# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using eribulin in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?



Issue date: November 2017

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using eribulin in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

**The key dates for this appraisal are:**

Closing date for comments: 18 December 2017

Second appraisal committee meeting: 16 January 2018

Details of membership of the appraisal committee are given in section 5.

# 1 Recommendations

1.1 Eribulin is not recommended for treating locally advanced or metastatic breast cancer in adults who have had only 1 chemotherapy regimen[1].

1.2 This guidance is not intended to affect treatment with eribulin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

### Why the committee made these recommendations

People with advanced breast cancer who have had 1 chemotherapy regimen are usually then offered an anthracycline, a taxane or capecitabine, depending on what they have had already. The clinical trial results for eribulin show that it increases overall survival by an average of 4.6 months compared with capecitabine, but doesn't increase progression-free survival. So, it's not clear whether the increase in overall survival is because of eribulin alone or because of effective treatments given after eribulin. However, there are no clinical trials assessing the effectiveness of eribulin at different stages of the treatment pathway.

Eribulin meets NICE's criteria to be considered a life-extending treatment at the end of life. The estimates of cost effectiveness for eribulin range from £36,244 to £82,743 per quality-adjusted life year. Because of the uncertainty in the clinical evidence, the most plausible cost-effectiveness estimates are likely to be at the top of this range, which is above what NICE normally considers to be acceptable for end-of-life treatments. Therefore, eribulin cannot be recommended as a cost-effective treatment

[1] A positive recommendation on eribulin for treating locally advanced or metastatic breast cancer in adults who have had 2 or more chemotherapy regimens is given in a separate NICE technology appraisal guidance.

for locally advanced or metastatic breast cancer in adults who have had only 1 chemotherapy regimen.

# 2 The technology

| **Eribulin (Halaven, Eisai)** | |
|---|---|
| **Marketing authorisation** | Eribulin is 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… Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments'. |
| **Recommended dose and schedule** | 1.23 mg/m$^2$ is administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle. |
| **Price** | £361.00 per 0.88 mg/2ml solution for injection vial and £541.50 per 1.32 mg/3ml solution for injection vial (excluding VAT; British National Formulary [BNF] online, accessed October 2017).<br><br>The company has agreed a patient access scheme with the Department of Health. If eribulin had been recommended, this scheme would provide a simple discount to the list price of eribulin with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS. |

# 3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Eisai and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

## *Symptoms and management of advanced breast cancer*

### Patients and their families value additional treatment options

3.1 The committee heard from a patient expert that locally advanced or metastatic breast cancer is a debilitating condition that can affect people of all ages, and leads to premature death. It also heard that the symptoms

of advanced breast cancer can differ substantially, depending on the type of disease and the site of metastases. The patient expert emphasised that living with advanced breast cancer is very difficult for patients and their families. The life expectancy of people for whom eribulin is licensed is short, and quality of life is very important. The committee heard that having more treatment options available would be very important for patients, giving hope to them and their families. It recognised that having additional treatment options for advanced breast cancer would be valued by patients and their families.

**Capecitabine is the relevant comparator for most people at this stage in the treatment pathway**

3.2 The clinical expert explained that most patients with locally advanced or metastatic breast cancer have had either an anthracycline or a taxane for early breast cancer, and have had whichever drug they did not have for early disease as the first chemotherapy regimen for advanced or metastatic disease. The committee understood that some patients with more aggressive disease are likely to have had an anthracycline and a taxane at an earlier stage, so would have capecitabine as the first treatment in the advanced or metastatic setting. The committee noted that the comparator in the company's submission was capecitabine, which was used in the Study 301 trial, from which people who had previously had capecitabine were excluded. The committee concluded that, although treatment sequences in the adjuvant and advanced setting could vary, in clinical practice, capecitabine was the relevant comparator for most people with locally advanced or metastatic breast cancer who had had 1 chemotherapy regimen.

## *Clinical trial evidence*

### The relevant evidence is from a post-hoc subgroup, which may not be sufficiently robust for decision-making

3.3 The evidence for eribulin came from Study 301, a phase 3 randomised controlled trial comparing eribulin with capecitabine in 1,102 patients with locally advanced or metastatic breast cancer who had had up to 3 chemotherapy regimens (up to 2 for advanced disease), including an anthracycline and a taxane. The company presented results for subgroup 1, which was a post-hoc defined subgroup comprising patients with HER2-negative disease who had had 1 chemotherapy regimen (186 in the eribulin arm and 206 in the capecitabine arm). The committee was aware that eribulin's marketing authorisation includes people with HER2-positive and HER2-negative disease. However, it noted that people with HER2-positive disease would be treated with specific HER2-targeted therapies rather than being considered for eribulin at this stage of the disease, and accepted that only patients with HER2-negative disease were relevant for the current appraisal. The committee were aware that 2 predefined patient characteristics (HER2-negative disease and line of therapy) had been combined to form this new post-hoc subgroup. It was mindful that post-hoc subgroup analyses could be unreliable (for example, because of reduced statistical power), and expressed concern about whether this subgroup was sufficiently robust for decision-making.

### The trial results show improved overall survival but little, if any, progression-free survival benefit

3.4 The results from subgroup 1 of Study 301 showed a small difference in the progression-free survival that was not statistically significant (the results are currently academic in confidence and are not reported here). However, the overall survival results did show a statistically significant benefit with eribulin compared with capecitabine (the results are currently academic in confidence and are not reported here). The ERG explained that these results were consistent with results in the subgroup of patients

with HER2-negative disease who had had at least 1 (and up to 3) chemotherapy regimens, in whom there was no statistically significant difference in progression-free survival but a trend towards overall survival benefit. The committee noted that the overall survival benefit for eribulin had only reached statistical significance in the post-hoc subgroup 1. The committee concluded that there was little, if any, progression-free survival benefit for eribulin compared with capecitabine.

**The overall survival benefit in the trial may not be directly attributable to eribulin alone**

3.5 The committee considered the plausibility of the statistically significant overall survival gain in light of the minimal progression-free survival gain. It noted that this discrepancy would indicate that most, if not all, of the survival gain occurred after the disease had progressed, when the patient was no longer having eribulin but instead having a subsequent treatment. It was aware that 57.5% of patients in the eribulin arm of the trial had capecitabine after their disease had progressed, which may have contributed to the improvement in overall survival in the treatment arm, whereas only 1 patient in the capecitabine arm (0.5%) had eribulin post progression. The clinical expert explained that eribulin is well tolerated but has a different side-effect profile to capecitabine. In clinical practice patients whose disease responds to eribulin tend to have subsequent treatments to which the disease also responds. The committee therefore concluded that eribulin is well tolerated but the survival benefit in the trial may not be directly attributable to eribulin alone.

**The available data do not address the most clinically relevant question**

3.6 The clinical expert hypothesised that, although eribulin did not delay disease progression (and therefore transition to subsequent treatment), it might enhance the effect of subsequent treatment with capecitabine. However, the committee noted that a direct comparison of the clinical effectiveness of eribulin then capecitabine with that of capecitabine then eribulin would be needed to substantiate this hypothesis. It considered

that the most clinically relevant question was therefore whether having eribulin before capecitabine was more clinically and cost effective than the current practice of having eribulin after capecitabine. The committee concluded that the available data did not address this question.

## *The economic model*

### The company's economic model is suitable for decision-making

3.7 The company presented a partitioned survival economic model comprising 3 states: stable disease, progressed disease and death. The committee accepted that the structure of the economic model was appropriate. The ERG made several amendments to the model. These comprised corrections for logic errors and errors relating to discounting and unit costs of eribulin and other chemotherapies, as well as assumptions that included alternative progression-free survival benefit, post-progression utility and subsequent treatment costs. The committee's considerations focussed on the 3 model inputs that were key drivers of the cost-effectiveness results. It concluded that the company's economic model, with the ERG's error corrections, was suitable for its decision-making.

## *Clinical parameters*

### Modelling no progression-free survival benefit increases the ICER substantially

3.8 The committee were aware that the trial results did not show a statistically significant progression-free survival benefit for eribulin compared with capecitabine (see section 3.4). Using the Kaplan–Meier data from the trial, the company modelled a small progression-free benefit of 0.57 months in their base case (incremental cost-effectiveness ratio [ICER] of £36,244 per quality-adjusted life year [QALY] gained). The ERG, when re-examining the data, found a close correspondence between the timing of disease progression in each arm of the trial (which was statistically

confirmed when tested), and so assumed no progression-free survival benefit for eribulin in its base case (ICER of £82,743 per QALY gained). The committee noted that the ERG's alternative approach meant that all the overall survival benefit occurred in the post-progression phase, and had a large impact on the ICER, increasing it by about £15,000 per QALY gained. The committee recalled its conclusion that eribulin had shown little, if any, progression-free survival benefit compared with capecitabine (see section 3.4) and noted that this had a substantial impact on the cost effectiveness estimate.

## *Utility values*

### The post-progression utility value is likely to be between the company's and ERG's estimates

3.9 The company estimated utility values by applying a mapping algorithm to the health-related quality-of-life data from the trial. The committee noted that the algorithm, published by Crott and Briggs (2010), had been developed using data from people with locally advanced but not metastatic breast cancer, and who had good baseline health status. It noted that this resulted in only a small decrease in the utility between the progression-free and post-progression health states in the company's model (about 3%), which the ERG considered to be implausible. The ERG instead used utility values from a study by Lloyd et al. (2006) which the committee noted were derived from general population estimates using Standard Gamble rather than the time trade-off method preferred in the NICE guide to the methods of technology appraisal (section 5.3), but have been used in other NICE appraisals. This resulted in a decline in utility of about 20% between the pre- and post-progression states, which increased the ICER by about £11,000 per QALY gained. The committee was mindful of its conclusion in NICE's technology appraisal guidance on eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens that accepted the use of the Lloyd study but concluded that while some decline would be expected, an immediate

decrease of 20% in health-related quality of life on progression may be an overestimate. It concluded that the most plausible utility value was likely to be somewhere between the company's and ERG's estimates.

## *Costs*

### The costs of subsequent treatments are likely to be closer to the ERG's estimates than the company's

3.10 The company applied an 8-month cap on the total treatments a patient could have in the model, meaning that all treatment costs ended after 8 months. The ERG considered that this underestimated the costs of subsequent treatments. Instead, it assumed that, after progression, 60% of patients would go on to have subsequent therapy until death, based on data on the proportion of breast cancer patients progressing from first- to fifth-line therapy (Kantar Health, 2014). The committee noted that the ERG's assumption increased the ICER by about £11,000 per QALY gained. The clinical expert commented that treatment duration varied between individuals, but that it was realistic to assume that most patients would still be having active treatment more than 8 months after starting eribulin. The exception would be a small proportion of patients with aggressive disease such as those whose disease was 'triple negative' (HER2 and hormone-receptor negative). The committee agreed that an 8-month cap on total treatment was therefore not clinically plausible. Taking into account the information from the clinical expert, the committee concluded that the costs of subsequent treatments were underestimated by the company and that the actual costs were likely to be closer to those assumed by the ERG.

## *Cost-effectiveness estimates*

### The most plausible ICER for eribulin is higher than the range normally considered cost effective

3.11 The committee considered the cost-effectiveness results for eribulin compared with capecitabine, noting that the company's base-case ICER, including the confidential patient access scheme discount, was £36,244 per QALY gained. It recognised that there were 3 main sources of uncertainty in the model inputs which had a large impact on the ICER: progression-free survival benefit; post-progression utility; and subsequent treatment costs. The ERG's base-case ICER, which included the confidential patient access scheme discount, corrections for errors within the company's model and alternative assumptions around the 3 key model inputs, was £82,743 per QALY gained. The committee acknowledged the uncertainty in the progression-free survival benefit (see section 3.8) and that the post-progression utility value could lie between the company's and the ERG's estimates (see section 3.9). However, it considered the ERG's assumptions about subsequent treatment costs to be more plausible than the company's (see section 3.10). It therefore concluded that the most plausible ICER was likely to be closer to the ERG's estimate than the company's base-case estimate.

## *End of life*

### Eribulin met the end-of-life criteria

3.12 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. The committee noted the company's model predicted a mean overall survival with capecitabine of about 17 months. The trial showed a mean overall survival benefit of more than 3 months for eribulin compared with capecitabine. The committee concluded that eribulin met the end-of-life criteria.

## *Other factors*

**The committee did not identify any other factors that would affect its recommendations**

3.13 No equality issues were identified. The committee heard from the company that it considered eribulin to be innovative because of its mechanism of action and convenient administration method. However, the committee concluded that it could not identify any specific health-related benefit that had not already been captured in the QALY calculation.

## *Conclusion*

**Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen is not a cost-effective strategy**

3.14 The committee considered that there was little, if any, increase in progression-free survival with eribulin compared with capecitabine when given after 1 chemotherapy treatment (see section 3.4). It also considered that the overall survival benefit shown in the trial results could not be directly attributable to eribulin alone (see section 3.5). It was concerned about the reliability of results from a post-hoc subgroup analysis (see section 3.3), and that the key uncertainties in the economic model had a large impact on the ICERs (see section 3.11). It noted that, even when using the most favourable assumptions for progression-free survival benefit and post-progression utility, assuming a longer duration of subsequent treatments would increase the ICER to above the range normally considered cost effective when the end-of-life criteria are applied. The committee was mindful that having eribulin after capecitabine was recommended in NICE's technology appraisal guidance on eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens, but having the treatments in the reverse order had not been proven to be cost effective. It concluded that the true ICER for eribulin followed by capecitabine was likely to be nearer the ERG's base case of £82,743 than the company's base case of £36,244 per

QALY gained (see section 3.11). It therefore was unable to recommend eribulin as a cost-effective use of NHS resources.

# 4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee A
November 2017

# 5 Appraisal committee members and NICE project team

## *Appraisal committee members*

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## *NICE project team*

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Anna Brett**
Technical Lead

**Eleanor Donegan**
Technical Adviser

**Thomas Feist, Marcia Miller**
Project Managers

ISBN: [to be added at publication]