National Institute for Health and Clinical Excellence

Fulvestrant for the treatment of locally advanced or metastatic breast cancer

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	CSAS	The topic seems appropriate	At the scoping workshop it was considered that this topic was appropriate for appraisal.
	South Staffordshire PCT	The topic seems appropriate, but not sure that it is a priority. Would question as to whether low-dose should also be considered in this TA	Comments noted. Low-dose fulvestrant is not an intervention in this appraisal because it has been superseded by high dose fulvestrant. However it was considered at the scoping workshop that low-dose fulvestrant would still be an appropriate comparator as it could be used in clinical practice.
	Breakthrough Breast Cancer and Breast Cancer Care	It would be appropriate to refer this topic to NICE for appraisal dependant on time lines fitting with expected data release from the key trials that will inform the appraisal (at the moment there are several ongoing trials but as yet limited evidence of effectiveness), as well as expected time lines for licensing.	Comments noted. Following referral the appraisal will be scheduled into the work programme to provide timely guidance to the NHS.
	Royal College of Pathologists	This is an appropriate study for a small subgroup of patients with advanced breast cancer.	Comments noted. At the scoping workshop it was considered that this topic was appropriate for appraisal.
Wording	CSAS	The wording seems appropriate.	Comments noted. No actions required.

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	South Staffordshire PCT	The wording seems appropriate, but there is a contradiction inthat the high dose (500mg) is not currently licensed but the remit is to consider its clinical and cost effectiveness within its licensed indication.	Comments noted. To provide timely guidance to the NHS, topics are scoped prior to marketing authorisation. Fulvestrant 500mg has now been licensed for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer. Following referral the appraisal will be scheduled into the work programme to provide timely guidance to the NHS that coincides with licensing dates.
	Breakthrough Breast Cancer and Breast Cancer Care	The wording of the remit does reflect the issues about this technology that NICE should consider; however the remit should also include the appraisal of the clinical and cost-effectiveness of low dose fulvestrant (250mg) according to its licensed indication.	Comments noted. Low-dose fulvestrant is not an intervention in this appraisal because it has been superseded by high dose fulvestrant. However it was considered at the scoping workshop that low-dose fulvestrant would still be an appropriate comparator as it could be used in clinical practice.
	Royal College of Pathologists	The wording is a reasonable reflection of current practice.	Comments noted. No actions required.
Timing issues	CSAS	CIC information removed	Comments noted. Following referral the appraisal will be scheduled into the work programme to provide timely guidance to the NHS that coincides with licensing dates.
	South Staffordshire PCT	CIC information removed The degree of urgency would depend on the balance of evidence of benefit of the higher dose. Lower- doses appear to be non- inferior to alternative treatments. PCTs will need to develop commissioning policies prior to any NICE TA being published.	Comments noted. Following referral the appraisal will be scheduled into the work programme to provide timely guidance to the NHS that coincides with licensing dates.

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	Breakthrough Breast Cancer and Breast Cancer Care	This drug is indicated for women with locally advanced or metastatic breast cancer whose disease has relapsed or progressed while on or following adjuvant therapy. This is very important as patients with metastatic breast cancer typically have limited treatment options. Many existing drugs, including hormone therapy, are routinely being used in the primary setting. As a result of this use in earlier stages, there may be treatment resistance issues for patients who later develop metastatic breast cancer. Therefore, it is timely for NICE to assess fulvestrant because it could be an effective treatment for women and who do not have other options available to them. Whilst fulvestrant has similar side effects to Arimidex [1], there seems to be less detrimental effects on bones and improved arthralgia (bone/joint pain), which has quality of life advantages for people with secondary disease. Understandably, patients want access to treatments that will give them the chance of both an increased length of survival and improved quality of life to spend more quality time with their families and friends. For women with metastatic breast cancer, the importance of quality of life cannot be underestimated. Fulvestrant is important in this regard as it is administered as an intra-muscular injection only once a month. In comparison to many other cancer treatments, this drug represents fewer hospital visits. It also has advantages over oral therapy as it removes the risk of patients not remembering to take additional pills. High dose fulvestrant has also been demonstrated to be generally well-tolerated with a safety profile similar to anastrozole [2]. We recognise the very urgent needs of this patient group and support the process going forward at this stage to ensure faster decisions after licensing. However, we would like to highlight that additional evidence from the SOFEA trial is due to be reported in 2011-2012 and that other data is also currently only in phrase II. Relevant forthcoming research should be taken into account for this appraisal.	At the scoping workshop it was considered that this topic was appropriate for appraisal. Following referral the appraisal will be scheduled into the work programme to provide timely guidance to the NHS that coincides with licensing dates.

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	Royal College of Pathologists	Mot particularly urgent	At the scoping workshop it was considered that this topic was appropriate for appraisal. Following referral the appraisal will be scheduled into the work programme to provide timely guidance to the NHS that coincides with licensing dates.
Additional comments on the draft remit	Breakthrough Breast Cancer and Breast Cancer Care	Comparing fulvestrant 500 mg with Fulvestrant 250mg is important as we would need to know whether any potential efficacy is drug or dose dependent. Although fulvestrant at a low dose (250mg) is shown only to be as at least as effective as anastrozole [3, 4], yet more costly [5], it should be considered for inclusion in the remit. Treatment is not being considered as a first-line therapy at this dose and therefore would be limited to being prescribed in situations where other methods of endocrine therapy are no longer effective. This both limits the cost implications to the NHS and increases the importance of this therapy to patients. *References included but not reproduced*	Comment noted. It was considered at the scoping workshop that low-dose fulvestrant would be an appropriate comparator as it could still be used in clinical practice.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	CSAS	Information from CRUK and in NICE guidance on advanced cancer (CG81) suggests that about 5% of women present with breast cancer that has spread (based on 1992-4 figures), compared to the 16-20% quoted. CG81 also reports that an additional 35% go on to develop metastases in the subsequent decade rather than the 50% quoted. Other than this the information appeared accurate.	Comment noted. This has been updated in the scope.

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	South Staffordshire PCT	Information from CRUK and in NICE guidance on advanced cancer (CG81) suggests that about 5% of women present with breast cancer that has spread (based on 1992-4 figures), compared to the 16-20% quoted. CG81 also reports that an additional 35% go on to develop metastases in the subsequent decade rather than the 50% quoted. Other than this the information appeared accurate.	Comment noted. This has been updated in the scope.
	Breakthrough Breast Cancer and Breast Cancer Care	The background information appears to be accurate and complete.	Comments noted. No actions requested.
	Royal College of Pathologists	It would be useful to know the number of patients who would have " … oestrogen receptor positive metastatic or locally advanced breast cancer, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) therapy." and copuld be randomised into a trial that includes treatments that have already been tried and have proved unsuccessful.	Comments noted. The scope document provides only a brief summary of the background. This detail is not required in the scope. No changes made.
	AstraZeneca	Astra\Zeneca would like to query the relevance of including the treatment of breast cancer in men in the background	Comments noted. This has been amended in the scope.
The technology/ intervention	CSAS	The description of the technology appeared accurate; the 500mg dose is given once every 4 weeks as an IM injection. Consideration should be given to inclusion of studies using high dose fulvestrant in combination with other treatments (e.g. anastrozole).	Comments noted, no changes required to the scope. The inclusion of studies of combination therapy will be dependent on the obtained marketing authorisation. NICE can only make recommendations for fulvestrant within its marketing authorisation.
	South Staffordshire PCT	The description of the technology appeared accurate; the 500mg dose is given once every 4 weeks as an IM injection. Consideration should be given to inclusion of studies using high dose fulvestrant in combination with other treatments (e.g. anastrozole).	Comments noted, no changes required to the scope. The inclusion of studies of combination therapy will be dependent on the obtained marketing authorisation. NICE can only make recommendations for fulvestrant within its marketing authorisation.

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	Breakthrough Breast Cancer and Breast Cancer Care	The description of the technology appears to be accurate.	Comments noted, no changes required to the scope.
	Royal College of Pathologists	Yes	Comments noted, no changes required to the scope.
	AstraZeneca	AstraZeneca would like it to be clarified that fluvestrant 250mg is administered by intramuscular injection every four weeks. The clinical studies that are referred to compared against exemestane is still ongoing and has yet to report. Therefore a mixed treatment comparison will have to be undertaken to obtain comparative data against exemestane	Comments noted, no changes required to the scope.
Population	CSAS	The population specified in the scope has metastatic or locally advanced breast cancer that has relapsed while on or after endocrine therapy (i.e. high dose fulvestrant would be a second line treatment). Depending on the agreed licensed indications. when these are known, the population could be expanded to include first line treatment for advanced breast cancer as the published clinical trial of high dose fulvestrant used it in this context.	Comments noted. The manufacturer has stated that the marketing authorisation will reflect treatment of breast cancer that has relapsed while on or after endocrine therapy. No changes to the scope required.
	South Staffordshire PCT	The population specified in the scope has metastatic or locally advanced breast cancer that has relapsed while on or after endocrine therapy (i.e. high dose fulvestrant would be a second line treatment). Depending on the agreed licensed indications. when these are known, the population could be expanded to include first line treatment for advanced breast cancer as the published clinical trial of high dose fulvestrant used it in this context.	Comments noted. The manufacturer has stated that the marketing authorisation will reflect treatment of breast cancer that has relapsed while on or after endocrine therapy. No changes to the scope required.

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	Breakthrough Breast Cancer and Breast Cancer Care	More clarity is needed in the scope as to whether it will be looked at as second line treatment or also third or fourth line. The draft states this appraisal will be for those women 'whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) therapy' but does not make it clear whether this is after just first line AIs or tamoxifen. This is relevant to Progestogens (megestrol acetate, medroxyprogesterone acetate) as comparators because these would be much less likely to be used as second line (i.e at first relapse of metastatic disease).	Comments noted. It was considered at the scoping workshop that progestogens would be used after fulvestrant in the care pathway and therefore were not relevant comparators. In accordance with the marketing authorisation the scope specifies disease relapse or progression on or after therapy with an anti-oestrogen rather than a specific line of therapy.
	Royal College of Pathologists	No (see background above)	Comments noted, no changes required.
	AstraZeneca	In keeping with what AstraZeneca believe to be the most likely wording for high dose fulvestrant, the population should be those who have relapsed whilst on or after anti-oestrogen therapy.	Comments noted. Following the scoping workshop it was considered that this was the most appropriate wording for the population.
Comparators	CSAS	The comparators seem appropriate.	Comments noted. It was considered at the scoping workshop that the aromatase inhibitors and low dose fulvestrant were appropriate comparators.
	South Staffordshire PCT	The comparators seem appropriate.	Comments noted. It was considered at the scoping workshop that the aromatase inhibitors and low dose fulvestrant were appropriate comparators.
	Breakthrough Breast Cancer and Breast Cancer Care	Aromatase inhibitors and tamoxifen would be the 'best alternative care' as these are the treatments recommended in the NICE guidance CG81.	Comments noted. It was considered at the scoping workshop that the aromatase inhibitors and low dose fulvestrant were appropriate comparators. Tamoxifen has been removed from the scope as this would be given before fulvestrant.

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	Pfizer	Exemestane is an appropirate comparator for this appraisal, however there are no head to head studies that compare exemestane to high dose (500mg) fulvestrant for the treatment of locally advanced or metastatic breast cancer.	Comments noted. It was considered at the scoping workshop that the aromatase inhibitors including exemestane were appropriate comparators.
	Royal College of Pathologists	Yes, except for caveat about suitability of failed treatments as comparitors.	Comment noted. Following the scoping workshop 'failed treatments' have been removed as comparators.
	AstraZeneca	AstraZeneca would like to make NICE aware that once a type II variation for high dose fluvestrant is granted, the posology for fulvestrant 250mg will be changed to reflect the high dose variation. However, AstraZeneca still feels that fulvestrant 250 mg is an appropriate comparator. In keeping with ABC NICE clinical guideline, AstraZeneca believes that Aromatase Inhibitors are the best alternative care in this setting	Comments noted. It was considered at the scoping workshop that the aromatase inhibitors and low dose fulvestrant were appropriate comparators.
Outcomes	CSAS	Time to the specified outcomes should be included (e.g. time to progression). Some of the existing trials use a combined outcome of objective response or stable disease for 24 weeks or longer. Given that the long term aim is improved survival - rather than simply a change in mode of death - higher priority should be given to data demonstrating overall survival than to progression-free survival or response rates. Measures of quality of life should be examined if available.	Comment noted. The outcomes as currently listed include response rate. This does not exclude the use of composite measures that capture response and stable disease. No changes to the scope made.
	South Staffordshire PCT	Time to the specified outcomes should be included (e.g. time to progression). Some of the existing trials use a combined outcome of objective response or stable disease for 24 weeks or longer. Given that the long term aim is improved survival - rather than simply a change in mode of death - higher priority should be given to data demonstrating overall survival than to progression-free survival or response rates. Measures of quality of life should be examined if available.	Comment noted. The outcomes as currently listed include response rate. This does not exclude the use of composite measures that capture response and stable disease. No changes to the scope made.

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	Breakthrough Breast Cancer and Breast Cancer Care	These outcome measures appear to capture the most important health related effects of the technology.	Comments noted. No actions required.
	Royal College of Pathologists	Yes	Comments noted no actions required.
	AstraZeneca	Response rates are traditionally very low in advanced breast cancer. AstraZeneca believe that clinical benefit rates to be a more relevant end point than response rate.	Comment noted. The outcomes as currently listed include response rate. This does not exclude the use of composite measures that capture response and stable disease. No changes to the scope made.
Economic analysis	CSAS	Cost effectiveness studies included in the NICE CG81 guideline on advanced breast cancer used a lifelong time horizon..	Comments noted. The economic model will incorporate a time horizon that is sufficient to capture all the benefits and costs of the technology under intervention.
	South Staffordshire PCT	Cost effectiveness studies included in the NICE CG81 guideline on advanced breast cancer used a lifelong time horizon. Consideration also needs to be given to the manufacturers pricing structure. As a 500mg dose is not currently licensed, the only product is a 250mg pre-filled syringe, which will currently double costs of a 250mg dose. An accurate pricing structure is needed to reliably assess cost-effectiveness. Consideration also needs to be given as to where this technology might be administered. GP's currently prescribe tamoxifen and Aromatase inhibitors, but many patients receiving Fulvestrant receive this from their cancer specialist. Continued out-patient appointments need to be factored into the analysis or a view given as to whether this should be administered in primary care.	Comments noted. The economic model will incorporate a time horizon that is sufficient to capture all the benefits and costs of the technology under intervention. The appraisal will be completed using publically available prices for fulvestrant and will include costs such as administration costs.
	Breakthrough Breast Cancer and Breast Cancer Care	The economic analysis appears to be appropriate.	Comments noted. No changes required.

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	AstraZeneca	AstraZeneca believe an appropriate time horizon would be ten years	Comments noted. The economic model should incorporate a time horizon that is sufficient to capture all the benefits and costs of the technology under intervention.
Equality	CSAS	If licensing permiits and evidence is available the scope could be extended to include men with advanced breast cancer.	Comments noted. The manufacturer confirmed that the appropriate population for this appraisal is post menopausal women.
	South Staffordshire PCT	If licensing permits and evidence is available the scope could be extended to include men with advanced breast cancer. See above regarding whether this technology is suitable (ie safe and appropriate) to be administered in primary care under shared care with a specialist. Access to specialist services may be difficult in rural areas.	Comments noted. The manufacturer confirmed that the appropriate population for this appraisal is post menopausal women.
	Breakthrough Breast Cancer and Breast Cancer Care	The scope does not appear to promote discrimination.	Comments noted. No changes required.
Other considerations	South Staffordshire PCT	Consideration may be given to the small subgroup of patients that may be willingly or unwillingly non com-pliant with oral alternatives.	It was considered that because compliance cannot be identified a priori then it would not be an appropriate subgroup for the appraisal.
	Breakthrough Breast Cancer and Breast Cancer Care	Practical considerations around the delivery of treatment should also be taken into account when appraising this treatment. As fulvestrant requires a once monthly injection, patients may not have to travel as frequently to hospital which can be very important to patients in terms of both quality of life and their financial costs. In addition, this may lead to improved compliance with the treatment as patients will not have to remember to take daily oral tablets.	Comments noted. The economic analysis will consider factors around administration where these impact on costs or on a person's health related quality of life. The Committee will also consider the wider benefits of treatment in their considerations. No changes to the scope required.
Questions for consultation	Breakthrough Breast Cancer and Breast Cancer Care	Responses to the other questions for consultations are covered in the draft scope comments.	Noted.

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Additional comments on the draft scope.	Breakthrough Breast Cancer and Breast Cancer Care	Fulvestrant has a novel mode of action in that after it binds to and blocks the oestrogen receptors preventing oestrogen from binding to cancer cells, it causes the receptors to change shape leading to the downregualtion in the number of oestrogen receptors.	Comment noted. The appraisal will consider the additional clinical benefits of the technology above those seen with current standard care. No changes to the scope required.

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

NHS Quality Improvement Scotland
Royal College of Nursing
Department of Health
Macmillan Cancer Support
Welsh Assembly Government
NPHS for Wales