PUBLIC SUMMARY DOCUMENT

Product: Eribulin mesilate, injection in vial, 1mg/2mL Halaven®
Sponsor: Eisai Australia Pty Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The resubmission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (+/-STREAMLINED) listings for the treatment of a patient with locally advanced or metastatic breast cancer who has progressed after at least two chemotherapeutic regimens for advanced disease.

2. Background

The PBAC rejected a submission for eribulin at the March 2013 meeting. The Public Summary Document from the March 2013 meeting is available on the PBS website.

3. Registration Status

Eribulin was registered by the TGA on 4 September 2012 as follows:

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.

4. Listing Requested and PBAC's View

Section 100 (Efficient Funding of Chemotherapy)
Private Hospital / Private Clinic Authority required
Public Hospital Authority required (STREAMLINED)

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.

The PBAC considered that as no data were presented to support the continued use of eribulin beyond disease progression, the PBS restriction should exclude this possibility.

The PBAC also considered that there is a risk of eribulin being used in combination with other agents for locally advanced or metastatic disease, including trastuzumab, and recommended that the PBS restriction specify that eribulin be used as the sole

PBS-subsidised treatment for the condition. The PBAC noted that this would align with the TGA registered indication for eribulin, which stipulates it be used as monotherapy.

The PBAC noted that the proposed restriction did not define what would be meant by a patient being "not suitable" for an anthracycline and a taxane. The PBAC noted that patients with metastatic disease may have received treatment with these drugs in the adjuvant setting and on this basis were not suitable for re-exposure to these drugs in the metastatic setting. The PBAC considered requiring provision of evidence that treatment with anthracyclines/taxanes was contraindicated for patients to be eligible for eribulin treatment, but noted comments from MOGA about decision making in the care of women with metastatic breast cancer, and did not add a specific definition of contraindicated to the restriction.

The PBAC noted that listings under the Section 100 Efficient Funding of Chemotherapy (EFC) program require listing with a maximum 'amount' rather than a maximum 'quantity'. The maximum amount is the amount of drug required to provide for a single infusion based on the patient having a body surface area (BSA) of 2.2 m^2. The submission's requested maximum quantity of 6 vials (6 mg) per month would be sufficient for 2 infusions based on an average dose per infusion of 2.44 mg for patients with an average BSA of 1.74 m^2 (consistent with the pivotal trial). Using the average dose from the trial, a single infusion for a patient with BSA of 2.2 m^2 would be 3.08 mg. The PBAC considered that a maximum amount of 3 mg (rounded down from 3.08 mg) was appropriate. The submission requested 13 repeats, which the PBAC considered appropriate.

5. Clinical Place for the Proposed Therapy

The submission proposed the place in therapy for eribulin is for patients who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane, unless contraindicated.

The PBAC recalled that the proposed place of therapy in the March 2013 submission, after the use of capecitabine, was considered clinically inappropriate. The PBAC considered that the appropriate place in therapy was likely to be after anthracyclines and taxanes but that eribulin may be used before or after capecitabine. The PBAC also noted that in HER2 positive breast cancer, clinicians may want to use eribulin in combination with trastuzumab.

The proposed clinical algorithm in the previous March 2103 submission had also suggested that a patient with low risk advanced breast cancer can access eribulin without prior anthracycline and taxane treatment, which contradicted the proposed PBS restriction. Moreover, the proposed clinical algorithm assumed every patient would have received capecitabine prior to the treatment with eribulin.

The PBAC considered that the resubmission had adequately addressed its previous concerns, and that the place in therapy proposed in the resubmission was

appropriate.

6. Comparator

The resubmission nominated vinorelbine as the comparator. This differed from the previous submission which nominated Treatment of Physicians' Choice (TPC) as the comparator.

The PBAC previously accepted that given the difficulty of identifying a single comparator, the pragmatic selection of vinorelbine as the comparator in the economic analysis was reasonable.

7. Clinical Trials

The primary and supporting trials were unchanged from the previous submission, with the major exception of additional analysis relating to the primary trial (EMBRACE), including complete overall survival (OS) data on a larger proportion of patients. These data were introduced in the pre-subcommittee response (PSCR) to the previous submission, and were described in more detail in the resubmission.

The PBAC considered the selection and interpretation of primary and supporting trials to be appropriate.

For details of published trials and associated reports presented in the submission, refer to the March 2013 PSD.

8. Results of Trials

With regard to comparative effectiveness, the overall survival data were presented based on three time cut-offs. The PBAC had previously seen these data, the first two time points in the previous submission and the third was provided in the PSCR. The PBAC had previously acknowledged that eribulin was an effective drug that offered a modest survival benefit at the end of life.

As in March 2013, having considered the arguments supporting extrapolation outlined in the Pre-PBAC response, the PBAC remained of the view that in light of the fact that the OS data are mature, extrapolation would introduce variability into the results, increasing uncertainty.

With regard to comparative harms, the resubmission presented limited additional safety information from the previous submission. Additional information was provided to address the concern highlighted by the ESC in March 2013 regarding a difference in the rates of alopecia.

The PBAC recalled its concerns from March 2013 that the claim of non-inferior toxicity was not adequately supported, based on additional granulocyte colony-stimulating factor (G-CSF) requirements, an issue that was not explicitly addressed in the re-submission. The PSCR argued that the incidence of neutropenia for eribulin and vinorelbine are very similar (51.7%

and 49.2%, respectively), and that the expected use of G-CSF would be similar between the two agents.

The PBAC agreed with the ESC that the issue that neutropenia, leukopenia and peripheral neuropathy were higher in the eribulin group than in the TPC group remained unresolved. A comparison of adverse events in patients treated with eribulin, TPC and vinorelbine is presented below.

Adverse events reported in EMBRACE for eribulin, TPC and vinorelbine

System organ class AEs	Eribulin N=503 n (%)	TPC N=247 n (%)	Vin. N=61 n (%)
Any AE	497 (98.8 %)	230 (93.1)	57 (93.4%)
Blood and Lymphatic			
Neutropenia	260 (51.7%)	73 (29.6 %)	30 (49.2%)
Anaemia	94 (18.7%)	56 (22.7%)	13 (21.3%)
Leucopoenia	116 (23.1%)	28 (11.3%)	10 (16.4%)
Nervous system			
Headache	*97 (19.3%)*	*29 (11.7%)*	*9 (14.8%)*
Peripheral neuropathy	*174 (34.6%)*	*40 (16.2%)*	*12 (19.7%)*

Overall, the PBAC considered that eribulin has an inferior safety profile to TPC and a different safety profile to vinorelbine. The higher rate of peripheral neuropathy with eribulin was noted.

9. Clinical Claim

The resubmission claimed that "eribulin has superior effectiveness in terms of OS compared to TPC, superior quality of life benefits via superior objective response rate (ORR), and a manageable non-inferior safety and tolerability profile in these heavily pre-treated patients".

The PBAC recalled that the claim of superior efficacy was previously accepted in March 2013.

The PBAC considered that the claim of non-inferior safety against TPC remained inadequately supported.

10. Economic Analysis

The resubmission presented a trial-based economic evaluation, based on the key direct randomised trial (EMBRACE) and implementing a modelled evaluation based on extrapolated survival curves.

The resubmission provided additional information to address the concern highlighted by the ESC for the March 2013 submission regarding a difference in alopecia which was not accounted for in the model. The ESC had considered it would have been appropriate to include a disutility for increased alopecia in the model. For the resubmission, the ESC noted the utilities included a decrement for alopecia.

The ESC noted that the PBAC recommendation at the March 2013 meeting was based on the revised ICER presented in the PSCR for that submission of between $45,000-75,000 per life year gained (LYG). The base case (extrapolated and modelled) ICER in the re-submission was between $15,000 and $45,000 per quality adjusted life year (QALY). The ICER for the trial based evaluation (not extrapolated) in the resubmission was between $15,000 and $45,000 per LYG.

The incremental cost in the model was decreased compared to the previous submission. The decrease in incremental cost was driven by the following factors:

- A reduction in the proposed cost of eribulin
- Dosage calculation based on the point estimate of mean BSA.
- The duration of vinorelbine treatment was assumed to be higher in the resubmission than in March 2013.

The PBAC noted that the duration of vinorelbine use in the model was based on the duration of treatment for all patients receiving TPC in EMBRACE, rather than just the patients receiving vinorelbine. This increased the treatment duration compared to the previous submission, which took the latter approach. After noting the arguments supporting this approach in the pre-PBAC response, including the similarity between the duration of TPC and the duration of vinorelbine use in Australia as judged from Medicare Australia data, the PBAC considered that this change was unsafe and inappropriately favoured eribulin. The PBAC considered that the most appropriate approach would use the duration of treatment with vinorelbine from EMBRACE.

The PBAC noted that the resubmission used the point estimate of the mean BSA of $1.7m^2$ to calculate eribulin dosage and utilisation. The PBAC considered that compared with using the distribution of BSA, this approach underestimated the utilisation and therefore the cost of eribulin.

The PBAC noted that the ICER was increased in sensitivity analyses in which these variables were adjusted:

1. If the distribution of BSA is accounted for;
2. If the duration of vinorelbine treatment is based on the mean duration of the vinorelbine component of TPC; and
3. If the within-trial OS estimates are used.

The PBAC noted that applying all three changes to the model yields a cost per QALY of between $45,000 and 75,000, compared to the base case ICER of between $15,000- 45,000 presented in the resubmission. The PBAC considered that the revised ICER represented the most reliable estimate of the incremental cost effectiveness of eribulin in breast cancer.

Regarding the disutility associated with eribulin treatment, the PSCR argued that estimates of disutilities associated with adverse events were presented in the submission, and noted that the ICER is not sensitive to the associated disutility scores. The PBAC considered that the resubmission did not adequately consider any treatment-related disutility other than that associated with alopecia. The PSCR argued that the incidence of neutropenia for eribulin and vinorelbine are very similar (51.7% and 49.2%, respectively), and that the expected use of G-CSF would be similar between the two agents. The PBAC agreed with the ESC that this did

not resolve the issue that neutropenia, leucopenia and peripheral neuropathy were higher in the eribulin group than in the TPC group.

The PBAC noted that in calculating the costs of managing adverse events in the economic model, neutropenia and peripheral neuropathy were costed differently to other adverse events. . The resubmission assumed that management of peripheral neuropathy is zero cost and managed only by dose reduction or discontinuation.

The PBAC agreed with the ESC that the model inputs did not appropriately capture the disutility associated with eribulin treatment. The PBAC considered that treatment-related toxicity and disutility are underestimated in the economic evaluation, especially compared with TPC rather than with vinorelbine alone.

11. Estimated PBS Usage and Financial Implications

The resubmission estimated less than 10,000 patients would be treated with eribulin in Year 5 of listing, (increased compared with the previous submission).

This was due to the fact that the previous submission restricted the population to those pre-treated with capecitabine (which reduced the number) and assumed a different uptake rate.

The PBAC noted the following factors affecting the reliability of the estimates:

- The proportion of patients who are in the third (or subsequent) line of therapy was based on a survey of 60 European clinicians. 15% of patients were estimated to be in the third or later line of therapy, but the resubmission did not provide adequate detail to allow critical appraisal of that figure.
- Assumptions regarding market uptake were based on the sponsor's experience of eribulin uptake in other markets, but no further detail was provided. It is unclear whether the experience in the Australian market will be similar.

Overall, the PBAC considered that while the approach taken in generating the estimates was reasonable, the reliability of the resulting figures was not known.

The PBAC was not convinced that eribulin would replace vinorelbine in all cases, and considered that in practice it may substitute for an earlier therapy and therefore displace vinorelbine to a later line of therapy. The PBAC noted the sponsor's view in the PSCR that "…the resubmission assumes no growth in the market due to the number of treatments available for this condition and with the better screening and early diagnosis of breast cancer then the number of patients needing treatment for metastatic cancer may decrease." Notwithstanding this, the PBAC considered the potential market growth to be a risk.

The submission estimated a total net cost to the PBS of between $10 – 30 million over the first 5 years of listing. The estimated cost was less than in the March 2013 submission, though in the same range.

The PBAC considered that the estimates appeared to be reasonable; noting that the PBAC's confidence in some of the assumptions was low but no alternative assumptions were more reasonable.

12. Recommendation and Reasons

The PBAC recommended the listing of eribulin for locally advanced or metastatic breast cancer, on the basis that it should be available only under special arrangements under the Section 100 (Efficient Funding of Chemotherapy) Program. The PBAC recommended the special arrangements described in the table below apply.

The PBAC was satisfied that eribulin provides, for some patients, a significant improvement in efficacy over vinorelbine; however noting that eribulin has an inferior safety profile to TPC and different to vinorelbine.

The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of eribulin would be acceptable if the price were to be reduced from that proposed in the submission, so that the ICER generated by the economic model, modified as recommended by the ESC, falls within the range $15,000-$45,000/QALY.

In making this recommendation, the PBAC again acknowledged that eribulin was an effective drug that offered a modest survival benefit at the end of life. The PBAC noted that this was in the context of a clinical area with various alternative PBS listed drugs. The PBAC noted the consumer comments from one health professional and one organisation on this item which, although supportive, were not as numerous as in the case of items for which there are no other PBS-listed alternatives. The PBAC also noted that the availability of multiple therapeutic alternatives is an important issue for patients and prescribers, and considered that eribulin does have a place in the treatment algorithm for locally advanced or metastatic breast cancer.

The PBAC noted that while eribulin has some demonstrated clinical effectiveness, it also appeared to cause higher rates of adverse events than potential comparators. Overall, the PBAC considered that the safety profile of eribulin is different to vinorelbine with higher rates of peripheral neuropathy, and worse than best supportive care and some other potential comparators.

The PBAC considered that the model structure was reasonable, but noted that many of the model inputs favoured eribulin. The PBAC particularly noted that extrapolation of mature OS data, the use of mean BSA for dosage calculation and the assumption of a longer duration of vinorelbine inappropriately favoured eribulin. The PBAC recommended that a price reduction would be required to bring the ICER into the range of $15,000-$45,000/QALY

The PBAC considered that the proposed restriction should specify that eribulin is the sole PBS-subsidised treatment for this condition. This restriction is consistent with the TGA indication.

The PBAC noted that PBS restrictions for breast cancer were not always reflective of clinical practice. This situation has arisen because many of the chemotherapies for breast cancer were listed over a decade ago and the restrictions have not been updated. Changes over the last decade have included the use if taxanes in adjuvant protocols and the use of sequential

monotherapies rather than combination therapy for the treatment of metastatic disease. The PBAC considered that a review of restrictions in breast cancer may be warranted in the future to ensure alignment with contemporary clinical practice.

The PBAC recommended that the Safety Net 20 Day Rule should not apply

The PBAC advised that eribulin is not suitable for inclusion in arrangements for prescribing by nurse practitioners.

In accordance with subsection 101(3BA) of the *National Health Act* 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of material available to it at its November 2013 meeting, eribulin should not be treated as interchangeable on an individual patient basis with any other listed drugs or medicinal preparations.

The PBAC noted that the submission does not meet the criteria for an Independent Review.

Outcome:
Recommended

Name, Restriction, Manner of administration and form	Max Amt	№.of Rpts	Proprietary Name and Manufacturer
ERIBULIN MESILATE eribulin mesilate 1 mg/ 2 mL injection, vial	3mg	13	Halaven Eisai

Severity:	Locally advanced or metastatic
Condition:	breast cancer
Restriction:	Section 100 (Efficient Funding of Chemotherapy) Private Hospital and Private Clinic Authority Required Public Hospital Authority Required (STREAMLINED)
Clinical criteria:	Patient must have progressive disease AND Patient must have failed at least two prior chemotherapeutic regimens for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition
Administrative advice	A patient who has progressive disease with eribulin is no longer eligible for PBS-subsidised eribulin.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor is pleased with the PBAC recommendation and is working towards a PBS listing.