National Institute for Health and Care Excellence

SingleTechnology Appraisal (STA)

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

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

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	Eisai	Yes.	Comment noted
	Breast Cancer Now	We are unsure why NICE is scoping this medicine at this time. NICE have previously carried out an appraisal on eribulin in this setting and issued negative guidance. This product is currently available through the Cancer Drugs Fund. We are aware the current proposals mean that NICE will be reassessing all of the drugs currently funded through the Cancer Drugs Fund. However, it does not appear that this scoping exercise is part of that reappraisal process. We have sought clarification from NICE about why this appraisal is being carried out but have not received a satisfactory response. We would therefore appreciate clarity on this matter	Eribulin has received an extension to the original marketing authorisation in 2014. It is now indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. This is a broader population than

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			the population that TA250 looked at, therefore the NICE Technology Appraisal Committee needs to discuss eribulin again, to be able to decide whether it is a cost-effective use of NHS resources within its current marketing authorisation.
	Pierre Fabre	None	Comment noted.
Wording	Eisai	Yes, it reflects the current EMA approved label.	Comment noted.
	Breast Cancer Now	The wording appears to be appropriate	Comment noted.
	Pierre Fabre	None	Comment noted.
Timing Issues	Eisai	It is urgent as eribulin is currently available to the NHS through the Cancer Drugs Fund (CDF) [redacted]. NICE has committed to appraising all products currently funded through the CDF during the course of 2016/17.	Comments noted..
	Breast Cancer Now	NICE have previously issued negative guidance about this treatment and this treatment is currently available through the Cancer Drugs Fund in England. There is currently uncertainty surrounding the future availability of this	Comments noted. Eribulin has received a licence extension from

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		treatment through the Cancer Drugs Fund. If this scoping exercise is intended to be part of NICE's work to bring Cancer Drugs Fund treatments into routine commissioning then we would urge NICE to proceed with this with haste to give patients clarity about the future availability of the treatment and peace of mind. This treatment has recently been approved for use in Scotland and a decision from the All Wales Medicines Strategy Group is pending. Approval of this medicine from NICE would ensure that patients in England have the same access to this treatment that their counterparts in Scotland enjoy.	the EMEA, therefore the NICE Technology Appraisal Committee will assess whether it is a cost-effective use of NHS resources within its current marketing authorisation.
	Pierre Fabre	None	Comment noted.
Additional comments on the draft remit	Eisai	No	Comment noted.
	Pierre Fabre	None	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eisai	The background information is complete and accurate	Comment noted.
	Breast Cancer Now	The background information appears to be accurate.	Comment noted.
	Pierre Fabre	None	Comment noted.

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The technology/ intervention	Eisai	Yes, the description of the technology is accurate.	Comment noted.
	Breast Cancer Now	The description of the technology appears to be accurate.	Comment noted.
	Pierre Fabre	None	Comment noted.
Population	Eisai	Yes, the population is defined appropriately. On the basis of current clinical practice and unmet clinical need, Eisai believe that there are two separate sub-groups within this population that should be considered separately, namely: 1. HER2-negative patients with locally advanced or metastatic breast cancer (LABC/MBC), whose disease has progressed after at least one prior chemotherapy regimen in the advanced setting. The subgroup of patients with HER2-positive MBC has been associated in the past with more aggressive disease and poorer patient outcomes; however with the recent development of HER2-positive targeted therapies, the prognosis of HER2-positive MBC has reversed . In a recent study, the HR-positive/HER2-negative subtype was associated with a significantly worse survival, as compared to the HR-positive/HER2-positive group (median 34.4 vs. 24.8 months) . *Figure was presented but not replicated here.* On the other side, not so many medical advancements have materialised for the HER2-negative patient population. Therefore, there is still a great medical	Comment noted. The other considerations section of the scope has been updated to include 'If the evidence allows, consideration will be given to subgroups according to HER2 status, oestrogen receptor and line of treatment'. No change to the population section of the scope is needed.

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		unmet need within this specific patients' subgroup and chemotherapy treatments such as eribulin continue to play a key role. 2. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated). Eribulin has been available in England since July 2011 through NHS Cancer Drug Fund. Published data from audits undertaken at the Royal Marsden Hospital (N=108 patients), Christie Hospital NHS Foundation Trust (N=75 patients) and Imperial College Healthcare NHS Trust (N=25 patients) showed that more than 80% of patients had received capecitabine prior to being prescribed with eribulin under the CDF.	
	Breast Cancer Now	The population appears to be appropriately defined. However, it is worth noting that when the Cancer Drugs Fund panel considered this treatment, they identified that a greater overall survival benefit is seen in patients with triple negative breast cancer than some other subgroups of patients. Patients with triple negative breast cancer have a limited number of treatment options available and it is therefore worth considering this subgroup separately.	Comment noted. The other considerations section of the scope has been updated to include 'If the evidence allows, consideration will be given to subgroups according to HER2 status, oestrogen receptor and line of treatment'. No change to the population section of the scope is needed.

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	Pierre Fabre	None	Comment noted.
Comparators	Eisai	The list of comparators is correct but not exhaustive. As indicated in the scope, NICE clinical guidelines clearly define vinorelbine monotherapy and capecitabine monotherapy as potential treatment options for patients with advanced breast cancer who are not suitable for anthracyclines because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting. However, the choice of treatment in real-life clinical practice depends on many more factors other than prior chemotherapy exposure and response, including HER2-status, tolerability, patient preference, availability of drugs, and the patient's quality of life. Therefore, gemcitabine (as defined in the background information of the scope), anthracyclines and taxanes should be included in the list of comparators in order to cover not only patients treated following one prior chemotherapy but also in later lines of therapy, as observed in the composition of treatment of the Treatment of Physician's Choice arm of the phase III EMBRACE clinical study for eribulin.	Comment noted. The current list of comparators is in line with current NICE guidance for locally advanced or metastatic breast cancer after at least one chemotherapy regimen. The marketing authorisation for eribulin also specifies that prior therapy should have included an anthracycline and a taxane. Therefore no change to the scope is needed.
	Breast Cancer Now	The comparators appear appropriate.	Comment noted.
	Pierre Fabre	As the appraisal is assessing health economics of drugs it is important to include the different formulations of each drug. Vinorelbine has both IV and Oral formulations. Acquisition and administration costs vary according to the formulation used.	All relevant costs will be included according to how the drugs are used in clinical practice.

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Outcomes	Eisai	Yes, the outcome measures listed are appropriate.	Comment noted
	Breast Cancer Now	These outcome measures will capture the most important benefits and harms of the technology. However, it is important that the emphasis is placed on patient quality of life since metastatic breast cancer is a life limiting condition. For patients with metastatic breast cancer the important of quality of life should not be underestimated. Access to the 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 friends and families is very important.	Comment noted. Health-related quality of life is included as an outcome. No change to the scope is needed.
	Pierre Fabre	None	Comment noted
Economic analysis	Eisai	No comments.	Comment noted
	Breast Cancer Now	No comment	Comment noted
	Pierre Fabre	The new and comparator technologies and their formulations (e.g. Oral) need to be compared on the basis of NHS service impact including cost and where administered. The Five year forward plan from NHS England supports new models of care, in particular, Patients receiving their care at home or away from the hospital environment. IV administration has an impact on outpatient capacity and therefore treatment waiting times. Additional costs due to the physical impact of IV administration such as, extravasation and any subsequent treatment for this, should be considered as part of the economic impact model.	All relevant costs will be included according to how the drugs are used in clinical practice.

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Equality and Diversity	Eisai	No comments.	Comment noted.
	Breast Cancer Now	The scope does not appear to promote discrimination.	Comment noted.
	Pierre Fabre	None	Comment noted.
Other considerations	Eisai	No comments.	Comment noted.
	Breast Cancer Now	-	
	Pierre Fabre	If not above then this is where the technologies impact on service provision and costs may be included. There is also a considerable impact on a patient's quality of life when receiving medication at home vs in hospital. The NHS England Five Year Forward Plan outlined the importance of making improvements in patient care by delivering treatments at home (oral chemotherapy). The NHS Mandate also stresses the importance of helping patients to take control of their end of life plan and control where they receive their treatment.	All relevant costs will be included according to how the drugs are used in clinical practice.
Innovation	Eisai	Eisai do consider eribulin to be innovative as it is a non-taxane inhibitor of microtubule dynamics, with a unique mechanism of action and it is the first and only single chemotherapy agent to demonstrate with low uncertainty, a statistically significant overall survival benefit in patients with late stage LABC/MBC versus other commonly used monotherapy agents. Eribulin has a unique Mechanism of Action that allows it to function by binding to exposed beta-tubulin subunits on the growing plus (+) ends of microtubules, thereby preventing their further polymerization and inducing the	Comment noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No changes to the scope required.

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		generation of non-productive tubulin aggregates. In turn, this prevents formation of functional mitotic spindles, leading to irreversible mitotic blocks, G2/M cell cycle arrest, and ultimately, cell death by apoptosis. Preclinical studies in human breast cancer models have shown that eribulin also exerts profound effects on tumor biology and microenvironment that are unrelated to its classical antimitotic effects. These effects include (i) tumor vascular remodeling, resulting in enhanced tumor core perfusion and elimination of hypoxia, (ii) reversal of epithelial-mesenchymal transition (EMT) resulting in less aggressive tumor phenotypes, and (iii) profound decreases in tumor cell migration and invasion capacity, parameters that directly affect tumor metastatic potential. In the patient population described in this scope, none of the current NICE-approved treatments have demonstrated a survival benefit over any other.	
	Breast Cancer Now	As stated earlier, the benefits of this treatment are seen particularly in patients with triple negative breast cancer. This is a patient group with very few treatment options available to them. Therefore, while the survival benefit provided by this treatment may appear modest, this additional time in invaluable to patients who are approaching the end of their lives and have very few treatment options available to them. It is also worth noting that while other, newer treatments demonstrate a greater survival benefit, these treatments are not appropriate for patients with triple negative breast cancer.	Comment noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No changes to the scope required.
	Pierre Fabre	None	Comment noted
Questions for consultation	Eisai	No comments.	Comment noted
	Breast Cancer Now	-	

Section	Consultee/ Commentator	Comments [sic]	Action
	Pierre Fabre	None	Comment noted
Additional comments on the draft scope	Eisai	No additional comments.	Comment noted
	Breast Cancer Now	-	
	Pierre Fabre	None	Comment noted

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

None