NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance

Published: 28 March 2018
www.nice.org.uk/guidance/ta515

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA250.

This guidance should be read in conjunction with TA423.

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 showed that it did not increase progression-free survival, but there was an average overall survival increase of 4.6 months compared with capecitabine. Since treatment is changed when the disease progresses, and eribulin would have been stopped at that stage, it is not clear whether the increase in overall survival is because of eribulin, or related to the treatments given after eribulin. Eribulin is already recommended after 2 previous chemotherapy treatments, and there are no trials which compare its effectiveness given after 1 or 2 previous treatments, so this remains uncertain.

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 £36,200 to £82,700 per quality-adjusted life year (QALY) gained. The most plausible estimate of cost effectiveness, based on a revised company model and the committee's preferred assumptions, is £69,800 per QALY gained. This is above what NICE normally considers to be acceptable for end-of-life treatments. Therefore, eribulin cannot be recommended as a cost-effective option for locally advanced or metastatic breast cancer in adults who have had only 1 chemotherapy regimen.

[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.

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/2 ml solution for injection vial and £541.50 per 1.32 mg/3 ml solution for injection vial (excluding VAT; British national formulary [BNF] online, accessed October 2017). 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 4) 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 and/or a taxane for early breast cancer, and have usually 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. A smaller number may be offered vinorelbine. The committee noted that the comparator in the company's original submission was capecitabine, which was used in study 301, from which people who had previously had capecitabine were excluded (see section 3.3). The committee concluded that, although treatment sequences in the adjuvant and advanced setting could vary, in clinical practice, capecitabine is the relevant comparator for most people with locally advanced or metastatic breast cancer who have had 1 chemotherapy

regimen.

Clinical trial evidence

The relevant evidence is from a post-hoc subgroup

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 received 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. After receiving consultation comments from the company, the committee accepted that, despite some limitations, the subgroup data are the only appropriate evidence that is currently available to assess the effectiveness of eribulin compared with capecitabine.

The trial results show improved overall survival but no statistically significant progression-free survival benefit

3.4 The median progression-free results from subgroup 1 of study 301 showed a very small numerical difference of 6 days in the progression-free survival between eribulin (4.2 months) and capecitabine (4.0 months), but the difference was not statistically significant (hazard ratio 0.86, p=0.192). However, the overall-survival results did show a statistically significant benefit with eribulin compared with capecitabine (16.1 months and 13.5 months respectively, hazard ratio [HR] 0.77, p=0.026). 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 or overall survival benefit. The committee noted that the overall survival benefit for eribulin had only reached statistical significance in the post-hoc subgroup 1. In the appraisal consultation document the committee had queried whether there was any progression-free survival benefit for eribulin compared with capecitabine. At the second appraisal meeting, the committee further considered the difference between progression-free survival and overall survival benefit.

The overall survival benefit in study 301 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 no significant 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 would have switched to 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 second line after capecitabine, as recommended in NICE's technology

appraisal guidance on eribulin after 2 or more chemotherapy regimens. The committee concluded that the available data did not address this question.

Post-progression treatment has a substantial effect on overall survival

3.7 During consultation the company presented additional evidence on the overall survival benefit of eribulin compared with capecitabine in the intention-to-treat population of study 301 and in the HER2-negative subgroup of study 301, to support the overall survival benefit of eribulin compared with capecitabine in subgroup 1. It also presented the Kaplan–Meier curves for the effect of different post-progression treatments on overall survival (which the European Medicines Agency had requested from the company). The committee was particularly interested in the impact of post-progression treatments on overall survival. It noted that eribulin or capecitabine followed by no further treatment had the worst prognosis and resulted in survival curves for eribulin and capecitabine that were closely aligned. It also noted that there was little difference in the overall survival for patients having eribulin followed by capecitabine, compared with capecitabine followed by any active treatment (which most closely, although not specifically relates to the question of whether overall survival is better with eribulin followed by capecitabine, compared with capecitabine followed by eribulin, as is currently used in the NHS).The best overall survival gain with eribulin was for patients who went on to have an active treatment other than capecitabine. The committee noted that recommendations on subsequent treatments that should be used are outside the scope of this appraisal. The committee concluded that patients with disease that progresses on eribulin would be very likely to have capecitabine on progression, and the company's evidence suggested that this not likely to result in better overall survival than current clinical practice (that is, capecitabine followed by another active treatment). The committee was not persuaded that a clear benefit had been shown for offering eribulin second line compared with third line, as recommended in NICE's guidance on eribulin after 2 or more chemotherapy regimens.

The economic model

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

3.8 The company presented a partitioned survival economic model comparing eribulin with capecitabine in subgroup 1 (that is HER2-negative adults whose

disease has progressed after 1 chemotherapy regimen in the advanced setting). The base-case incremental cost-effectiveness ratio (ICER) for this model was £36,244 per quality-adjusted life year (QALY) gained. The ERG made several amendments to the original 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 base-case ICER, which incorporated all of the ERG's corrections and preferred assumptions, was £82,743 per QALY gained. The committee considered that the company's economic model, with the ERG's error corrections and assumptions, was most suitable for its decision-making. During consultation the company submitted a revised model with 4 changes: a new comparator (mix of capecitabine and vinorelbine), continued inclusion of a progression-free survival benefit (which had been excluded by the ERG), an updated post-progression utility value, and a different cap on treatment duration. The company's base-case ICER for the revised model, which incorporated all of the changes, was £50,808 per QALY gained. The committee considered the appropriateness of each of the updated model parameters and the subsequent impact on the ERG's amended model.

Clinical parameters

Capecitabine is the most relevant comparator for use in the economic model

3.9 The company's original model assumed that all patients in the comparator arm had capecitabine but the revised model, received during consultation, changed the comparator in the base case to an equal split of capecitabine and vinorelbine (with all of the vinorelbine administered intravenously). This assumption reduced the ERG's original ICER of £82,743 by £11,094 per QALY gained. The committee noted that the new 'blended' comparator was based on the advice of 1 expert (who attended the first meeting), but it is not consistent with the comparator in study 301. The company assumed that it had the same effectiveness as capecitabine (based on clinical expert opinion). The committee considered that the company could suggest an alternative comparator, in this case, vinorelbine, particularly if it was included in the scope of the appraisal. However, the modelling of eribulin compared with the new comparator should be supported by evidence of the effectiveness of that comparator. The company did not provide this for vinorebine. In addition, the company's blended

comparator used an equal split of capecitabine and vinorelbine, with no supporting evidence for the proportions used. The company also suggested that only intravenous, not oral, vinorelbine should be considered as a comparator, but did not provide any comparative evidence of the effectiveness of the 2 routes of administration, or clear rationale for this. The committee accepted that not all patients in the NHS would have capecitabine as second-line treatment, but it considered that an equal split of capecitabine and intravenous vinorelbine was arbitrary, and not adequately supported by evidence. It concluded that capecitabine is the most relevant comparator for the majority of patients in the NHS, and there is direct trial evidence available to inform that comparison.

Modelling no progression-free survival benefit increases the ICER substantially

3.10 The committee was 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 study 301, the company modelled a small mean progression-free benefit of 0.57 months in their original base-case model. 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 (resulting in an ICER of £82,743 per QALY gained). The committee noted the continued difference of opinion between the company's assumption of progression-free survival benefit of approximately 17 days with eribulin in its revised model, and the ERG's assumption of no progression-free survival benefit. It noted that the inclusion of this very modest, and not statistically significant progression-free survival benefit, has a substantial effect on the ICER, reducing the ERG's preferred ICER by £5,905 per QALY gained. The company representative agreed that the progression-free survival gain with eribulin was small and not statistically significant. The committee noted the ERG's exploratory analysis of a small progression-free survival gain in the first 17 months, which only reduced the ICER by £408 per QALY gained. The committee concluded that no significant progression-free survival benefit had been demonstrated in study 301 (see section 3.4). On this basis, a substantial reduction in the ICER of nearly £6,000 from incorporating a very small progression-free survival benefit, did not seem reasonable.

The post-progression utility value could be between the company's and ERG's estimates

3.11 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 original 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) have been used in other NICE appraisals. This method resulted in a decline in utility of about 20% between the pre- and post-progression states, which increased the ICER for the original model 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, which 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. The committee concluded that the most plausible utility value could be somewhere between the company's and ERG's estimates. The company updated the utility for progressive disease from 0.679 in its original model to 0.59 in the revised model. This represents the midpoint of the utility values in the company's and ERG's original models (0.679 and 0.496 respectively). This is consistent with the committee's preferred assumption for progressive disease in the appraisal consultation document. The committee noted the uncertainty about the most appropriate utility values to use in advanced breast cancer but accepted the updated utility for progressive disease in the revised company model, which reduced the ERG's preferred ICER by £12,900 per QALY gained.

Costs

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

3.12 The original company model 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 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 at its first meeting that an 8-month cap on total treatment was not clinically plausible. In its revised model the company changed the cap on the duration of treatment in both arms of the model from 8 months to 21.3 months (the average survival in the eribulin arm). This reduced the ERG's preferred ICER by £8,289 per QALY gained. The ERG noted that a substantial number of people in the eribulin arm of study 301 had more than 21 months of treatment. The committee concluded that in clinical practice patients who live longer than 21 months would still have treatment and therefore it did not accept this assumption.

Cost-effectiveness estimates

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

3.13 The committee considered the cost-effectiveness results for eribulin compared with capecitabine. The committee considered the appropriateness of all changes in the revised company model and their impact on the ICER. It considered only the updated utility value for progressive disease to be justified. It noted that the ICER for eribulin only approached a level that might be considered cost effective when all of the changes to the company's revised model were accepted and if the criteria for special consideration of life-extending treatment at the end of life were met. The committee did not consider

that the 17 day improvement in progression-free survival in the model (non-significant 6 days benefit in the trial), which resulted in a large reduction in the ICER of £6,000 per QALY, was justified. In addition, the committee did not accept the blended comparator of capecitabine and intravenous vinorelbine (section 3.9). Even if the blended comparator had been accepted, along with the updated utility for progressive disease, the ICER would have been £58,749 per QALY gained, and so the committee did not consider it further. The committee concluded that the most plausible ICER for eribulin compared with capecitabine, using the revised company model with the committee's preferred assumptions, is approximately £69,843 per QALY gained which does not represent a cost-effective use of NHS resources. It also noted that eribulin is already recommended after 2 previous chemotherapy regimens, and there remained considerable doubt about whether giving it earlier in the treatment pathway conferred a true benefit.

End of life

Eribulin met the end-of-life criteria

3.14 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 in the intention-to-treat population. 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

3.15 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.

4 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.

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ISBN: 978-1-4731-2914-6

Accreditation