National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Eribulin for the treatment of locally advanced or metastatic breast cancer

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Breast Cancer Care and Breast Cancer Campaign	Yes, the disease trajectory of locally advanced and metastatic breast cancer can mean patients require multiple lines of treatment to prolong life and control symptoms. Eribulin appears to offer another treatment option.	Comment noted. This topic has been referred to NICE as an STA.
	Breakthrough Breast Cancer	Patients with advanced/metastatic breast cancer have limited treatment options. It is therefore important that effective options which could delay progression or improve survival be made available to patients as quickly as possible. There needs to be a range of treatments available as not all existing options will be appropriate for every individual. The appraisal of new drugs for the treatment of advanced/metastatic breast cancer is essential as many existing chemotherapy drugs and the targeted drug Herceptin, are now routinely used in the primary setting. As a result of this use in earlier stages, there will increasingly be treatment resistance issues for patients who later develop metastatic breast cancer.	Comment noted. This topic has been referred to NICE as an STA.
	CSAS	Topic seems appropriate.	Comment noted. This topic has been referred to NICE as an STA.

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	Eisai	Despite recent advances with targeted therapies, there is a significant unmet need with respect to chemotherapies proven to extend survival for patients suffering from late stage breast cancer. To date, no treatment, either targeted or chemotherapy, has demonstrated an improvement in overall survival in such a heavily pre-treated population and thus an evaluation of such a technology would be appropriate. NICE clinical guideline 81 recommends further research to optimise chemotherapy sequencing in advanced breast cancer. The Eribulin study specifically addresses this recommendation and has a primary endpoint of overall survival.	Comment noted. This topic has been referred to NICE as an STA.
	NHS Camden	Topic seems appropriate.	Comment noted. This topic has been referred to NICE as an STA.
	Roche	This is an appropriate topic	Comment noted. This topic has been referred to NICE as an STA.
	Royal College of Pathologists	It is appropriate to refer this topic to NICE for approval.	Comment noted. This topic has been referred to NICE as an STA.
Wording	Breast Cancer Care and Breast Cancer Campaign	Yes	Comment noted. No action required.
	Breakthrough Breast Cancer	The wording appears to be appropriate for this piece of work.	Comment noted. No action required.
	CSAS	Wording appears appropriate.	Comment noted. No action required.
	Eisai	The wording accurately reflects the issues that should be considered.	Comment noted. No action required.

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	NHS Camden	Wording appears appropriate.	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Timing Issues	Breakthrough Breast Cancer	It is appropriate to be prepared to review this drug technology. Understandably patients want access to treatments that will give them a chance of both an increased length of survival and improved quality of life to spend more time with their families and friends. Eribulin is important in this regard as phase III trials (Twelves et al., 2010) have shown positive results in terms of manageable toxicity profile and prolonged survival. Further phase III results (E7389 versus physician´s choice) will be available from September 2011.	Comment noted. This topic has been referred to NICE as an STA and will be scheduled into the work programme to provide timely guidance to the NHS.
	CSAS	[redacted]	Comment noted. No action required.
	NHS Camden	[redacted]	Comment noted. No action required.
	Eisai	The pivotal data for eribulin will be presented at a Global oncology meeting in the US on June 8th. Given the lack of proven therapies in this space and the implications of the data that will be presented, Eisai has prioritised the regulatory submissions of the compound. [redacted] It would be in the best interests of patients and prescribers alike to have access to eribulin via the NHS at the time of the regulatory approval.	Comments noted. This topic has been referred to NICE as an STA and will be scheduled into the work programme to provide timely guidance to the NHS.
	Royal College of Pathologists	No level of urgency is indicated. The suggested timing is appropriate.	Comment noted. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft remit		None received	

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Breakthrough Breast Cancer	The background information is largely accurate however, there are some points that should be amended. Cancer Research UK has published updated breast cancer statistics on their website which should be quoted. The statistics relating to incidence should read 'Over 40,000 women and almost 300 men were newly diagnosed with breast cancer in England and Wales during 2007'. Furthermore, mortality rates should be changed to reflect 2008 figures - the statistic of over 12,000 breast cancer deaths is correct however, this accounts for 0.2 deaths per 100,000 men, not 0.3 deaths. Data on metastatic breast cancer is not currently collected in the UK so we are unaware if your reported figures are correct. This may cause some issues around costing.	Comment noted. The background section of the scope has been amended accordingly.
	CSAS	Figures appear broadly accurate. Cancer Research UK statistics report that almost 45,700 women and 227 men were diagnosed with breast cancer in the UK in 2007, with over 12,000 deaths from breast cancer in 2008 (age standardised rate 26.2 per 100,000 women and 0.2 per 100,000 men).	Comment noted. The background section of the scope has been amended accordingly.
	CSAS	The current background information seems most relevant to metastatic breast cancer (NICE CG81) rather than locally advanced breast cancer. Further information could be added about the treatment of locally advanced breast cancer.	Comments noted. At the scoping workshop it was noted that at the point in the treatment pathway where eribulin is proposed women with locally advanced and metastatic disease would be treated in a similar way. No changes to the scope required.
	Eisai	The information presented is accurate but we would suggest the inclusion of some specific additional information. Over recent years breast cancer has become more of a chronic disease in terms of how it is treated. It is not uncommon today for a woman to live with breast cancer for many years. New technologies have improved the ability to delay disease progression. However, therapies proven to extend overall survival are still critically important and a gap exists in this area.	Comments noted. The scope document provides only a brief summary of the background. This level of detail is not required in the scope. No changes made.

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	NHS Camden	Figures appear broadly accurate. Cancer Research UK statistics report that almost 45,700 women and 227 men were diagnosed with breast cancer in the UK in 2007, with over 12,000 deaths from breast cancer in 2008 (age standardised rate 26.2 per 100,000 women and 0.2 per 100,000 men). The current background information seems most relevant to metastatic breast cancer (NICE CG81) rather than locally advanced breast cancer. Further information could be added about the treatment of locally advanced breast cancer.	Comments noted. The background section of the scope has been amended accordingly. Comments noted. At the scoping workshop it was noted that at the point in the treatment pathway where eribulin is proposed people with locally advanced and metastatic disease would be treated in a similar way. No changes to the scope required.
	Roche	For completeness, capecitabine in combination with docetaxel should be listed alongside gemcitabine in combination with paclitaxel for the treatment of metastatic breast cancer.	The scope quotes NICE technology appraisal TA116 as background information, which recommends gemcitabine in combination with paclitaxel for the treatment of metastatic breast cancer. Through the scoping process, capecitabine, gemcitabine and vinorelbine were identified as the most suitable comparators. It was noted that treatment with taxanes would be more relevant at an earlier stage in the treatment pathway.
	Royal College of Pathologists	The statement that 16-20% of women presenting with breast cancer have advanced disease with distant metasteses seems to be rather high.	The background section has been amended to reflect updated information from the NICE clinical guideline for advanced breast cancer.

Section	Consultees	Comments	Action
The technology/ intervention	Breast Cancer Care and Breast Cancer Campaign	Yes	Comment noted. No action required.
	Breakthrough Breast Cancer	The technology description is accurate however, it may be worth noting that following prolonged mitotic bloackage eribulin exerts it's anti-cancer effects by triggering cancer cells apoptosis.	Comments noted. The scope document provides only a brief description of the technology. This level of detail is not required in the scope. No changes made.
	CSAS	The description of the technology appears accurate.	Comment noted. No action required.
	Eisai	Overall the description is correct but we would suggest that the fact that eribulin is a 'non-taxane' inhibitor of microtubules is specified. This is because our research has shown that the taxanes are a class of drug that are synonymous with microtubules. In light of this it is important to stress that eribulin is a new class of agent that acts on the microtubules in a different way to the conventional taxanes and other available therapies.	Comments noted. The scope document provides only a brief description of the technology. This level of detail is not required in the scope. No changes made.
	NHS Camden	The description of the technology appears accurate.	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Population	Breast Cancer Care and Breast Cancer Campaign	Question: is it appropriate for Eribulin to be given after an anthracycline but without prior treatment with a taxane due to intolerance or contraindication? Could eribulin be given when an anthracycline and/or taxane would be considered inappropriate due to intolerance or contraindication?	It was recommended at the scoping workshop that it would not be appropriate to amend the population to include people who had not received prior anthracycline and / or a taxane because eribulin is being studied in clinical trials in people who have received anthracyline and taxane treatment.

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	Breakthrough Breast Cancer	The population appears to be accurate.	Comment noted. No further action required.
	CSAS	Consider whether separate technology appraisals for locally advanced breast cancer and for metastatic breast cancer may be appropriate, particularly if treatments differ.	During the scoping workshop the clinical consultees explained that although locally advanced and metastatic disease had different characteristics, the clinical management of both would be similar at this point in the care pathway. Therefore it was recommended that the population should not be split according to the stage of disease.
	Eisai	The description is accurate and based upon the study population. One practical consideration, which we have encountered in our studies, is the value of eribulin for patients who may not be suitable for anthracyclines or taxanes. This may be due to prior exposure to these treatments, for example in the adjuvant / early breast cancer setting. The NICE approval of docetaxel in the adjuvant setting has had an impact on the subsequent use of docetaxel in the metastatic setting. This is the environment within which eribulin was studied and thus it is important that a 'real-world' population is described in this section.	NICE will only issue guidance in accordance with the marketing authorisation.

Section	Consultees	Comments	Action
	NHS Camden	Consider whether separate technology appraisals for locally advanced breast cancer and for metastatic breast cancer may be appropriate, particularly if treatments differ.	During the scoping workshop the clinical consultees explained that although locally advanced and metastatic disease had different characteristics, the clinical management of both would be similar at this point in the care pathway. Therefore it was recommended that the population should not be split according to stage of disease.
	Roche	The population is described as patients with locally advanced or metastatic breast cancer, however it also requires that patients have received at least two prior chemotherapy regimens. By this 3rd line setting, it is considered highly unlikely to have only "locally advanced disease". Does locally advanced disease correpond with the existing clinical data in this setting?	During the scoping workshop the manufacturer confirmed that the pivotal trial on which the marketing authorisation will be based is in people with locally advanced or metastatic disease. It was recommended that the population should not exclude people with locally advanced breast cancer.
	Royal College of Pathologists	HER2 positive disease should probably be identified as they will be amenable to anti-HER2 therapy in this setting. Such therapies will not be appropriate for HER2 negative disease.	The manufacturer confirmed at the scoping workshop that eribulin had been developed as a treatment for both HER2 positive and HER2 negative locally advanced or metastatic breast cancer. Therefore it was agreed that population should not specify that it would only include people with HER2 positive breast cancer.

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Comparators	Breast Cancer Care and Breast Cancer Campaign	Vinorelbine and capecitabine are appropriate comparators for Eribulin and are routinely used as monotherapies for people with metastatic breast cancer.	Comment noted. No further action required. These comparators were included in the draft scope.
	Breakthrough Breast Cancer	Gemcitabine in combination with paclitaxel may also be used to treat metastatic breast cancer within its licensed indication. It is recommended as an option for the treatment of metastatic breast cancer when docetaxel monotherapy or docetaxel combined with capecitabine are also considered appropriate (CG81).	It was agreed at the scoping workshop that gemcitabine monotherapy should be included as a comparator in the draft scope. It was considered that appropriate comparators for eribulin would be other monotherapies, because clinicians would use double therapies in preference to monotherapies where these were still available treatment options.
	CSAS	Comparators are appropriate for metastatic breast cancer, they may not be appropriate for locally advanced disease. Comparators appropriate for use in locally advanced disease should be considered.	It was agreed at the scoping workshop that at this point in the care pathway people with locally advanced disease would be treated with chemotherapy in same way as those with metastatic disease.

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	Eisai	Whilst the interventions mentioned could conceivably be used in this setting, it is important to consider the lack of comparability of the datasets. Eribulin will be the only product with a prospectively designed phase III study in over 700 patients with metastatic breast cancer. Eribulin is the only single agent to demonstrate an improvement in overall survival in a clinical study in this patient population. There is currently no single standard of care for this population. In light of this, it was recommended by physicians treating these patients that the control arm of any study in this setting should allow physician choice (TPC). This decision was also endorsed by regulatory authorities. It is important that all primary analysis is based upon the comparison to TPC rather than a specific comparator. Therefore, it would be inappropriate to focus on comparisons to specific agents given that the study was not designed to evaluate this. From a regulatory perspective the labels for capecitabine and vinorelbine would suggest that these are appropriate comparators. Best supportive care may be an appropriate consideration. Additional relevant treatments used in this setting are the taxanes, including abraxane. The only other treatments used in this setting are hormonal therapies. However, in our trial we have seen less than 5% of patients treated with hormones.	At the scoping workshop it was recommended that the appropriate comparators were other monotherapy chemotherapy treatments including capecitabine, vinorelbine and gemcitabine monotherapies.
	NHS Camden	Comparators are appropriate for metastatic breast cancer, they may not be appropriate for locally advanced disease. Comparators appropriate for use in locally advanced disease should be considered.	It was agreed at the scoping workshop that people with locally advanced disease would be treated with chemotherapy in same way as those with metastatic disease.

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	Roche	When considering the eribulin evidence base from the international (mainly U.S.) clinical trial which uses treatment of physician's choice as the comparator, it may be challenging to adjust for potential selection bias which may occur when considering patients who received therapy relevant specifically to the UK setting (i.e. vinorelbine or capecitabine monotherapy).	Comment noted. No amendments to the scope required.
	Royal College of Pathologists	Anti-HER2 therapy should be included where appropriate. Best supportive care with endocrine therapy as appropriate is "best alternative care".	It was recommended at the scoping workshop that the comparator best supportive care should be removed from the scope because the profile of eribulin meant that it was most appropriately considered in comparison with other active therapies.
Outcomes	Breast Cancer Care and Breast Cancer Campaign	Yes	Comment noted. No action required.
	Breakthrough Breast Cancer	The outcome measures listed are appropriate. It should be noted that for patients with metastatic breast cancer health related quality of life is of high importance.	Comment noted. No action required.
	CSAS	The outcomes appear appropriate. Duration of response could be added as an outcome.	It was agreed at the scoping workshop that the outcome measure ‘response rate’ could also include the duration of response.
	Eisai	These outcomes are appropriate and clearly overall survival would be the most important. The measurement of quality of life is important but it is important to recognise that in such a heavily pre-treated population, there is significant scope for bias in the reporting of QoL. It is also very difficult to capture this information from patients in this setting.	Comment noted. No action required.

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	NHS Camden	The outcomes appear appropriate. Duration of response could be added as an outcome.	It was agreed at the scoping workshop that the outcome measure 'response rate' could also include the duration of response.
	Roche	These outcomes are appropriate.	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Economic analysis	Breakthrough Breast Cancer	It is important that economic analysis is placed on patient qulaity of life since advanced/metastatic breast cancer is a life limiting condition.	Comment noted. The economic analysis will take account of gains in both survival and health related quality of life.
	Eisai	The reference case is appropriate but we would also stress the importance of the cost per life year gained measure. This is especially true where a significant improvement in survival is observed. In addition, the cost per life year is also more appropriate when robust utilities data is not available.	Comment noted. The appraisal will be completed in accordance with the published guide to the methods of technology appraisal. This includes the calculation of quality adjusted life years.
	Royal College of Pathologists	This seems appropriate.	Comment noted. No action required.
Equality and Diversity	Breakthrough Breast Cancer	it is essential that clinically effective drugs are available to all patients that may benefit from the drug, through the NHS. When this is not the case, Primary Care Trusts must make decisions regarding the prescription of drugs on an individual basis (exceptional case funding) and some patients may not, therefore, have access to the most effective treatments. With the decision to allow patients to supplement their NHS care ('top-up') further variation amongst the population could arise as for many patients this option will not be feasible.	Comment noted. No action required.

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	Royal College of Pathologists	No issues.	Comment noted. No action required.
Other considerations	Eisai	Given the lack of a standard treatment in this setting and the need to design studies that are patient and physician centric, Eisai designed the pivotal study with a control arm of treatment of physician choice. This decision ensured an 'active' and 'real-world' comparator was investigated in this study. Eisai recognises the methodological challenges such an approach may have but we would like the institute to consider the rationale behind the decision and bear this in mind when evaluating the alternative methdologies that may be proposed by both Eisai and the HTA groups. Eisai believes that the study design directly addresses challenges that have been presented to the industry from regulators and payers alike. That is the challenge of designing meaningful studies that address current treatment standards and provide patients with the best possible opportunities for an improved outcome.	Comment noted. The scope of the appraisal specifies the individual therapies that may be displaced by the use of eribulin. The appraisal will be completed in accordance with the published guide to the methods of technology appraisal.
	Royal College of Pathologists	The oestrogen receptor and HER2 status of all patients' tumours should be known.	Comment noted. No action required.
Questions for consultation	Breast Cancer Care and Breast Cancer Campaign	Eribulin potentially offers another line of chemotherapy treatment. ***References included but not reproduced here***	Comment noted. No action required.
	Breakthrough Breast Cancer	Following phase III studies it has been shown that patients receiving eribulin demonstrated significant improvements in overall survival compared to patients receiving other treatments. Eribulin can also be used by patients whose disease is resistant to other tubulin targeting agents. Indeed, it has also been shown to have efficacy in women with heavily pretreated and taxane-resistant metastatic breast cancer. Additionally, the side effects of eribulin seem to have a manageable profile and consist mainly of neutropenia, fatigue and a low incidence of peripheral neuropathy. ***References included but not reproduced here***	Comment noted. No amendments to the scope required.

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	Eisai	The primary consideration has to be the impact of the technology on overall survival. In association with this consideration of the impact on the patients well being in terms of side effect profile is also very important. In addition, the committee should also consider other attributes of the technology that could have a broader impact beyond the patient, i.e. upon the service delivery. Eribulin has a major advantage as it can be easily prepared and can be administered by a bolus injection over 2 to 5 minutes , thus saving the patient inconvenience and the support NHS costs associated with longer infusions. The product does not require use of premedications to prevent hypersensitvity reactions such as steroids. These attributes do need to be included in the consideration.	Comment noted. The administration of eribulin was discussed at the scoping workshop. It was noted that capecitabine was an oral therapy and that vinorelbine was available in an oral formulation while gemcitabine was an infusion therapy. The economic model will be expected to account for any administration and premedication costs.
	NHS Camden	With regards to whether the population should include people who have not received previous anthracycline and / or taxane therapy due to intolerance or contraindication, such individuals appear to have been included in at least one of the eribulin trials, so they could be included here. These individuals could be considered separately in the appraisal if possible. If two separate appraisals are not to be carried out for locally advanced and metastatic breast cancer, these populations could be considered separately within the existing appraisal.	It was highlighted during the scoping workshop that eribulin is being studied in people with locally advanced or metastatic breast cancer, the majority of whom have received both an anthracycline and a taxane. NICE will issue guidance in accordance with the marketing authorisation.
	Royal College of Pathologists	The suggested outcome measures appear appropriate for the assessment.	Comment noted. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft scope.	Breakthrough Breast Cancer	Although we recognise responsive care varies throughout the UK it is important that it is provided to a patient from the time they are diagnosed with metastatic breast cancer and continues for as long as required. This should be co-ordinated by an accessible key worker, ideally a breast care nurse who has specialist knowledge of metastatic breast cancer. This is to try and help improve the patient's symptoms, provide access to and awareness of support services and to enable patients, their carers and families to access high quality information, care and treatment. Open communication between healthcare professionals and patients is crucial as is the recognition for the patient's preferences of care. Breakthrough would like to see more treatment options available for women with metastatic breast cancer. Therefore, we would welcome sound evidence which shows eribulin could be safe and effective as a first line treatment. Treatment options for patients with triple negative breast cancer are limited. Therefore, it would be useful to consider eribulin as a treatment for triple negative breast cancer.	Comment noted. Triple negative disease was discussed at the scoping workshop but it was decided not to list it as a specific subgroup in the scope as sufficient evidence was not anticipated. In general, evidence permitting, NICE is interested in looking at relevant subgroup analyses that are particularly clinically and cost effective in accordance with the Methods Guide.
	CSAS	With regards to whether the population should include people who have not received previous anthracycline and / or taxane therapy due to intolerance or contraindication, such individuals appear to have been included in at least one of the eribulin trials, so they could be included here. These individuals could be considered separately in the appraisal if possible. If two separate appraisals are not to be carried out for locally advanced and metastatic breast cancer, these populations could be considered separately within the existing appraisal.	It was highlighted during the scoping workshop that eribulin is being studied in people with locally advanced or metastatic breast cancer, the majority of whom had received both an anthracycline and a taxane. NICE will issue guidance in accordance with the marketing authorisation.
	Eisai	We would ask the Institute to consider whether the End of Life criteria for appraisal would apply to this technology.	Comment noted. No amendments to the scope required.

Section	Consultees	Comments	Action
	NHS Camden	How will best alternative / supportive care be defined? Are there any subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately, for example receptor status, such as HER2? Eribulin is not yet licensed in the UK or US for use for the treatment of locally advanced and metastatic breast cancer, or for other indications. UK costs of eribulin are therefore not known. [redacted]	The manufacturer explained during the scoping workshop that 96% of the trial population on which the marketing authorisation will be based received an active chemotherapy treatment. The clinical consultees at the scoping workshop also confirmed that people eligible for treatment with eribulin for locally advanced or metastatic disease would not receive best supportive care until later in the treatment pathway. It was recommended at the scoping workshop that the comparator best supportive care should be removed from the scope.

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

Royal College of Nursing
Department of Health
Marie Curie Cancer Care
RICE - Research Institute for the Care of Older People
UKONS
Welsh Assembly Government
Medicines and Healthcare products Regulatory Agency