Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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# Re-Submission:

## eribulin (mesilate), 0.44mg/mL solution for injection (Halaven®)

SMC No. (1065/15)

## Eisai Ltd.

05 February 2016

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 NHS Scotland. The advice is summarised as follows:

**ADVICE**: following a re-submission under the end of life and orphan equivalent process

**eribulin (Halaven®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** 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.

**SMC restriction:** for use in patients with locally-advanced or metastatic breast cancer who have progressive disease after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated.

In a randomised, phase III, open-label study, median overall survival was extended by 2.5 months in patients treated with eribulin compared with the comparator, treatment of physician's choice, which included a range of single agent chemotherapy treatments. In the subgroup of patients previously treated with capecitabine the extension to median overall survival was 2.9 months.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of eribulin. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

This supersedes previous advice for eribulin (SMC No. 726/11).

Overleaf is the detailed advice on this product.

**Chairman**
**Scottish Medicines Consortium**

## Indication

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.

## Dosing Information

Eribulin 1.23mg/m$^2$ (equivalent to 1.4mg/m$^2$ eribulin mesilate) administered intravenously (as the ready to use solution)* over two to five minutes on days one and eight of every 21-day cycle. The dose may be diluted in up to 100mL of sodium chloride 9mg/mL (0.9%) solution for injection. 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.

*In the EU the recommended dose refers to the base of the active substance (eribulin). Calculation of the individual dose to be administered to a patient must be based on the strength of the ready to use solution that contains 0.44 mg/mL eribulin and the dose recommendation of 1.23 mg/m$^2$.

## Product availability date

June 2014
Eribulin meets SMC end of life and orphan equivalent criteria.

## Summary of evidence on comparative efficacy

Eribulin is a novel, non-taxane, antineoplastic agent indicated for the treatment of patients with locally advanced breast cancer or metastatic breast cancer (LABC/MBC). It exerts its effect via a tubulin-based antimitotic mechanism, leading to $G_2$/M cell-cycle block and disruption of mitotic spindles, causing prolonged mitotic blockage and apoptotic cell death.[1]

The submitting company has requested that SMC considers eribulin when positioned for use in patients with LABC/MBC who have progressive disease after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated. Eribulin has previously been reviewed by SMC for use in patients with anthracycline and taxane pre-treated LABC/MBC, who progressed after at least two chemotherapeutic regimens for advanced disease (SMC No. 726/11), reflecting the licensed indication at that time. In 2014, the indication was extended to patients who have had at least one prior chemotherapeutic regimen for advanced disease.

Clinical evidence derives from a phase III, randomised, open-label study (EMBRACE) to evaluate overall survival (OS) in women with heavily pre-treated locally recurrent or MBC.[2,3] The study recruited adult women with histologically or cytologically confirmed breast cancer who had received two to five previous chemotherapy regimens, including an anthracycline and a taxane, and two or more regimens for locally recurrent or MBC. Patients were required to have progressed within six months of previous chemotherapy, have adequate bone marrow, liver, and renal function, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and a life expectancy of at least

three months. Prior to study recruitment, 99% of patients had received an anthracycline and taxane, and the median number of previous chemotherapy regimens was four.[2]

Patients were randomly allocated in a 2:1 ratio to treatment with intravenous (IV) eribulin 1.23mg/m$^2$ on days one and eight of each 21-day treatment cycle (n=508), or to treatment of physician's choice (TPC) (n=254). TPC was 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. TPC was chosen and confirmed prior to randomisation. In those patients assigned to TPC, 96% (238/247) received chemotherapy, including vinorelbine (25% [61/247]), gemcitabine (19% [46/247]), capecitabine (18% [44/247]), a taxane (15% [38/247]), an anthracycline (10% [24/247]), or other chemotherapy (10% [25/247] including cisplatin, carboplatin, cyclophosphamide, etoposide, mitomycin, fluorouracil, or methotrexate). A small proportion of patients received hormonal therapy (3.6% [9/247]) including fulvestrant, letrozole, exemestane, and tamoxifen. Patients continued treatment until disease progression, development of unacceptable side effects, patient or physician request to discontinue treatment, or serious protocol non-compliance. No patient received supportive care alone.[2]

The primary outcome was OS, analysed in the intention-to-treat (ITT) population. At the primary analysis (12 May 2009), there were 274 deaths (54%) in the eribulin group and 148 deaths (58%) in the TPC group (HR 0.81, 95% confidence interval [CI]: 0.66 to 0.99; p=0.041). Median OS was significantly increased by 2.5 months in the eribulin treatment group compared with the TPC group, with a median OS of 13.1 months in the eribulin group and 10.6 months in the TPC group. Kaplan-Meier one-year survival rates were 54% and 44% in the eribulin and TPC groups, respectively. The primary analysis was confirmed following a subsequent updated analysis of the primary outcome (03 March 2010), with 386 deaths (76%) in the eribulin group and 203 deaths (80%) in the TPC group (HR 0.81, 95% CI: 0.67 to 0.96; p=0.014). Median OS was 13.2 months in the eribulin group and 10.5 months in the TPC group.[2]

An exploratory subgroup analysis was performed in those patients who had previously been treated with capecitabine (73% [559/762]). The proportion of patients in the eribulin and TPC groups, respectively, who had received prior treatment with capecitabine was 73% (370/508) and 74% (189/254).[2] At the March 2010 analysis of the post-capecitabine subgroup, 79% [291/370] of patients had died in the eribulin group and 82% (154/189) had died in the TPC group. Median OS was 13.0 months in the eribulin group and 10.1 months in the TPC group (HR 0.79; 95% CI: 0.64 to 0.96; p=0.018). In the eribulin and TPC treatment groups, respectively, one-year survival rates were 54% and 42%.[3]

Secondary outcomes compared progression-free survival (PFS), objective response rates, and duration of response and were reported for the ITT population.

Independent review of PFS found no significant difference between treatment groups, with median PFS 3.7 months in the eribulin group and 2.2 months in the TPC group (HR 0.87; 95% CI: 0.71 to 1.05; p=0.137). However, investigator assessment of PFS did find a significant difference in favour of eribulin (eribulin group 3.6 months and TPC group 2.2 months; HR 0.76; 95% CI: 0.64 to 0.90; p=0.002).[2]

Independent review of objective response rate (including complete and partial response) was found to be 12% (57/468) and 4.7% (10/214) in the eribulin and TPC groups, respectively (p=0.002). The objective responses were predominantly partial responses; three patients (0.6%) in the eribulin group achieved a complete response. Median duration of response was 4.2 months for the eribulin group, and 6.7 months for the TPC group (p=0.159), however comparison of the groups was considered inappropriate by the authors of the published study as only ten patients responded to treatment in the TPC group.[2]

Health-related Quality of Life (HRQoL) data are available from a phase III, open-label, randomised study (Study 301).[4] Adult women with LABC/MBC who had received previous treatment with up to three chemotherapy regimens and up to two chemotherapy regimens for advanced/metastatic disease (including prior treatment with an anthracycline and a taxane) were allocated to treatment with eribulin (n=554) or capecitabine (n=548) as first-, second-, or third-line chemotherapy. HRQoL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) and breast module Quality of Life Questionnaire BR23. Global health status improved in both eribulin and capecitabine treatment groups over time, and no significant differences between the groups were demonstrated. There was also no significant difference in the co-primary end points of OS or PFS between the eribulin and capecitabine groups.[4]

## Summary of evidence on comparative safety

Safety was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).[2] In the eribulin and TPC groups respectively, adverse events were reported in 99% (497/503) and 93% (230/247) of patients, with serious adverse events occurring in 25% and 26% of patients. Treatment discontinuation, as a result of adverse events, was reported in 13% and 15% of patients in the eribulin and TPC groups respectively. The most common adverse event leading to discontinuation of eribulin treatment was peripheral neuropathy (5% [24/503]).[2]

The most common adverse events occurring in all grades of CTCAE in both the eribulin and TPC groups were asthenia/fatigue (54% versus 40%, respectively) and neutropenia (52% versus 30%). Neutropenia was managed with eribulin dose delays or reductions, and the administration of Granulocyte Colony Stimulating Factor (G-CSF). G-CSF was received by 18% and 7.7% of patients in the eribulin and TPC groups, respectively. Febrile neutropenia occurred in 4.6% of patients in the eribulin group and in 1.6% of patients in the TPC group.[2] Other adverse effects included alopecia (45% versus 10%), nausea (35% versus 28%), and constipation (25% versus 21%).[2]

Adverse events of grade 3 or 4 occurring more frequently in the eribulin group compared with the TPC group were neutropenia (45% versus 21%), leucopenia (14% versus 5.7%), and peripheral neuropathy (8.2% versus 2.0%).[2] Post-marketing retrospective audits conducted in France/Switzerland (n=258) and the UK (n=108) of patients treated with eribulin reported occurrence of grade 3 or 4 adverse events: neutropenia in 21% and 32% of patients; and peripheral neuropathy or neurotoxicity in 3.9% and 2% of patients, respectively.[5,6] Febrile neutropenia (grade 3 or 4) was reported in 5.0% of patients in the French/Swiss audit.[5]

Treatment-related fatal adverse events were reported in 1.0% (5/503) of patients on eribulin, and included febrile neutropenia (one patient), lung infection (one patient), bronchopneumonia (one patient), and dyspnoea (two patients); in the TPC group, fatal adverse events were considered treatment-related in 0.8% (2/247) of patients, and included febrile neutropenia (one patient) and aspergillosis (one patient).[3]

Another retrospective study of 75 patients treated with eribulin in the UK found that patients received a median of six cycles of eribulin. The most commonly reported toxicities were lethargy (55%), neuropathy (33%) and nausea (32%). Neutropenia was reported in 17% of patients; one patient died from neutropenic sepsis and there were eight hospital admissions resulting from neutropenia.[7]

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

## Summary of clinical effectiveness issues

Eribulin is a novel, non-taxane, antineoplastic agent indicated for the treatment of patients with LABC/MBC. Treatment of advanced breast cancer currently involves the use of anthracycline- or taxane-based regimens; other treatment options include capecitabine or vinorelbine. European guidelines recommend eribulin, capecitabine, or vinorelbine as the preferred single-agent treatment options in patients who do not require combination chemotherapy and have been pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane.[8]

The submitting company has requested that SMC considers eribulin when positioned for use in patients with LABC/MBC who have progressive disease after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless contraindicated. Eribulin meets SMC end of life and orphan-equivalent criteria.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area due to the limited treatment benefits and treatment options available at this stage of the condition.

Advanced breast cancer is a treatable but usually incurable disease, with median overall survival around two to three years. Treatment goals aim to increase survival and improve quality of life.[8] In the subgroup of patients with previous treatment with capecitabine in the EMBRACE study, median OS was 13.0 months for eribulin and 10.1 months for TPC, an extension in median survival of 2.9 months.[3] It is unknown if subsequent treatments following the use of eribulin would confound overall survival results.

PFS is also considered an important benefit in the treatment of advanced breast cancer, as time without tumour progression, and the associated symptoms and psychological effects, can significantly impact on the quality of remaining life.[3] PFS was found to be significantly longer for eribulin than TPC following investigator assessment but not following independent review. This was as a result of fewer patients being censored (and therefore more progression events occurring) in the investigator assessment.[2] The European Medicines Agency (EMA) concluded that there was high concordance between the investigator assessment and independent review, and that important bias in investigator adjudication could be excluded.[3]

Although comparative data are available against TPC (in which a variety of treatments were used), and a supportive phase III study provides comparative data of eribulin versus capecitabine (suggesting eribulin was similar to capecitabine), there are no other comparative data versus single agent treatments. HRQoL data are restricted to the study in comparison with capecitabine.

The EMA noted that no important differences in safety were observed between the eribulin and TPC groups, and that pre-medication for hypersensitivity reactions is not routinely required.[3] In patients treated with eribulin in EMBRACE, just over a third experienced nausea (all grades),[2] and antiemetic prophylaxis, including corticosteroids, should therefore be considered.[1] More than half of eribulin-treated patients developed neutropenia (all grades), with 18% requiring G-CSF. Post-marketing retrospective audits suggest the incidence of neutropenia and grade 3 or 4 neutropenia is lower in clinical practice.[5-7] Complete blood counts should be monitored in all patients prior to each dose of eribulin.[2]

Some chemotherapy for LABC and MBC may be administered orally; however, eribulin requires IV administration on days one and eight of every 21-day cycle.

Clinical experts consulted by SMC considered that eribulin is a therapeutic advancement as it improves overall survival.

## Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of eribulin, as an end of life and orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Prognosis for women with metastatic breast cancer is very poor, particularly for those with triple negative disease and also those who have already received more than two lines of therapy, who on average have less than a year to live.

- Once patients have exhausted anthracyclines, taxanes and capecitabine, very few cytotoxic treatment options remain available.

- Eribulin offers a very valuable treatment option as it is the only agent that has shown a significant overall survival benefit at this stage in the disease in a heavily pre-treated group of patients, and importantly increased survival has been shown versus 'treatment of physician's choice'. A potential two to three months increased survival is particularly meaningful for patients and their families in the context of limited remaining months.

- Clinicians indicated that the option of eribulin would protect patients from alternative agents with an inferior quality of supporting evidence, and would give patients a choice between treatments with different side-effect profiles.

- Clinicians also indicated that eribulin is associated with manageable toxicity and similar side-effect frequency to other chemotherapy agents used in this setting.

- Patient groups highlighted that, for most patients, the benefits of possible increase in quality time with loved ones far outweighed any increase in trips to hospital for administration of treatment or side-effects.

- The PACE group felt that this medicine would be a significant addition to the treatment options currently available in the NHS in Scotland. Participants supported use in patients with good performance status and in-line with the company's positioning i.e. those who have progressive disease after at least two lines of therapy for advanced disease. It was noted that treatment may be particularly beneficial for patients with triple negative breast cancer.

## Summary of comparative health economic evidence

The company submitted a cost utility analysis comparing eribulin with TPC for the treatment of patients with LABC/MBC who have progressed after at least two chemotherapeutic regimens for advanced disease, which includes capecitabine if indicated. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless contraindicated. A Markov model was used which consisted of three health states i.e. stable, progression and death. The time horizon was five years.

The clinical data used to support the economics were taken from EMBRACE study where patients progressed through health states according to time dependent transition probabilities. The primary outcome in the study was OS. The base case analysis used a proportional hazards model whereby a gamma function was fitted. These data were extrapolated in the base case as 23% of patients were still alive at the trial cut-off. It should be noted that PFS data were mature and therefore no extrapolation was applied. The company has provided additional analyses whereby individual survival functions have been applied to the study data.

Drug acquisition costs, IV administration costs and adverse event management costs were included in the analysis. Drug costs for the TPC arm were based on a weighted average, and data taken from the EMBRACE study. Health care costs associated with both stable and progressive disease health states were included and estimated on a monthly basis. Within the stable disease health state, patients received a monthly medical oncologist visit, GP contact and a CT scan (once every three months). It should be noted that health care resource utilisation was based on expert opinion. For the progressive disease health state, costs consisted of palliative care and end of life care costs. End of life care costs were based on a weighted average of hospital, hospice and home care use, patient proportions were based on data from NICE Clinical Guidance for Breast Cancer.

Utility values were estimated using HRQoL data from study 301, because of the absence of data from the EMBRACE study. A published mapping algorithm was used to derive EQ-5D scores from QLQ-C30 data. It should be noted that for the progressive health state, both treatment arms were assumed to have a utility value of 0.695, while treatment-specific utilities were calculated for the stable disease state i.e. 0.717 and 0.715 for eribulin and TPC respectively. The values were estimated via linear regression and take into account baseline status, tumour response and disutilities (associated with grade 3 or 4 adverse events).

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in Scotland. Under the PAS, a simple discount was given on the list price of the medicine. With the PAS, the incremental cost-effectiveness ratio (ICER) was estimated to be £18,463 per quality-adjusted life-year (QALY) gained for eribulin monotherapy compared to TPC. The incremental costs associated with eribulin stem mainly from increased drug costs, while the incremental QALY and life-year gain were a result of patients remaining in the post progression health state for longer duration.

A range of sensitivity analyses were provided including one-way, scenario and probabilistic sensitivity analysis. Results were most sensitive to the use of the Gompertz parametric function; with the PAS, the ICER increased to £31,205. The results were also sensitive to a 20% increase in direct health care costs in the eribulin arm of the model; with the PAS, the ICER increased to £25,619. Furthermore, a 20% increase in eribulin drug costs resulted in an ICER of £24,013. It should be noted that results were not overly sensitive to a 20% increase in adverse event prevalence for eribulin. The company provided additional analysis combining a number of conservative assumptions i.e. overall survival based on Kaplan-Meier data (34 months), utility value for progressed health state reduced to 0.62 and a 20% increase in both the prevalence and disutility associated with grade 3 and 4 adverse events (in the eribulin arm only). Based on this analysis, the with-PAS ICER increased to £23,816.

The Committee also considered the benefits of eribulin in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy was satisfied. In addition, as eribulin is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted eribulin for use in NHS Scotland.

## Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from Breast Cancer Now, which is a registered charity.
- Breast Cancer Now has received pharmaceutical company funding in the past two years, but not from the submitting company.
- While secondary breast cancer can be controlled, it cannot be cured and it is a terminal disease, with a life expectancy after diagnosis of approximately two years. It affects women in different ways. However, due to limited treatment options for women at this stage of disease, all will face increasingly debilitating symptoms. These can have a significant impact on everyday activities, ability to work, social life, and on personal and family relationships.
- Eribulin would provide a valuable extra option for clinicians treating patients nearing the end of their lives. Although it is a systemic chemotherapy drug and is therefore associated with many side effects, these are not the same side effects as caused by other chemotherapy treatments. This therefore gives patients who have had several chemotherapy regimens an additional option.
- Eribulin is used for patients who are nearing the end of their lives and may provide patients with valuable additional months of life. For patients who experience few side effects, these additional months of good quality life that eribulin may provide are priceless.

## Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published a clinical guideline on the diagnosis and treatment of advanced breast cancer in July 2014.[9] NICE recommends that patients, in the majority of cases, should be offered systemic sequential chemotherapy. Combination chemotherapy may be considered in patients who are willing to accept and tolerate increased toxicity levels. The following systemic chemotherapy treatment schedule should be implemented in patients who are not suitable for treatment with anthracyclines:

- 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).

NICE recommends gemcitabine in combination with paclitaxel as a treatment option for metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.

Joint consensus guidelines on the treatment of advanced breast cancer were published by the European School of Oncology (ESO) and European Society of Medical Oncology (ESMO) in 2014.[8] The guideline makes the following recommendations regarding treatment with chemotherapy:

- Anthracycline- or taxane-based regimens, preferably as a single agent, should usually be considered as first-line chemotherapy for HER-2-negative metastatic breast cancer in those patients who have not received these regimens as adjuvant treatment. Other options are also effective including capecitabine and vinorelbine.

- Taxane-based therapy, preferably as a single agent, would usually be considered as the treatment of choice in patients with taxane-naive and anthracycline-resistant metastatic breast cancer, or in those with anthracycline cumulative dose or toxicity. Other options are also effective including capecitabine and vinorelbine.
- A taxane may be considered for re-use in the metastatic setting if it has already been given in the adjuvant setting.
- Each regimen (except anthracyclines) should usually be given until progression of disease or unacceptable toxicity.
- Bevacizumab in combination with chemotherapy as first- or second-line therapy provides moderate benefit in progression-free survival and no benefit in overall survival. Bevacizumab cannot be recommended for general use due to the lack of evidence to support patient selection. Bevacizumab is not recommended after a first/second line.

The guideline notes that eribulin has been shown to demonstrate improved overall survival in heavily pretreated patients and makes the following recommendation:

- Single agent capecitabine, vinorelbine or eribulin are the preferred treatment choices in patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, and who do not require combination chemotherapy.

## Additional information: comparators

Chemotherapy (including vinorelbine, capecitabine, or a taxane [e.g. docetaxel, paclitaxel]). Comparators relevant to the licensed indication under review have been included.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost per three-week cycle (£) |
|---|---|---|
| **Eribulin** | **1.23mg/m$^2$ by intravenous injection or infusion on days one and eight of a 21-day cycle** | **2,166** |
| Docetaxel | 100mg/m$^2$ by intravenous infusion every three weeks | 1,163 |
| Vinorelbine capsules | 60mg/m² orally once weekly for three weeks then 80mg/m² once weekly thereafter | 726 |
| Paclitaxel | 175mg/m$^2$ by intravenous infusion every three weeks | 668 |
| Vinorelbine infusion | Monotherapy: 25 to 30mg/m² by intravenous infusion once weekly | 420 to 509 |
| Capecitabine | 1,250mg/m$^2$ orally twice daily for 14 days of a 21-day cycle | 155 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and MIMS Online on 26 November 15 and based on body surface area of 1.8m$^2$. Costs do not take any patient access schemes into consideration.

## Additional information: budget impact

The submitting company estimated the number of patients eligible for treatment to be 206 in all years with an estimated uptake rate of 10% in year 1, rising to 30% in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget impact with the PAS.

References

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


1. Eisai Ltd. Halaven 0.44mg/ml solution for injection. Summary of product characteristics. Last updated July 2015.

2. 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.

3. European Medicines Agency. European public assessment report for eribulin (Halaven®). EMEA/H/C/002084. 20 January 2011.

4. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2015. Published ahead of print as 10.1200/JCO.2013.52.4892

5. Dell'Ova M, De Maio E, Guiu S, et al. ERIBEX: a retrospective, international, multicenter study on the efficacy and safety of eribulin mesylate in metastatic breast cancer. Poster presented at ESMO 2014 Congress, Madrid. 26 to 30 September 2014

6. Thanopoulou E, Omarini C, Yeo B et al. Safety and efficacy of eribulin mesylate (EM) in patients with advanced breast cancer: the Royal Marsden experience. J Clin Oncol 2014: 32 (suppl.): abstr e12004.

7. Walshaw RC, Shaukat S, Chan K et al. Eribulin for advanced breast cancer: clinical experience in the real world. J Clin Oncol 2014; 32 (suppl.): abstr e12003.

8. Cardoso F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Annals of Oncology 2014; 25: 1871-88. and The Breast 2014; 23: 489-502.

9. National Institute for Health and Care Excellence (NICE). Clinical guideline 81. Advanced breast cancer (update): Diagnosis and treatment. (July 2014). https://www.nice.org.uk/guidance/cg81.


This assessment is based on data submitted by the applicant company up to and including 08 January 2016.

**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. 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.*