Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

eribulin 0.44mg/mL solution for injection (Halaven®) SMC No. (726/11)

Eisai Ltd.

09 September 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

eribulin (Halaven®) is not recommended for use within NHS Scotland.

Indication under review: eribulin monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

In a randomised, phase III, open-label study eribulin-treated patients had 2.5 months additional survival compared to the comparator, treatment of physicians choice, which included a range of single agent chemotherapy treatments.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Eribulin monotherapy is indicated for the treatment of patients with locally advanced breast cancer (LABC) or metastatic breast cancer (MBC) who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

Dosing Information

Eribulin 1.23mg/m^2 (equivalent to 1.4mg/m^2 eribulin mesylate) administered intravenously over two to five minutes on days one and eight of every 21-day cycle. Patients may experience nausea or vomiting. Anti-emetic prophylaxis including corticosteroids should be considered.

Eribulin should be administered in units specialised in the administration of cytotoxic chemotherapy and only under the supervision of a qualified physician experienced in the appropriate use of cytotoxic medicinal products.

Product availability date

17 March, 2011

Summary of evidence on comparative efficacy

Eribulin is a first in class, non-taxane inhibitor of microtubule dynamics of the halichondrin class of anti-cancer drugs.

One phase III, multi-centre, randomised, open-label study has been conducted to evaluate overall survival with eribulin versus treatment of physician's choice (TPC) in 762 women with heavily pre-treated locally recurrent breast cancer or MBC. Patients aged 18 years or over with histologically or cytologically confirmed breast cancer and measurable or evaluable disease were recruited. Patients were required to have received between two and five previous chemotherapy regimens including an anthracycline and a taxane; at least two regimens for locally recurrent or MBC and to have progressed within six months after previous chemotherapy. Patients were also required to have adequate bone marrow, liver and renal function, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 and a life expectancy of at least three months.

Prior to randomisation, the TPC (defined as any single agent chemotherapy or hormonal or biological treatment approved for the treatment of cancer and to be administered according to local practice, radiotherapy or symptomatic treatment alone) was chosen and confirmed. Patients were subsequently randomised to eribulin 1.23mg/m^2 intravenously (iv) on day one and eight of a 21 day cycle (n=508) or TPC (n=254). Of the patients who received TPC the following treatments were given: vinorelbine (25% [61/247]); gemcitabine (19% [46/247]); capecitabine (18% [44/247]); taxanes (15% [38/247]); anthracyclines (10% [24/247]); other chemotherapies (10% [25/247]) and hormonal therapies (3.6% [9/247]). Treatment continued until disease progression, unacceptable toxic effects, patient or physician request to discontinue, or serious protocol non-compliance.

The primary outcome was overall survival defined as time from randomisation to death or to last date known alive (censored). At a cut-off date of 12 May 2009 there were 274 (54%) deaths in the eribulin group and 148 (58%) deaths in TPC group; hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.66 to 0.99, p=0.041. Median overall survival was 13·1 months (95% CI 11·8 to 14·3) in the eribulin group and 10·6 months (95% CI 9·3 to 12·5) in the TPC group. One year survival rates were 54% in the eribulin group and 44% in the TPC group. An updated analysis of overall survival (not protocol pre-specified) was requested by European and US regulatory authorities (cut-off date of 3 March 2010) and confirmed the original analysis. There were 386 deaths (76%) in the eribulin group and 203 (80%) in the TPC group; HR 0·81; 95% CI 0·67 to 0·96; p=0·014.

There was no significant difference between groups for the secondary endpoint, independent review of median progression free survival (PFS), defined as time from randomisation to the earliest date of disease progression or death from any cause or censored at last known date alive. Median PFS was 3.7 months versus 2.2 months (HR 0.87; 95% CI 0.71 to 1.05). However, investigator assessment of median PFS resulted in a significant difference in favour of eribulin; 3.6 months versus 2.2 months (HR 0.76; 95% CI 0.64 to 0.90). The independently reviewed objective response rate (complete plus partial responses) was significantly higher for eribulin (12% [57/468]) than TPC treated patients (4.7% [10/214]). The median duration of response was 4.2 months for eribulin treated patients and 6.7 months for TPC treated patients. The authors of the published study considered this comparison was not important as there were only 10 responders in the TPC group. A higher proportion of eribulin- than TPC-treated patients discontinued the study because of disease progression according to RECIST criteria, 67% (335/503) compared with 62% (152/247), respectively.

The company's submission to SMC also included unpublished post-hoc analyses of overall survival for the eribulin group versus two particular treatments from the TPC group. These data remain commercial in confidence.

Two open-label single-arm phase II studies support the efficacy of eribulin in patients with locally recurrent breast cancer or metastatic breast cancer previously treated with chemotherapy including an anthracycline and a taxane. Overall response rates of 9% to 15%, median PFS of 2.6 months and median overall survival of 9 to 10 months were observed.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Non-haematological adverse events (AE) (all grades) in the eribulin versus TPC groups included asthenia/fatigue (54% [270/503] versus 40% [98/247]), alopecia (45% [224/503] versus 10% [24/247]), peripheral neuropathy (35% [174/503] versus 16% [40/247]), nausea (35% [174/503] versus 28% [70/247]), constipation (25% [124/503] versus 21% [51/247]) and arthralgia/myalgia (22% [109/503] versus 12% [29/247]). The most common AE leading to treatment discontinuation in the eribulin group was peripheral neuropathy (4.8% [24/503]).

Grade 3/4 neutropenia occurred in 45% (227/503) of eribulin treated patients and in 21% (52/247) of TPC treated patients and was managed with dose delays, reductions, and granulocyte colony stimulating factor (G-CSF). Eighteen percent of patients in the eribulin group versus 7.7% of patients in TPC group received G-CSF. Febrile neutropenia occurred in

4.6% (23/503) versus 1.6% (4/247) of patients respectively. Other haematological AEs (all grades) included leucopenia (23% [116/503] versus 11% [28/247]) and anaemia (19% [94/503] versus 23% [56/247]).

In the pivotal study hypersensitivity related to eribulin was low (<1% [4/503]) and the European Medicines Agency (EMA) considered that the frequency of hypersensitivity reactions did not justify routine pre-medication.

Summary of clinical effectiveness issues

The primary endpoint of the pivotal study was a direct health outcome measure, overall survival. Eribulin-treated patients had a survival of an additional 2.5 months compared to TPC-treated patients. Demonstration of a significant difference in overall survival is rare for the primary endpoint in a study of metastatic breast cancer. However the EMA noted that strong support for other outcome measures is required when a single study is used for the application of marketing authorisation. There was no significant difference between the groups for independent review of PFS (where there was twice as many patients censored); however, there was a significant difference for the investigator assessment. The EMA considered that "important bias by the investigators can be excluded due to the high level of concordance between the independent review and investigator assessment".

Eribulin was shown to be superior to TPC but comparative efficacy relative to randomised single agent chemotherapies in a sufficiently powered study is unknown. In the pivotal study, TPC included single agent vinorelbine (in 25% of patients) and capecitabine (in 18% of patients). SMC experts considered that these are relevant comparators. The company included a post hoc sub-group analysis from the pivotal study to compare eribulin versus single agent capecitabine and vinorelbine in the ITT and region 1 (North America, Western Europe and Australia) populations. However this post hoc analysis has limitations in terms of imbalances in baseline characteristics in treatment groups, small patient numbers and lack of statistical power for these comparisons. Therefore, it is not possible to draw robust conclusions regarding relative efficacy of eribulin versus capecitabine and vinorelbine monotherapy.

Eribulin is given intravenously on day one and eight of a 21-day cycle. However other chemotherapy treatments for LABC and MBC may be administered orally. Quality of life data are not available from the pivotal study. Therefore the impact of eribulin other than on clinical endpoints is unknown.

The EMA considered that there were no important differences with respect to safety between the eribulin and TPC arms. Pre-treatment for hypersensitivity reactions with steroids and antihistamines is not routinely required with eribulin. However, in the pivotal study nausea (any grade) occurred in approximately one third of eribulin treated patients and therefore concurrent use of anti-emetics [including steroids] should be considered. Furthermore, neutropenia (all grades) was observed in half of eribulin-treated patients and 18% of patients required G-CSF.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of eribulin compared to (i) TPC, reflecting the pivotal study described previously, (ii) vinorelbine and (iii) capecitabine. The latter

comparisons were based on post-hoc sub-groups of the pivotal study. Prior to randomisation, the local physician agreed with each patient what treatment the patient would receive if they were to receive TPC; the sub-groups were based on those who pre-selected vinorelbine or capecitabine respectively, and compared them to those who pre-selected the same option but were randomised to receive eribulin. The efficacy estimate was thus a comparison between eribulin and TPC for each of those groups.

Data from the trial on overall survival and progression-free survival were modeled and extrapolated using parametric techniques and, of the different methods compared, the Weibull was said to have the best 'goodness-of-fit' measure. These data were then used in a lifetime Markov model, which had four health states "treated", "progressed", "terminal" and "dead". In the model it was assumed no patient died of causes other than breast cancer.

The data from the trial reflected the ITT population but only for what the pivotal study defined as "Region 1 countries", i.e. Western Europe, North America and Australia, representing 64% of the patients in the ITT population. Otherwise all patients were included so the economics case was not for a niche role.

Medicine doses were based on the relevant summary of product characteristics and the prices were taken from the British National Formulary. Treatment was assumed to continue until disease progressed. In the base case, vial wastage was assumed but in a sensitivity analysis a 'cost per mg' basis was used (i.e. all of the vial or pack was used). Administration of each medicine was on an out-patient basis, with a cost being incurred for each treatment of an iv regimen (of which there may be several per cycle) and each cycle of an oral medicine. Costs were taken from English NHS Reference Costs. Costs of on-going care of breast cancer varied by whether the patient's disease had progressed or not, and were especially high for the terminal care state. Resource use was based on the opinion of UK clinical experts and costed using English NHS Reference Costs.

Utilities were taken from published literature studies and included 0.82 for responders, 0.76 for stable disease, 0.5 for progressed disease, and 0.16 for the terminal state (roughly speaking, the last month of life). Adverse event utility loss was included but only for Grade 3 or 4 events where the incidence exceeded 10%; no costs or utilities were attached to alopecia, which was common with eribulin in the main clinical study.

The results were as follows:

ERIBULIN	**Versus TPC**	**Versus vinorelbine**	**Versus capecitabine**
Net economic cost	£9,169	£8,100	£22,750
QALY gain	0.112	0.196	0.518
Cost per QALY	£81,852	£41,377	£43,885

Sensitivity analysis showed key variables included the hazard ratio for overall survival (OS), the price and dose of eribulin, and the utility value of the progressed disease state. The hazard ratio for PFS and assumed body surface area also played a role.

The company proposed a patient access scheme (PAS) that offered a simple discount on the list price of eribulin. The PAS was accepted by the Patient Access Scheme Assessment Group (PASAG) therefore it was considered by SMC as part of the health economic case. The effect of the PAS was to reduce the cost per QALY figures for eribulin presented above. As SMC has not recommended use of the medicine, however, the PAS cannot be implemented in NHS Scotland.

Following receipt of advice from the New Drugs Committee, the submitting company asked SMC to consider eribulin when positioned for use within its licensed indication for patients who have already received capecitabine. In the context of this proposed positioning, the most relevant comparator would be vinorelbine.

There were two important concerns with the clinical data used in the economic model, and a further concern about the utility values used.

First, there was a concern about the selection of clinical data from the main randomized trial to be used in the economic model. The comparisons with capecitabine and vinorelbine rest upon unplanned post-hoc analyses. While these do seem to be appropriate choices of comparator for third and fourth line treatment, the numbers of patients in these sub-groups were small and potentially highly selective, with the economics results resting on data for 53 patients in the comparison with capecitabine (7% of the RCT population) and 139 patients in the comparison with vinorelbine (18% of the RCT population). The other issue was with the use of data from Region 1 of the clinical trial only in the economics model; insufficient data were presented to demonstrate that these patients were a better match to Scottish patients than the overall ITT population of the study.

The second concern was the method used to extrapolate from the clinical trial data. Within this, there were the following issues:

- Economics models of medicines for advanced cancer generally fit extrapolation curves to Kaplan-Meier plots of observed trial data, yet in this case hazard ratios were modeled instead. The submitting company argued that while using Kaplan-Meier was legitimate, the approach broke the randomization and the new approach used was more appropriate. The technique used also makes the assumption of proportional hazards for overall survival but inspection of the observed clinical data raised concerns about whether that assumption held in this case.
- The reliance on hazard ratios produced some strange relationships between observed survival data and estimated QALY gains. For example, based on a sub-group analysis of the clinical study the difference in survival between eribulin and capecitabine was 174 days compared to a difference of 189 days for eribulin versus vinorelbine, but the QALY gain was much bigger in the capecitabine comparison (0.52 versus 0.2). The company explained that this was because the QALY gain was based on the extrapolation using the hazard ratio (0.35 and 0.58 respectively). However, because of the small numbers of patients already noted, the confidence intervals around these hazard ratios was wide (0.15 to 0.81 for capecitabine and 0.37 to 0.92 for vinorelbine) yet the submission assumes these differences are robust when estimating very different QALY gains.

The Committee had concerns about the approach to the extrapolation of clinical data.

A further issue was that disease progression caused a steep fall in utility from 0.76 to 0.5. When the description of progression from the published study of utility values was compared to this definition of progression in the trial, it was not clear that the state valued in the published study matched the state described as progression in the RCT and economic model. This raises a question about whether a utility value for ‘progression’ taken from another study can simply be applied to a state labeled ‘progression’ in the current study. In response to a question from SMC the company acknowledged utility may not fall in this way but asserted that this did not

favour eribulin as the survival gains occurred in the progression phase of the model. There remains some uncertainty in relation to the validity of the utility values used.

The issues with the handling of resource use and costs were as follows:

- First, the handling of administration costs was over-complicated and the results showed some sensitivity to changes in the assumptions used, with the ICERs rising by around 20% when alternative assumptions were used.
- Secondly, terminal care costs seemed high, but since these should apply equally to each treatment arm, this should not make a difference.

Given these uncertainties, the economic case was not demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Breast Cancer Care
- Breakthrough Breast Cancer

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN 84; Management of breast cancer in women, in December 2005. The guideline recommends either capecitabine or vinorelbine should be considered for patients with advanced breast cancer.

The National Institute for Health and Clinical Excellence (NICE) published Clinical Guideline 81 Advanced breast cancer; diagnosis and treatment in February 2009. The guideline updates and replaces NICE technology appraisal guidance 62 (capecitabine), 54 (vinorelbine) and 30 (taxanes). The guideline recommends the following:

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), systemic chemotherapy should be offered in the following sequence:

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine
- third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).

Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.

Both guidelines predate the availability of eribulin for the treatment of patients with locally advanced or metastatic breast cancer.

Additional information: comparators

Capecitabine monotherapy or vinorelbine monotherapy are indicated for the treatment of advanced and/or metastatic breast cancer.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 3-week cycle (£)
eribulin	**1.23mg/m^2 intravenous infusion on days 1 and 8 of a 21-day cycle.**	**1,878**
vinorelbine capsules	60mg/m^2 orally once weekly for 3 weeks then 80mg/m^2 once weekly thereafter	up to 924*
vinorelbine infusion	25 to 30 mg/m^2 intravenous infusion once weekly	420 to 509*
Capecitabine	1,250mg/m^2 orally twice daily for 14 days of a 21-day cycle	279

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 21 June 2011 and MIMs (June 2011). Doses based on a body surface area of 1.8m^2. *costs are for three weeks treatment.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 169 patients. Based on an estimated uptake of 10% in year 1 and 30% in year 5, the impact on the medicines budget was estimated at £191K in year 1 and £573K in year 5 without the PAS. Savings were only estimated in terms of capecitabine and vinorelbine medicines costs. The net medicines budget impact was estimated at £114K and £342K.

The budget impact includes medicines costs only. In the economics model there are additional implications for NHS resources in terms of switching patients from oral treatments to intravenous eribulin and in terms of longer survival with breast cancer – these were not included in the estimates provided.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011 Mar 12;377(9769):914-23.

Vahdat LT, Pruitt B, Fabian CJ et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2009 Jun 20;27(18):2954-61.

Cortes J, Vahdat L, Blum JL et al. Phase II Study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. J Clin Oncol. 2010 Sep 1;28(25):3922-8.

European Medicines Agency. European Public Assessment Report for eribulin (Halaven®). EMEA/H/C/002084. 20 January 2011.

This assessment is based on data submitted by the applicant company up to and including 31 August 2011.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.