accurate.	Comments noted. No action required.
Population	Association of Breast Surgery	The majority of patients who are metastatic will have had previous endocrine treatments. There is a bigger group of patients who do not have locally advanced breast cancer who are not fit for surgery or choose not to have surgery. Fulvestrant may be a better treatment in this group.	Comments noted. The population in the scope reflects the population in the clinical trials of fulvestrant, which excluded patients who had received any prior hormonal treatment for breast cancer. The committee will appraise the technology within the boundaries of its marketing authorisation.
	AstraZeneca	It should be made clear that of the patients with locally advanced disease, only those with tumours not considered amenable to surgery or	Comment noted. Until the marketing authorisation is received, it is preferable to keep the population in the scope broad. The committee will appraise

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		radiotherapy of curative intent are considered in the appraisal.	the technology within the boundaries of its marketing authorisation. The company can make a case in its submission, with clear justification, for targeting a subgroup of the scoped population.
	Breast Cancer Now	The population appears to be appropriately defined although it is worth noting that the population refers to 'people' while the discussion of the marketing authorisation refers specifically to 'women'. The majority of breast cancers in men are hormone receptor positive so, while breast cancer is much more common in women, this treatment would be relevant to those men who do get the disease. Therefore, it is appropriate to refer to 'people' rather than 'women'.	Comments noted. The population refers to 'people' instead of 'women' to include transgender men. This is to eliminate unlawful discrimination in relation to gender reassignment, which is defined as a protected characteristics in the Equality Act 2010. For more information see NICE's equality report.
	Novartis	Yes Could consider: (i) older/younger patients (ii) Impact of intramuscular administration on certain subgroups of patients	Comments noted. The company will be able to fully describe differences in fulvestrant's clinical or cost effectiveness across different subgroups in its evidence submissions, which will then be considered by the appraisal committee. Consultees and commentators are also encouraged to submit evidence on the patient perspective and patient preferences, which the committee will consider alongside evidence on clinical and cost effectiveness. Legislation on human rights, discrimination and equality requires that patients are not denied access, or have different or restricted access, to NHS care because of their age or other protected

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			characteristics (Social Value Judgements; 'Principles for the development of NICE guidance', principle 6). The NHS aims to provide free, necessary and appropriate treatment to the whole UK population. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.
Comparators	Association of Breast Surgery	At present Tamoxifen, Letrozole, Exemestane and occassionaly Megace are the standard treatments but newer endocrine treatments; everolimus and pabociclib are starting to be used.	Comments noted. The scoping workshop attendees agreed that exemestane, Megace and everolimus were not relevant comparators because they are used later in the treatment pathway (for disease that has progressed following anti-oestrogen therapy). Fulvestrant has been studied in clinical trials in people who have not received any prior endocrine therapy. Palbociclib is not established clinical practice in the UK. No action required.
	AstraZeneca	The current comparators are appropriate. Chemotherapy is normally reserved for very specific groups of patients and should not be considered a comparator in the patients described in the Population section of the scope. In the first line palliative setting, tamoxifen is generally used in patients intolerant to or unsuitable for treatment with an aromatase inhibitor.	Comments noted. The scoping workshop attendees stated that chemotherapy was not a relevant comparator for this population.

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	Breast Cancer Now	As stated earlier, the list of aromatase inhibitors excludes exemestane. Should this be added as a comparator?	Comment noted. The scoping workshop attendees agreed that exemestane was not a relevant comparator because its marketing authorisation positions it later in the treatment pathway (following 2-3 years of adjuvant tamoxifen therapy, or for disease that has progressed following anti-oestrogen therapy). Fulvestrant has been studied in clinical trials in people who have not received any prior endocrine therapy.
	Novartis	Yes Yes	Comments noted. No action required.
Outcomes	Association of Breast Surgery	Compliance should also be included. One of the main problems with endocrine therapy is compliance with up to 25% of patient being non-compliant. As this drug is an IM injection then compliance would not be an issue.	Comments noted. Consultees and commentators are encouraged to submit evidence on the patient perspective (including patient preferences and compliance), which the committee will consider alongside evidence on clinical and cost effectiveness.
	AstraZeneca	The outcome measures are appropriate.	Comment noted. No action required.
	Breast Cancer Now	The outcome measures appear to be appropriate.	Comment noted. No action required.
	Novartis	Yes	Comment noted. No action required.
Economic analysis	AstraZeneca	No comment.	No action required.

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Equality and Diversity	Association of Breast Surgery	No issues. It may be easier for certain groups of patients to receive a drug IM rather than orally. Currently all endocrine treatment have to be administered orally.	Any potential equality issues will be considered during the course of the appraisal and the committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. No action required.
	AstraZeneca	No comment.	No action required.
	Breast Cancer Now	This scope does not appear to promote discrimination.	Comment noted. No action required.
Innovation	Association of Breast Surgery	ER positive metastatic disease is often a chronic condition where patients receive numerous endocrine treatments over the course of their disease when they progress. This would enable another endocrine treatment to be given and so would be a step change.	Comments noted. The company and other consultees will be able to fully describe why they consider fulvestrant to be innovative in their evidence submissions, which will then be considered by the appraisal committee. No action required.
	AstraZeneca	The use of fulvestrant in eligible patients has the potential to prolong life and extend the duration of endocrine therapy prior to chemotherapy.	
	Breast Cancer Now	Results from early trials suggest that when given in the first line setting, fulvestrant extends overall survival when compared to anastrozole. However, it should be noted that phase III data is not yet available for this product and therefore it is not	

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		currently possible to fully assess the effectiveness of this product.	
Questions for consultation	Association of Breast Surgery	Tamoxifen is frequently used in ER patients with metastatic disease if they have received previous aromatase inhibitors. I do not think that chemotherapy should be used in the comparator if Fulvestrant is only being used when a patients had not had any previous endocrine therapy.	Comments noted. The background section of the scope has been amended to clarify that tamoxifen can be used to treat metastatic disease. The scoping workshop attendees that chemotherapy was not a relevant comparator for this population.
	AstraZeneca	Are there any subgroups in whom fulvestrant is expected to be more effective? One of the pre-specified subgroups in the pivotal trial was 'visceral/non-visceral disease', but other subgroups of interest may arise following complete analysis of the study data.	Comments noted. These subgroups have been included in 'other considerations'.
	Novartis	• *Given that chemotherapy is normally used only if disease is life-threatening or requires early relief of symptoms, should chemotherapy be included as a comparator?* Yes chemotherapy could be considered as a comparator • *Is tamoxifen used for metastatic hormone receptor-positive breast cancer in postmenopausal women? Or is it only used in locally advanced disease?* It can be used	Comments noted. The background section of the scope has been amended to clarify that tamoxifen can be used to treat metastatic disease. The scoping workshop attendees stated that chemotherapy was not a relevant comparator for this population.

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		in hormone receptor positive locally advanced or metastatic breast cancer • *Are there other relevant comparators for fulvestrant?* No	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Pfizer