Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Eribulin mesilate

Proprietary Product Name: Halaven

Sponsor: Eisai Australia Pty Limited

May 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://ww.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New Chemical Entity
Decision:	Approved
Date of Decision:	30 August 2012
Active ingredient:	Eribulin mesilate
Product Name:	Halaven
Sponsor's Name and Address:	Eisai Australia Pty Ltd 288-292 Churchill Avenue Subiaco WA 6008
Dose form:	Solution for injection
Strength:	1 mg/2 mL (equivalent to 0.88 mg eribulin per vial)
Container:	Glass vial
Pack sizes:	1 and 6 vials
Approved Therapeutic use:	Halaven 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.
Route of administration:	Intravenous (IV) infusion
Dosage (abbreviated):	Halaven 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. The recommended dose of Halaven as the ready to use solution is 1.4 mg/m^2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21 Day Cycle.
ARTG Number:	187136

Product background

This AusPAR describes the application by Eisai Australia Pty Ltd (the sponsor) to register the new chemical entity, eribulin mesilate,[1] for use in the treatment of breast cancer.

Eribulin mesilate is a non-taxane, microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. Eribulin is a structurally simplified synthetic analog of halichondrin B, a natural product isolated from the marine sponge Halichondria okadai. Eribulin is stated to inhibit the growth phase of microtubule dynamics without affecting the shortening phase and to sequester tubulin into non-productive aggregates.

Regulatory status

The product received initial Australian Register of Therapeutic Goods (ARTG) Registration on 4 September 2012. At the time of the Australian application, eribulin mesilate was approved in 37 countries, including the USA (in November 2010), Canada (December 2011) and 27 European countries (March 2011).

Product Information

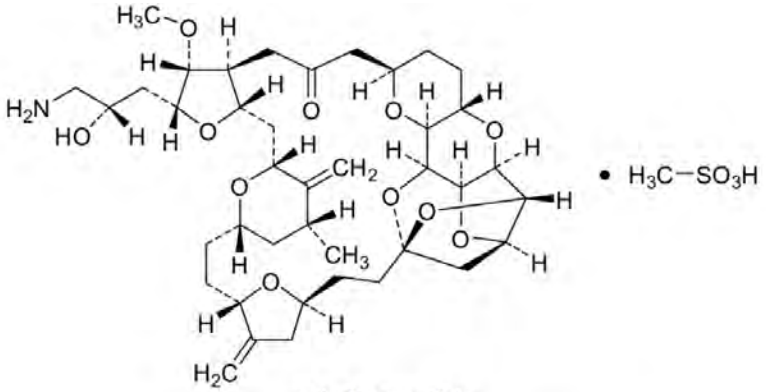
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Eribulin is new chemical entity. It is an unusually complex, fully synthetic, polycyclic ether, proposed for use in the treatment of breast cancer.

Eribulin is entirely synthetic; it does not appear to be structurally related to other drugs. It is probably the most complex synthetic drug substance which has been proposed for registration to date. It is chiral with 19 asymmetric carbons; it is presented as a single enantiomer. The drug substance is the mesilate salt. The structure and molecular weight (MW) of eribulin mesilate are shown in Figure 1:

Figure 1. Structure of eribulin mesilate.



[1] Note that 'eribulin mesilate' and 'eribulin' are used interchangeably in this AusPAR.

Drug substance

Eribulin is a structurally simplified analogue of halichondrin B, a natural product isolated from a marine sponge (Halichondria okadai). Whereas halichondrin B is a macrocyclic lactone, eribulin is carbocyclic. Eribulin also has a pendant primary amine group (making it basic and allowing salt formation), while halichondrin B is non-nitrogenous.

Eribulin mesilate is soluble in both water (with some pH dependence) and ethanol. Controls on the drug substance are considered acceptable.

Drug product

Halaven is a clear, colourless aqueous solution for injection containing 1 mg eribulin mesilate in 2 mL of solution. The injection is formulated with ethanol, hydrochloric acid, sodium hydroxide and water for injection. It is filled into (relatively large) 5 mL glass vials with Teflon-coated, butyl rubber stoppers and flip-off aluminium seals. The pack sizes are cartons of 1 or 6 vials.

Eribulin mesilate is soluble in water. The ethanol is included for manufacturing convenience. The same solution formulation has been used in all clinical studies.

Sterility and endotoxin aspects are acceptable. Chemistry and quality control aspects for the injection are considered acceptable.

According to the proposed PI, the recommended dose is 1.4 mg/m^2 (mass of eribulin mesilate) administered IV over 2 to 5 minutes on Days 1 and 8 of a 21 Day Cycle. Dose reduction to 0.7 mg/m^2 is recommended under various clinical circumstances. The dose "may be" diluted in up to 100 mL of 0.9% saline but can also be given by direct injection. (The saline diluted infusion is acceptably stable, whereas dilution in 5% glucose injection led to formation of an unidentified reaction product, probably from reaction of the primary amine and the anomeric carbon of glucose).

Labelling

The proposed Australian Approved Name (AAN) eribulin mesilate follows the current International Nonproprietary Name (INN) convention in using mesilate, not mesylate. The TGA is currently planning for a transition of older AANs to corresponding INNs, which will include changing the names of various mesylates currently in use.

Each Halaven vial contains a nominal 1.0 mg of eribulin mesilate, equivalent to 0.88 mg of eribulin base. (An overfill volume is actually used to ensure that this labelled content can be removed from the vial.) Current practice, however, is to label the amount of the active moiety (that is, eribulin 0.88 mg), not the amount of the salt (1.0 mg).

The sponsor argued for the proposed labelling (1.0 mg) on the basis that, without the 'round' label claim, various recommended reduced dosages would become confusing and may lead to dosing errors. However, there is now no international consistency, with Europe labelling[2] the product as 0.88 mg per vial but the USA labelling it as 1 mg per vial. The European dosing direction is then 1.23 mg/m^2 eribulin, not 1.4 mg/m^2. Labelling consistent with the European product is recommended, in keeping with guidelines adopted in Australia.

Other significant revisions to the presentation (both labels and PI) are suggested. Details of these are beyond the scope of this AusPAR.

Bioavailability

No bioavailability or pharmacokinetics (PK) data are reviewed by the TGA for intravenous (IV) solutions.

[2] European Summary of Product Characteristics for Halaven, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002084/WC500105112.pdf

Pharmaceutical Sub-Committee (PSC) considerations

The submission was considered at the 143rd meeting of the PSC (2012/1). The PSC endorsed all of the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic issues and had no objection to the registration, if all outstanding issues were addressed to the satisfaction of the TGA. The PSC explicitly supported tightening impurity limits for the drug substance and labelling in terms of the active moiety, eribulin base. Impurity limits have now been tightened.

Recommendation

Registration is recommended with respect to chemistry and quality control aspects. The labelling issues with the presentation will be finalised after the Advisory Committee on Prescription Medicines (ACPM) meeting.

III. Nonclinical findings

Introduction

Most of the submitted nonclinical studies were of high quality and were in general accordance with the Guideline[3] on the *Nonclinical Evaluation for Anticancer Pharmaceuticals* (2009). Pivotal studies examining the repeat-dose toxicity and genotoxicity of eribulin were conducted under Good Laboratory Practice (GLP) conditions. Safety related studies not performed under GLP were conducted in established laboratories and were mostly adequately documented.

Animals in several studies were euthanised at the end of 14 day recovery periods, with no animals euthanised at the end of the dosing period. Therefore, acute or transient treatment related effects occurring directly after dosing were not assessed in those studies and the toxicity of eribulin may have been underestimated. Also, the exposures to eribulin mesilate were subclinical in the animal studies, and therefore the full spectrum of safety issues may not have been adequately addressed in the submitted dossier. This was for the most part unavoidable as the maximum feasible dose was used in the pivotal toxicity studies.

Pharmacology

Primary pharmacology

Consistent with other microtubule inhibitors including paclitaxel, vinblastine and vinflunine, eribulin inhibits tubulin polymerisation and microtubule dynamics. This inhibition results in interference with mitotic spindle formation, leading to GAP 2/Mitosis (G2/M) cell cycle arrest. This prolonged mitotic blockage can lead to apoptotic cell death.[4,5]

Eribulin predominantly inhibits microtubule growth, but not shortening, and sequesters tubulin into non-productive aggregates. This is in contrast to other antimitotic drugs (such as vinblastine and paclitaxel) that suppress both the shortening and growth phases of microtubule dynamic instability. The result of the inhibition of microtubule growth is formation of abnormal mitotic spindles that cannot pass the metaphase/anaphase checkpoint.[6]

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) tripartite Guideline: EMEA/CHMP/ICH/646107/2008

[4] Towle M.J. *et al*. *In vitro* and *in vivo* anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. *Cancer Res* 2001;61:1013–1021.

[5] Kuznetsov G. *et al*. Induction of morphological and biochemical apoptosis following prolonged mitotic blockage by halichondrin B macrocyclic ketone analog E7389. *Cancer Res* 2004;64: 5760–5766.

[6] Jordan M.A. *et al.* The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. *Mol Cancer Ther* 2005;4:1086–1095.

In *in vitro* primary pharmacodynamic (PD) studies, eribulin mesilate inhibited the growth of a wide range of established human cancer cell lines at half-maximal inhibitory concentration (IC_{50}) values in the nanomolar range. Human cell lines tested included breast cancer cells (MDA-MB-231, MDA-MB-435, MDA-MB-468 and HCC1806), ovarian cancer cells (A2780/1A9), small cell lung cancer cells (NCI-H82), non-small cell lung cancer cells (H23, H441, H520, H522-T1), colon cancer cells (HT-29, COLO 205 and DLD-1), FaDu pharyngeal squamous cell carcinoma (head and neck cancer) cells, promyelocytic leukemia cells (HL-60), melanoma cells (LOX), histiocytic lymphoma cells (U937), prostate cancer cells (LNCaP and DU 145), and uterine sarcoma cells (MES-SA).

Eribulin mesilate showed comparable antiproliferative activity against paclitaxel-resistant (with mutated β-tubulin) 1A9PTX10 and 1A9PTX22 human ovarian carcinoma cells, compared with the parent cell line (non-resistant) A2780/1A9. In contrast, eribulin showed reduced potency *in vitro* against multi-drug resistant (with P-glycoprotein (P-gp) over expression) MES-SA/Dx5-Rx1 human uterine sarcoma cells, compared with the parent cell line (MES-SA). There was no *in vitro* study on the activity of eribulin on drug-resistant breast cancer cells.

In conclusion, eribulin mesilate inhibits tumour cell growth *in vitro* in a wide range of established human cancer cell lines.

In vivo studies showed that administration of eribulin mesilate causes the delay of tumour growth and in some cases complete regression of a variety of human cancer xenograft models grown subcutaneously (SC) in athymic mice at a range of doses between 0.05 and 1.7 mg/kg/dose (0.15-5.1 mg/m^2/dose, compared with the clinical dose of 1.4 mg/m^2); higher doses were lethal. A variety of dosing schedules was used, ranging from every 1 to 7 days for 1 to 4 weeks. The cancer models grown SC in these studies were NCI-H82 (small cell lung), U251 (glioblastoma), MDA-MB-435, UISO-BCA-1 and MX-1 (breast), NCI-H522 and NCI-H322M (non-small cell lung), PANC-1 (pancreas), HT-1080 (fibrosarcoma), SR475 (head and neck), COLO 205 (colon), LOX (melanoma), and NIH:OVCAR-3 (ovary), and the treatments were started between 3 and 40 days after implantation of the tumour. In general, the anticancer effect was higher when the treatment was started closer to the time of tumour implantation.

In studies in SC MDA-MB-435 human breast cancer xenograft models in athymic mice, using a variety of administration schedules, the effect of the frequency of administration was hard to evaluate as the number of deaths and the number of complete tumour regression seemed to depend more on the dose than on the frequency of administration. Doses at 0.25 mg/kg every 2 days (3 doses/week) for 4 weeks, or 1.5 mg/kg every 4 days or once a week for 3 weeks significantly suppressed tumour growth. Daily dosing of ≥ 0.9 mg/kg, equivalent to 2.7 mg/m^2) was lethal to the tumour bearing mice.

The effect of eribulin mesilate on lifespan was evaluated in intracranial human cancer xenograft studies using the U251 and SF-295 human glioblastoma models in athymic mice. Eribulin doses of 0.22-0.8 mg/kg daily or every 2 days for 2 or 3 weeks prolonged the life span only by ≤7 days or < 65%.

Secondary pharmacodynamics and safety pharmacology

No secondary PD studies were submitted for Halaven. The *Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals* (EMEA/CHMP/ICH/646107/2008) states that *'Understanding the secondary pharmacodynamic properties of a pharmaceutical could contribute to the assessment of safety for humans, and those properties might be investigated as appropriate'.* However, due to the nonspecific cytotoxicity of eribulin mesilate as a result of its primary mode of action as a microtubule inhibitor, and the significant toxicity of microtubule inhibitors even at therapeutic doses, the lack of secondary PD studies is considered acceptable.

Six specialised safety pharmacology studies covered the central nervous system (CNS), peripheral nervous system (PNS), and the cardiovascular and respiratory systems. All studies except the PNS one were GLP compliant.

Intravenous administration of eribulin to rats at ≤ 0.25 mg/kg produced no effects on respiratory or central nervous system (CNS) function. Administration to mice of ≥ 0.88 mg/kg IV every 2 days, 3 times per week for 2 weeks, caused axonopathy of the sciatic nerve and dorsal root ganglia, although there were no observed effects of eribulin on nerve conduction velocity or amplitude in caudal and digital nerves at doses up to the maximum tolerated dose (MTD) of 1.75 mg/kg/dose. Axonopathy of dorsal root ganglia (but not the sciatic nerve) also occurred in rats treated with paclitaxel in the same study. Results from the repeat dose toxicity studies (sciatic nerve fibre degeneration in rats, discussed below) further support the finding that eribulin mesilate affects peripheral nerve function. The mechanism of neurotoxicity may involve the drug's perturbation of neurofilament structure and function, secondary to its binding to tubulin, as hypothesised for some other agents.[7,8] The potential effects on the PNS is adequately addressed in the proposed PI document with a warning that patients should be closely monitored for signs of peripheral motor and sensory neuropathy.

In vitro treatment with 30 μM eribulin mesilate produced no inhibition of human ether-à-go-go-related gene (hERG) potassium currents in HEK293 cells or effects on action potential parameters in isolated Purkinje fibres of dogs. In conscious dogs, following a single IV infusion for 60 min of 0.04 mg/kg eribulin mesilate, there were no effects on body temperature or the electrocardiogram (EGC) parameters PR interval, QRS duration and QT interval. However, there were decreased systolic and diastolic blood pressures, mean arterial pressure and heart rate, and prolonged RR interval ≥ 30 minutes after the start of infusion. The potential for cardiac arrhythmias was only explored in a very limited manner (ECG only examined in 1 study in dogs, with no findings) in the general repeat dose toxicity program. However, it is noted that the proposed PI document includes a precaution that QT prolongation[9] was observed on Day 8 of an uncontrolled, open label ECG study in 26 patients, independent of plasma eribulin concentration.

Although the results from these studies suggest that eribulin mesilate has a low potential for exerting adverse effects on the respiratory and central nervous systems, plasma levels are estimated to be subclinical in these studies and thus, little weight can be placed on the negative findings. There were no clinical signs of CNS toxicity or respiratory depression in repeat-dose toxicity studies in rats and dogs, but again plasma levels of eribulin mesilate were similar to or below clinical plasma levels. Therefore, the submitted animal studies are not adequate to predict potential acute adverse CNS or respiratory effects.

Pharmacokinetics

After IV administration, dose proportionality was difficult to assess due to variability of exposure and low numbers. In PK IV studies (3 doses each), no accumulation was observed in mice or dogs, but it was observed in rats. In the pivotal repeat-dose toxicity studies, toxicokinetics was evaluated using a dosing schedule of every 7 days and 3 doses per Cycle for 6 Cycles with 14 day recovery after each Cycle. In these studies, the area under the plasma concentration-time curve (AUC) in rats and dogs was higher on Day 141 (after 16 doses) than on Day 1, with the exception of female dogs at the higher dose. In general, the terminal plasma half life ($t_{½}$) of eribulin was long (4-12 h in mice, 4.3-28 h in rats, 11-45 h in dogs, and 27-66 h in human). Clearance was slow to moderate (0.9-2.8 L/h/kg in mice, 1.4-2 L/h/kg in rats, 0.7-1.1 L/h/kg in dogs, 1.16-2.5 L/h/m^2 in humans).

After single IV administrations of radiolabelled (^{14}C)-eribulin acetate to male rats, volume of distribution was large, with eribulin distribution to most organs and tissues. Penetration of the blood-brain barrier was very poor, and no affinity for melanin was observed. Transfer through the placenta or through mammary gland into milk was not evaluated.

[7] Minami Y., Murofushi H. and Sakai H. Interaction of tubulin with neurofilaments: formation of networks by neurofilament-dependent tubulin polymerization. *J. Biochem* 1982;92:889–898.
[8] Sager P.R. and Matheson D.W. Mechanisms of neurotoxicity related to selective disruption of microtubules and intermediate filaments. *Toxicology* 1988;49:479–492.
[9] The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) is a risk factor for ventricular tachyarrhythmias and sudden death.

Concentration independent protein binding by eribulin was only moderate in human plasma (approximately 49-65% bound) and similarly low in the plasma of the laboratory animal species examined (29-36% for mouse, 23-34% for rat and 17-26% for dog). At plasma concentrations in patients at the proposed clinical dose and detected in animal toxicity studies, the protein binding is approximately 34% for rats, 26% for dogs and 57% (mean value of 65% at 100 ng/mL and 49% at 500 ng/mL) for humans. These protein binding values are taken into consideration in the calculation of animal/human exposure ratios.

Following single IV administration, eribulin mesilate showed penetration into LOX human melanoma tumour xenografts in mice (tumour exposures > 20 times that in plasma). Repeated administration into mice caused tumour regression of the same xenograft model.

Twelve putative metabolites of eribulin mesilate identified or postulated, were primarily isomeric monohydroxylates. Unchanged eribulin was by far the dominant circulating species in rats and dogs as observed in humans. Cytochrome P450 3A4 (CYP3A4) was identified as the P450 isoform chiefly responsible for the limited metabolism of the drug in *in vitro* experiments.

Following single IV dosing with ^{14}C-eribulin acetate, excretion of radioactivity was primarily *via* the faeces in humans, rats and dogs (approximately 82%, 65% and 86% of the dose, respectively). In bile, high concentrations were found (making it a likely major route for excretion), while only between 9% (humans and dogs) and 15% (rats) of dosed radioactivity was excreted in the urine (which seems to be the secondary route of elimination). Most of the administered dose is excreted unchanged.

In bile-duct cannulated rats, biliary excretion was demonstrated after IV dosing. The detection of radioactivity in the faeces of these animals suggested possible excretion directly across the gut wall. After a single oral dose, peak plasma concentrations were typically reached within 4 h in mice and rats. Bioavailability of eribulin after oral administration (although not relevant for the proposed route of administration) was low (< 7% in mice and < 2.5% in rats). In P-gp deficient mice and in rats receiving a P-gp inhibitor, the bioavailability after oral administration was significantly higher (53% for mice and 18% for rats). In P-gp deficient mice, brain tissue penetration after IV dosing was increased (compared with wild-type mice), with brain exposure (AUC) being more than twice that of plasma. Taken together, these results confirm that eribulin mesilate is a substrate for P-gp (which is present in the brain-blood barrier, and which also may contribute to biliary excretion of eribulin).

The PK profiles in the laboratory animal species used in the pivotal repeat-dose toxicity studies was sufficiently similar to allow them to serve as appropriate models for the assessment of drug toxicity in humans.

Pharmacokinetic drug interactions

In human liver microsomes *in vitro*, eribulin mesilate inhibited CYP3A4 activity with concentrations required to decrease the maximal rate of the reaction to half (Ki values) ranging from 3-30 μM (2.2-22.2 μg/mL compared with the clinical maximum concentration (Cmax) of 0.519 μg/mL). Eribulin may inhibit CYP3A4 at the proposed clinical dose.

Eribulin mesilate did not significantly inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP2E1; nor did it induce CYP1A, CYP3A, CYP2C9 or CYP2C19. Based on this data, and given the limited contribution of metabolism to the clearance of eribulin mesilate, the elimination of eribulin is unlikely to be significantly affected by CYP450 inhibitors or inducers, and eribulin is unlikely to affect the PK of drugs that are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP2E1.

In an *in vitro* assay with the human intestinal Caco-2 cells and digoxin as the substrate, eribulin mesilate displayed only weak inhibitory activity against P-gp at >1 μM, with a IC_{50} value of >10 μM (>7.3 μg/mL compared with the clinical C_{max} of 0.519 μg/mL). Inhibition of P-gp is unlikely in clinical practice. As discussed above, eribulin is a substrate of P-gp and is mainly eliminated by biliary excretion. P-gp inhibitors may decrease elimination and increase plasma concentrations of eribulin.

Toxicity

Acute toxicity

No single-dose toxicology studies were submitted. This is in accordance with the current recommendations from the European guidelines (CHMP/SWP/302413/08 and EMA/CHMP/SWP/81714/2010),[10] although these guidelines have not been adopted by the TGA. The acute toxicity of eribulin mesilate is addressed by the preliminary repeat dose studies in rats and dogs (see discussion below).

Repeat-dose toxicity

Repeat dose toxicity studies were conducted with IV infusion (clinical route) of eribulin in rats and dogs. All except two non-pivotal studies were conducted according to GLP principles. The treatment schedules in the studies consisted of 3 doses, each administered every 4 or 7 days (Q4D × 3 or Q7D × 3) followed by 3, 14 or 26 days recovery period. Two studies (one using rats and one using dogs) included 6 Cycles of 3 times weekly treatments followed by 14 days recovery period (total of 18 doses and 169 days). The choice of species (rat as the rodent and dog as the non-rodent species), the duration of pivotal studies, group sizes, and the use of both sexes were consistent with International Conference on Harmonization (ICH) guidelines.

In the repeat dose toxicity studies, eribulin mesilate caused toxicity of the haematopoietic and lymphoid organs (with atrophy of the bone marrow, thymus and lymphoid tissue, and decrease in peripheral blood cell counts), non-reversible testicular degeneration, and hepatic toxicity (liver necrosis and increase in hepatic enzymes) and effects on the PNS.

In safety pharmacology studies, infusion of IV eribulin for 60 min at 0.04 mg/kg in dogs (0.6 times the exposure in humans based on body surface area (BSA in m^2)), transiently decreased systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate, and prolonged RR interval ≥ 30 minutes after the start of infusion. Body temperature, PR interval, QRS duration or QT interval was unaffected. In a repeat dose toxicity study, no effects in ECG evaluations were observed when dogs received up to 0.045 mg/kg/dose; however, it was not documented in the study report when ECG was undertaken after dosing. In human clinical trials, QT prolongation was observed after 2 doses of eribulin mesilate (and not after 1 dose). In safety pharmacology assessments, treatment with 30 μM eribulin produced no inhibition of HERG tail current in HEK293 cells, or effects on cardiac action potentials in isolated dog Purkinje fibers, suggesting low potential for QT interval prolongation in patients. Based on the safety pharmacology study in dogs, caution should be exercised in patients with heart diseases or taking other medicines known to affect the cardiovascular system.

In a safety pharmacology study, axonopathy of the sciatic nerve and of dorsal root ganglia was observed in mice receiving eribulin IV every 2 days 3 times weekly for two weeks at dose levels of ≥ 0.88 mg/kg/dose, although there were no effects of eribulin on nerve conduction velocity or amplitude in caudal and digital nerves, with doses of up to 1.75 mg/kg/dose. Intravenous administration of eribulin to rats at 0.1 or 0.25 mg/kg produced no effects on respiratory or CNS function, and central neurotoxicity was not observed in the repeat-dose toxicity studies. In repeat-dose toxicity studies, non-reversible sciatic nerve fibre degeneration was observed at 0.2 mg/kg/dose in rats (relative exposure 0.1 based on AUC), and transient skeletal myocyte degeneration was observed also in rats at 0.2 mg/kg/dose (relative exposure 0.9 based on BSA). Toxicity of the PNS has been reported for other approved cytotoxic agents and it is addressed in the proposed PI document, in which it is advised that patients are closely monitored for signs of peripheral motor and sensory neuropathy.

Thymus atrophy was observed in both rats and dogs. In rats, thymus atrophy occurred at ≥ 0.1 mg/kg/dose (relative exposure ≥ 0.03 based on AUC) where necropsies were performed ≤ 6 days after the final dose. Thymic atrophy was not observed in rats receiving > 0.1 mg/kg/dose

[10] Questions and answers on the withdrawal of the *'Note for guidance on single dose toxicity'*.

after a recovery of between 11 and 23 days. In the only dog study in which 1 dog/sex was necropsied 3 days after the last dose (all the others had a 14 day recovery period), thymic atrophy was not observed at up to 0.04 mg/kg/dose (relative exposure 0.2 based on AUC). Of the dog studies in which necropsies were performed after a 14 day recovery period, thymic atrophy was only observed when eribulin mesilate was administered for 6 Cycles (relative exposure 0.05 based on AUC). It appears that thymic atrophy occurs early after dosing in rats and is reversible, and in dogs it occurs after repeated cycles of administration and it is not reversible within 14 days. Due to the low exposures at which thymus toxicity was observed in rats and dogs, it is expected that the potential for thymic toxicity in humans is high.

Bone marrow atrophy or hypocellularity consistently occurred in rats receiving eribulin at ≥ 0.1 mg/kg/dose (relative exposure ≥ 0.03 based on AUC). In contrast dogs displayed bone marrow hypercellularity or hyperplasia at between 0.045 (relative exposure ≥ 0.04 based on AUC) and 0.075 mg/kg/dose (relative exposure 1.1 based on BSA). The effect on the bone marrow of the rats was transient when 1 cycle of treatment was administered and was still present in dogs and rats 14 days after the last of 6 treatment cycles. Effects in the thymus and the bone marrow were usually associated with extramedullary haematopoiesis and with reductions in leukocyte populations and red blood cells (red blood cell counts, haemoglobin, haematocrit) in both species examined. In *in vitro* studies in which the myelotoxicity of eribulin mesilate was evaluated, eribulin mesilate inhibited cultured bone marrow cells from humans, dogs and mice, with IC_{50} values of 0.5-0.6 nM for human, 0.4 nM for dog, and 1-2.2 nM for mouse cells. In another study, the IC_{50} values for inhibiting proliferation of multipotential bone marrow stem cells were around 15.9 nM for human, 11.4 nM for dog, and 147.9 nM for mouse cells. The human cells were more sensitive to eribulin mesilate than to paclitaxel and vinblastine, and values for human cells are below the clinical C_{max} of 0.6-0.7 μM. Bone marrow toxicity is expected after administration of eribulin mesilate to patients.

Spleen weight was increased after rats received 0.15 mg/kg/dose (relative exposure 0.1 based on AUC) 3 times for 6 Cycles with a 14 day recovery period after each Cycle. In another study, spleen weight was not increased 3 days after the last of 3 doses in rats receiving up to 0.25 mg/kg/dose but it was increased 14 days after the last dose in rats receiving ≥ 0.2 mg/kg/dose (relative exposure ≥0.1 based on AUC) in the same study. Increased spleen weights were probably secondary to compensatory increased extramedullary haematopoiesis. Non-reversible (within 24 days) lymphoid atrophy of the spleen was also observed in dogs receiving ≥ 0.03 mg/kg/dose (relative exposure ≥0.12 based on AUC). Peyer's patch lymphoid depletion (in males) and mesenteric lymph node lymphoid depletion were observed in dogs receiving 0.045 mg/kg/dose (relative exposure 0.05, based on AUC). Since lymphoid depletion occurred at low relative exposures and included non-reversible effects on the spleen, it is expected that lymphoid depletion occurs in patients due to the administration of eribulin mesilate.

Liver effects were observed in rats, such as increase in liver weight at ≥ 0.05 mg/kg/dose (relative exposure 0.03-0.13 based on AUC), increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cholesterol at 0.15 mg/kg/dose (relative exposure 0.13 based on AUC), and focal liver necrosis at ≥0.015 mg/kg/dose in males (associated with bacterial infections). This is consistent with findings in the clinical trials, in which increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were common adverse effects. In dogs, liver effects were not observed up to doses of 0.04 mg/kg/dose and relative exposures of 0.2 (based on AUC). Only in moribund dogs which had received 2 doses of 0.075 mg/kg (relative exposure 1.5 based on BSA), signs such as alkaline phosphatase elevation and albumin decrease were observed, associated with significant GIT toxicity.

Gastrointestinal (GIT) findings included necrosis and hyperplasia of intestine crypts/glands and small intestine villous atrophy, and GIT clinical signs such as emesis and diarrhoea. These dogs also presented decreases in the level of electrolytes (sodium, potassium and chloride), together with increased blood urea nitrogen. Rats receiving doses of 0.15 mg/kg/dose (relative exposure 0.12 based on AUC) in the 6 month study, showed increased kidney weights, without histopathological or electrolyte changes. The animal studies predicted the clinical trial findings in terms of renal and GIT effects. In clinical trials, renal disorders were uncommon as adverse effects, whereas GIT adverse effects (such as nausea, constipation, diarrhoea and vomiting) were very common.

Non-reversible testicular atrophy and hypocellularity and epididymal hypospermia or aspermia was observed in rats receiving ≥ 0.15 mg/kg/dose (relative exposure of 0.13, based on AUC). In dogs, a non-reversible decrease in testes weight, and hypocellularity of epididymides and testes were observed at 0.045 mg/kg/dose (relative exposure 0.06 based on AUC). Hypospermia/apermia of the epididymides was also observed in one out of 4 dogs at lower doses (0.0045 and 0.015 mg/kg), without testicular findings. Since the testes and epididymides were clearly target organs of toxicity, the low incidence of epididymyal changes even without observable testicular effects was probably related to eribulin treatment.

The repeat dose toxicity studies revealed a toxicological profile for eribulin mesilate that is similar to other approved anti-microtubule agents, and is consistent with the expected effects of a microtubule disruptor, with atrophy/degeneration produced in those tissues with rapidly dividing cells as well as cytopenias and peripheral neuropathy. Eribulin presents a high order of acute toxicity via the clinical route.

Relative exposure

Exposure ratios have been calculated based on animal:human plasma AUC from time zero to 24 h ($AUC_{0-24\,h}$) values for eribulin and plasma protein binding of approximately 34% for rats, 26% for dogs and 57% (mean value of 65% at 100 ng/mL and 49% at 500 ng/mL) for humans (see Tables 1 and 2, below). Very low multiples of the anticipated clinical systemic exposure were obtained in the animal studies. Exposure data for the dose levels used come from toxicokinetic analyses performed in the pivotal studies. With administration once per week during 3 weeks, exposures in rats or dogs were below the anticipated clinical systemic exposure level, with animal doses limited by mortality.

Table 1. Relative exposure in repeat-dose toxicity studies

Study details	Dose (mg/kg/dose)	Dose (mg/m² IV)	Day of sampling	$AUC_{0\text{-}24\ h}$* (ng.h/mL)		Normalised AUC♣		Normalised exposure ratio#♣	
				male	female	male	female	male	female
7306 Fischer F-344 **rats** Days 1, 8, 15 (Q7D×3)	0.1	0.6	15	35.1	16.5	23.2	10.9	0.06	0.03
	0.2	1.2	15	59.3	49.9	39.1	32.9	0.10	0.08
	0.25	1.5	15	77.4	61.4	51.1	40.5	0.13	0.10
7640 Fischer F-344 **rats** Q7D×3 with 14 day recovery (× 6 Cycles)	**<u>0.015</u>**	0.09	141	5.3@ ($_{0\text{-}1h}$)	4.7$ ($_{0\text{-}2h}$)	3.5	3.1	0.01	0.01
	0.05	0.3	141	18.3 ($_{0\text{-}4h\ to\ 0\text{-}8h}$)	22.3 ($_{0\text{-}8h\ to\ 0\text{-}24h}$)	12.1	14.7	0.03	0.04
	0.15	0.9	141	79.2	73.1^	52.3	48.2	0.13	0.12
G465520D (a) Beagle **dogs** Days 1, 5, 9 (Q4D×3)	0.03	0.6	9	177.0$	61.9	131.0	45.8	0.33	0.12
	0.04	0.8	9	109.1	96.0	80.7	71.0	0.21	0.18
6288 Beagle **dogs** Days 1, 8, 15 (Q7D×3)	**<u>0.014</u>**	0.3	15	8.9	5.5	6.6	4.1	0.02	0.01
	0.028	0.6	15	23.0	14.5	17.0	10.7	0.04	0.03
	0.035	0.7	15	28.0	26.6	20.7	19.7	0.05	0.05
6528 Beagle **dogs** Q7D×3 with 14 day recovery (× 6 Cycles)	**<u>0.0045</u>**	0.09	141	3.5 ($_{0\text{-}1h\ to\ 0\text{-}24h}$)	2 ($_{0\text{-}1h\ to\ 0\text{-}2h}$)	2.6	1.5	0.007	0.004
	0.015	0.3	141	8.7 ($_{0\text{-}2h\ to\ 0\text{-}24h}$)	7.4 ($_{0\text{-}1h\ to\ 0\text{-}8h}$)	6.4	5.5	0.02	0.01
	0.045	0.9	141	29.3	21.1 ($_{0\text{-}4h\ to\ 0\text{-}24h}$)	21.7	15.6	0.06	0.04
DDD2005-39 (Study 101 PK) 1-h IV infusion on Days 1, 8, 15 of a 28 Day treatment Cycle (n=4 **patients** with advanced solid tumours)	–	1.4 mg/m²	15	913 (a)		392.6		–	

*=unless otherwise stated; #=calculated as animal:human AUC considering exposure in animals following each administration; a= the value was expressed as $AUC_{0\text{-}infinity}$; $=result from 1 animal; @=result from 2 animals; ^=result from 3 animals as the 4th animal died; No Observable Adverse Effect Levels (NOAELs) are underlined; -=not applicable; ♣=Normalised using fraction unbound to proteins (protein binding values used were 34% for rats, 26% for dogs and 57% for humans).

Mortality

Table 2. Relative exposure at which drug related deaths occurred in repeat-dose toxicity studies

Study details	Species	Dose		$AUC_{0\text{-}24\ h}$* ng.h/mL	Drug related deaths*	Relative exposure	
		mg/kg	mg/m²			AUC♣	mg/m²
7306 Q7Dx3 n=10/sex	Rats	0.2	1.2	59.3 (♂)	2/10♂(1-2 doses)	0.1	0.9
		0.25	1.5	77.4 (♂)	1/10♂ (1 dose)	0.13	1.1
G465520A Q4Dx3 n=3♂	Rats	0.25	1.5	-	1/3 (3 doses)	-	1.1
		0.75	4.5	-	3/3 (2 doses)	-	3.2
		1	6	-	2/3 (2 doses)	-	4.3
		1.5	9	-	3/3 (1 dose)	-	6.4
		2	12	-	3/3 (1 dose)	-	8.6
G465520B Q4Dx3 n=1/sex	Dogs	0.075	1.5	-	2/2 (2 doses)	-	1.1
DDD2005-39 (Study 101 PK) Q7Dx3 n=4 patients with cancer	Humans	-	1.4	913	-	-	-

*=or sacrificed moribund; ♣=Normalised using fraction unbound to proteins.

One or two IV doses of 0.2 or 0.25 mg/kg eribulin mesilate caused 10-20% of the male rats to die (at relative exposures of approximately 0.1 based on AUC and 0.9 based on BSA). Two IV doses of 0.75 mg/kg in rats (relative exposure of 3.2 based on BSA) and 2 doses of 0.075 mg/kg in dogs (relative exposure of 1.1 based on BSA) were lethal to all the animals. Mortality in rats was associated with thymic atrophy, bone marrow and testicular toxicity, and sciatic nerve fibre degeneration, whereas mortality in dogs was associated with diarrhoea, emesis, and intestinal histopathological changes.

The maximum non lethal doses for eribulin mesilate by the IV route were < 0.15 mg/kg/dose in rats, and 0.045 mg/kg/dose in dogs, and the maximum exposures achieved with these doses were below the anticipated clinical exposure (0.12 times the clinical $AUC_{0\text{-}24\ h}$ in rats and 0.05 times in dogs). The low relative exposures at which deaths were observed are a significant issue, as the animals used in the studies were healthy, not like cancer patients undergoing therapy with eribulin mesilate. Eribulin mesilate has a high order of toxicity.

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered only embryofetal development in rat study with a small number of animals (8/group). Because the doses were limited by maternal toxicity, maximum exposures achieved in the study (based on BSA) were below the anticipated clinical exposure.

In the developmental toxicity study, pregnant rats which received IV infusions of eribulin mesilate during organogenesis on gestation days 8, 10, and 12, displayed increased incidence of embryofetal death/early resorptions and decreased fetal weights at 0.10 and 0.15 mg/kg (0.43 and 0.64 times the recommended human dose based on dose per BSA, mg/m²) and severe external or soft tissue malformations in offspring at 0.15 mg/kg.

Malformations included the absence of lower jaw, tongue, stomach and spleen. Maternotoxic effects were observed at ≥ 0.43 times the recommended human dose, based on BSA (mg/m^2), and included enlarged spleen, reduced maternal weight gain and decreased food consumption.

In conclusion, administration of eribulin mesilate to pregnant rats caused embryotoxicity and fetotoxicity at 0.43 times the recommended human dose based on BSA (mg/m^2), and teratogenicity at 0.64 times the recommended human dose based on BSA (mg/m^2), in rats. The positive teratogenic potential observed is consistent with the pharmacological effect of eribulin mesilate (a microtubule inhibitor).

Nonclinical findings in repeat-dose rat and dog toxicology studies strongly suggest that male fertility may be compromised by treatment with eribulin mesilate. When rats received 6 cycles of 1 dose per week for 3 weeks (with 2 weeks between cycles), small epididymides and hypocellularity of seminiferous epithelium were observed at 0.13 times the exposure expected in humans (based on AUC data). When only 1 cycle was administered to rats, small testes, testicular hypocellularity and epididymal hypospermia or aspermia were observed at ≥ 0.06 times the exposure expected in humans (based on AUC data). When dogs received 6 cycles of 1 dose per week for 3 weeks (with 2 weeks between cycles), decreased testes weight, testicular hypocellularity, and epididymal hypo/aspermia were observed at 0.007 times the exposure expected in humans (based on AUC data). When only 1 cycle was administered to dogs, no testicular toxicity was observed with exposures of up to 0.21 times (based on AUC data); however, as exposures in this study were well-below the anticipated clinical exposure, little weight can be placed on the predictive value of the negative findings. Testicular toxicity in both rats and dogs was not reversible during the recovery period of 14 days.

No studies on fertility or post-natal development were submitted, which is considered acceptable given the intended patient group, that teratogenic potential and embryo-fetal toxicity of eribulin mesilate were demonstrated in the rat embryo-fetal developmental toxicity study at less than the expected clinical exposure, and that irreversible testicular toxicity was observed in both dogs and rats at less than the expected clinical exposure. It is expected that, when administered in humans at the proposed therapeutic dose, eribulin mesilate would cause embryotoxicity, fetotoxicity and teratogenicity, as well as toxic effects in the male reproductive system.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[11] This Pregnancy Category is considered appropriate and consistent with the categories for other microtubule inhibitor anticancer drugs and embryofetal toxicity findings in the rat study.

Genotoxicity

The potential genotoxicity of eribulin mesilate was investigated in two bacterial mutations assays (Ames test), two *in vitro* genotoxicity studies in mammalian cells (mouse lymphoma mutation assays) and one *in vivo* micronucleus assay in rats.

The conduct of the studies was in accordance with ICH guidelines. Concentrations/doses were appropriate and limited by cytotoxicity/bone marrow toxicity. A suitable set of *Salmonella typhimurium* and *Escherichia coli* strains were used in the bacterial gene mutation assay. All assays were appropriately validated.

[11] *Category D is for Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*

Eribulin mesilate was not mutagenic in the Ames test, with or without rat liver microsomal fraction (S9) metabolising enzymes, but (as expected of a microtubule inhibitor) it was positive in the 5178Y/TK$^{+/-}$ mouse lymphoma mutagenesis assay and in the *in vivo* rat micronucleus assays.

Impurities

Several impurities in the drug substance and drug product exceeded the qualification threshold recommended in the ICH Guidelines for impurities Q3A (R) and Q3B (R), that is, 0.15% in drug substance and 1% in drug product, but they have been adequately qualified by repeat dose toxicity and genotoxicity studies.

Carcinogenicity

No carcinogenicity studies were submitted. This is acceptable as carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH Topic S9, Nonclinical Evaluation for Anticancer Pharmaceuticals, EMEA/CHMP/ICH/646107/2008).

Local tolerance

No local tolerance studies were submitted.

Local effects on injection and infusion sites of formulations with concentrations of up to 1 mg/mL were evaluated macro- and microscopically in IV repeated dose toxicity studies in rats and dogs (in which the pH of the formulation used was not stated). In these, no eribulin mesilate related effects were observed at injection and infusion sites. Animals showed local effects such as injection site swelling, oedema, mononuclear cell infiltrates, microgranulomas, fibrosis, folliculitis, vascular inflammation, and perivascular haemorrhage and/or inflammation. These effects were not concentration or dose dependent and were observed even in vehicle control animals. There were no reports of delayed treatment due to venous irritation/blockage but this could have been due to the intervals between IV administrations in the repeat-dose toxicity studies.

The TGA requested the sponsor address the following matter: *The proposed pH for the product is 6-9. As no local tolerance studies were provided, please indicate which toxicity studies used batches in which that range of pH was tested.*

In response, the sponsor stated: *For the five batches used for toxicology studies, no pH data is available from the time of release testing. The pH is only tested for drug product release and none of these batches were processed to drug product. Stand-alone local tolerance studies were not conducted but the injection site was examined histopathologically in all GLP toxicology studies except for one rat study (Study No. G465520C). No significant findings indicating local irritation were noted.*

The reply from the sponsor is acceptable to the TGA.

Potential irritation through the paravenous routes was not assessed in any of the studies, and cannot be ruled out. In the proposed PI document, it is stated that *'There is no evidence that eribulin mesilate is a vesicant or an irritant. In the event of extravasation, treatment should be symptomatic'*. It is noted that the concentration of undiluted eribulin mesilate in the clinical formulation is 0.5 mg/mL and the product can be diluted in saline solution before IV administration.

There is no evidence that eribulin mesilate is an irritant when applied IV but extravasation should be avoided as paravenous irritation is likely.

Paediatric use

Eribulin is not proposed for paediatric use and no specific studies in juvenile animals were submitted by the sponsor.

Nonclinical Summary and Conclusions

- The sponsor has conducted generally adequate studies on the PD, PK and toxicity of eribulin mesilate according to the relevant guidelines. All definitive toxicity studies were conducted under GLP conditions.
- Eribulin inhibits microtubule growth, but not shortening, and sequesters tubulin into non-productive aggregates, resulting in the formation of abnormal mitotic spindles that cannot pass the metaphase/anaphase checkpoint.
- Cytotoxicity to human cancer cell lines was shown in vitro at therapeutically relevant concentrations. Antiproliferative potency was reduced in vitro against multi drug resistant (with P-gp overexpression) cancer cells, but was not reduced against paclitaxel resistant (mutated β-tubulin) cell lines, compared to the parent cell lines. Antitumour activity was demonstrated in vivo against xenografts of breast and other human tumour types borne by nude mice.
- A set of safety pharmacology studies revealed axonopathy of the sciatic nerve and dorsal root ganglia, which is considered to be clinically relevant. In vivo treatment with eribulin mesilate decreased systolic and diastolic blood pressures, mean arterial pressure and heart rate, and prolonged the RR interval, although QT interval (which was prolonged in clinical trials) was not affected. Blood pressure was not examined in toxicity studies.
- The plasma t½ of eribulin mesilate was generally longer in humans (32-66 h) than in laboratory animal species (4-10 h in mice, 4-28 h in rats, and 11–45 h in dogs). Dose proportionality was difficult to assess due to variability of exposure and low numbers. In PK IV studies, no accumulation was observed in mice or dogs but it was observed in rats. IV administration of radiolabelled eribulin mesilate to rats resulted in extensive tissue distribution. Penetration of the blood-brain barrier was very poor and no affinity for melanin was observed. Protein binding was variable among the tested species, with 34% bound to proteins in rats, 26% in dogs and 57% in humans at relevant concentrations.
- Metabolism of eribulin mesilate was very limited and chiefly mediated by CYP3A4. Unchanged eribulin mesilate was the dominant circulating species in all species examined (rats, dogs and humans). Excretion was predominantly via the faeces, with biliary excretion demonstrated in rats. Eribulin mesilate is a substrate for the P-gp drug efflux pump and a weak inhibitor of P-gp. Inhibition of CYP3A4 occurred in human liver microsomes in vitro, with Ki values ranging from 3-30 μM (2.2-22.2 μg/mL, compared with the clinical Cmax of 0.519 μg/mL).
- Pivotal repeat-dose toxicity studies were conducted in rats and dogs (1 or 6 cycles of 1 dose per week for 3 weeks, with 14 day recovery after each cycle). Major toxic effects were evident in the lymphoid (depletion), haematopoietic (bone marrow atrophy/depletion; reductions in red and white cell populations), peripheral nervous (axonopathy/degeneration of sciatic nerve) and male reproductive tissues (atrophy/degeneration of the testes and epididymides). Some effects were also observed in the liver, kidney, GIT and skeletal muscle. These toxic effects occurred at exposure levels below or only marginally higher than the anticipated clinical systemic exposure level.

- Eribulin mesilate displayed a high order of IV toxicity in laboratory animal species, including causing deaths at less than the exposure expected in patients receiving the drug at the recommended clinical dose.
- The potential genotoxicity of eribulin mesilate was examined in the standard battery of tests. Eribulin mesilate was not mutagenic in the Ames test, but was positive in the mouse lymphoma mutagenesis assay and in the in vivo rat micronucleus assays, as expected for a tubulin inhibitor. Carcinogenicity studies were not performed.
- Placental transfer and excretion in milk of eribulin mesilate were not examined. Impairment of male fertility is predicted by the significant gross and microscopic changes in male reproductive tissues observed in rats and dogs in the general toxicity studies, which occurred at low relative exposure levels. Administration of eribulin mesilate to pregnant rats during the period of organogenesis produced embryofetal lethality, decreased fetal weight and teratogenicity at exposure levels below the clinical exposure at the recommended human dose.

Conclusions and recommendation

- Considering the lesser requirements for drugs of its type, the nonclinical studies were sufficient. However, acute or transient treatment related effects occurring directly after dosing were not assessed since animals in pivotal studies were euthanised at the end of 14 day recovery periods, with no animals euthanised at the end of the dosing period.
- Primary pharmacology studies, showing in vitro cytotoxicity and in vivo antitumour activity (including against ovarian carcinoma resistant to paclitaxel), support the drug's use for the proposed indications.
- The lymphoid, haematopoietic, peripheral nervous, hepatic and male reproductive organs were identified as the major targets of eribulin mesilate toxicity in repeat-dose studies. High multiples of the anticipated clinical systemic exposure were not attainable in the repeat-dose studies due to poor tolerance in laboratory animal species. The studies revealed a toxicological profile for eribulin mesilate that is similar to taxanes and other approved cytotoxic agents in terms of the targeted tissues, with atrophy/degeneration produced in those tissues with rapidly dividing cells as well as cytopenias and peripheral neuropathy.
- Eribulin mesilate is clastogenic, consistent with genotoxic profiles of anti-microtubule agents.
- Eribulin mesilate caused deaths in animals at less than the exposure expected in patients receiving the drug at the recommended clinical dose.
- The significant gross and histological changes evident in the general toxicity studies suggest that eribulin mesilate has the potential for impairment of male fertility. Developmental toxicity studies revealed embryolethality, fetotoxicity and teratogenicity in rats at very low relative exposure levels.
- Given the significant toxicity (including lethality) in animal species at exposures less than the human exposure at the recommended clinical dose and absence of examination directly after dosing in the repeat dose toxicity studies, the nonclinical evaluator has reservations regarding the registration of Halaven. However, the application is approvable provided that the above risks identified in animal studies are addressed by the clinical data, and any predicted toxicities can be sufficiently managed in the clinic.

- Several revisions are recommended to nonclinical information in the PI. Details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Background and rationale

The proposed indication for eribulin mesilate stated in the proposed PI is *monotherapy 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.*

> **Evaluator's Comment**: The proposed indication does not require that prior therapy should have included treatment with either capecitabine and/or vinorelbine. However, monotherapy with both capecitabine and vinorelbine could be used in Australia, consistently with their approved indications, for third-line treatment of locally advanced or metastatic breast cancer previously treated with taxanes and anthracyclines. If eribulin is approved for the proposed indication it will be an alternative to capecitabine and vinorelbine for treatment of the proposed patient population.

Rationale

The sponsor's clinical rationale for developing eribulin is based on a *'definite medical need for a new agent that prolongs life.. in patients with advanced breast cancer that has recurred following initial therapy, and that is .. reasonably well tolerated, and can be easily administered in an out-patient setting in order to improve patients' quality of life'*.

> **Evaluator's Comment**: The sponsor's rationale for developing eribulin is acceptable. Breast cancer is the most common cancer among women in Australian.[12] In Australia, capecitabine is the only drug specifically approved for the third-line treatment of locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. In addition, the approved broad indication of vinorelbine for the treatment of breast cancer in Australia could also support its use as monotherapy for the third-line treatment of locally advanced or metastatic breast cancer after anthracyclines and taxanes. However, there are no data suggesting that monotherapy with either capecitabine or vinorelbine provides an overall survival (OS) benefit for women with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Consequently, there is a need for alternate treatments for women with this disease which can offer a survival benefit without causing undue toxicity.
>
> In 2007, breast cancer accounted for 27.1% of all cancer diagnosed in women in Australia, and was the second most common cause of female deaths after lung cancer (2,680 and 2,911 deaths, respectively).[13] It has been estimated that the mean age of

[12] Australian Institute of Health and Welfare & Australian Association of Cancer Registries 2010. Cancer in Australia: an overview 2010. Cancer series no. 60. Cat. no. Can 46. Canberra. AIHW.
[13] ibid

first diagnosis of women with breast cancer in Australia is about 60 years, and the risk of breast cancer occurring in women to 75 years of age to be 1 in 11, increasing to 1 in 9 to 85 years of age. The age standardised rates of death due to breast cancer in women in Australia fell from 30.8 deaths per 100,000 females in 1994 to 22.1 deaths per 100,000 females in 2007, and the five-year relative survival increased following a diagnosis of breast cancer from 72.6% between 1982-1986 to 88.3% between 2000-2006. In 2010, breast cancer was the leading cancer cause of burden of disease for females in Australia accounting for 61,000 disability-adjusted life years (DALYs) with 40,600 years of life being lost due to premature death and 20,500 years of healthy life lost due to disease, disability or injury.[14],[15]

There are no national Australian data on the staging of breast cancer at the time of diagnosis or on relative survival rate according to breast cancer staging, but there are relevant state data from Queensland and NSW. In NSW (1995-2004), around 4% of breast cancer cases in all patients (women and men) were diagnosed when the breast cancer had spread to distant sites. In NSW (1999-2003), the relative 5 year survival for all patients (women and men) diagnosed with breast cancer was lowest for those with "distant" breast cancer (41%) and highest for those with localised tumour (91%). While the NSW data for diagnosis and relative survival based on staging relate to total breast cancer cases (that is, women and men), it is likely that the data for women alone are virtually identical to the total data as nearly all the data relate to women with the disease (for example, 99% of people with breast cancer between 1999 and 2003 in NSW were female).

Scope of the clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety studies. The submission contained the following clinical information:

- 8 clinical pharmacology studies, including 8 that provided PK data and 4 that provided PD data.
- 1 population PK analyses.
- 2 Phase II dose finding studies.
- 1 pivotal Phase III study in patients with locally advanced and metastatic breast cancer previously treated with chemotherapy.
- 2 supportive Phase II efficacy and safety studies in patients with locally advanced and metastatic breast cancer previously treated with chemotherapy.
- 15 other completed or ongoing Phase I/II/III studies in patients with various advanced solid tumours submitted to support safety.
- 1 pooled analysis of efficacy and safety in all eribulin treated patients (AETP), 1 pooled analysis of efficacy and safety in eribulin treated breast cancer patients (BCP), 1 integrated summary of efficacy, and 1 integrated summary of safety.
- References, and sponsor's response to the European Medicines Agency (EMA) 120 questions.

[14] Australian Institute of Health and Welfare & Australian Association of Cancer Registries 2010. Cancer in Australia: an overview 2010. Cancer series no. 60. Cat. no. Can 46. Canberra. AIHW.
[15] Australian Institute of Health and Welfare & National Breast and Ovarian Cancer Centre 2009. Breast cancer in Australia: an overview, 2009. Cancer series no. 50. Cat. no. CAN 46. Canberra AIHW.

Paediatric data

The submission did not include paediatric data. It is considered that such data are not relevant to the submission.

Good clinical practice

Statements warranting that all Eisai sponsored studies had been conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) were provided in the clinical study reports (CSRs).

Pharmacokinetics

Studies providing pharmacokinetic data

Key PK and PK/PD data from the 8 individual PK studies in patients with advanced solid tumours and the population PK study are provided and their significance discussed. None of the PK studies had deficiencies that excluded their results from consideration.

In addition to the PK and PK/PD data derived from *in vivo* studies in humans with advanced solid tumours, the submission also included 8 *in vitro* studies using human biomaterials. These 7 studies are designated DSD2003-01, DS2004-03, DDDM2005-3, DMKP2003-13, DSD2001-31, DSDM2004-009, DDDA-2008-004 and DMPKM2010-003.

Evaluator's overall conclusions on pharmacokinetics

The PK of eribulin have been reasonably well characterised by the submitted studies and there are no PK issues that should preclude approval of eribulin for the proposed indication.

The population PK study demonstrated that the best final PK model for eribulin was a three compartment model with linear elimination. Following IV administration, eribulin undergoes a rapid distribution phase followed by a prolonged elimination phase with a terminal t½ of about 42 h. The drug has a large volume of distribution with the range of means for volume of distribution at steady state from the Eisai sponsored PK studies being 41.0 to 114.2 L/m^2. The drug undergoes minimal preferential distribution from the plasma into red blood cells. Protein binding is low, ranging from approximately 49% to 65%, and is independent of eribulin concentration from 100 to 1000 ng/mL.

There was no formal dose proportionality study in the submission. However, pooled data from the three Eisai dose escalation studies showed that eribulin exposure (AUC) increased with dose over the range 0.25 to 4.0 mg/m^2. In addition, the data showed that clearance, t½ and volume of distribution at steady state were independent of dose, confirming that the PK of eribulin were linear. The PK of eribulin following the second or third weekly dose in the first cycle were similar to the PK following the first dose, and no accumulation occurred after repeat dosing at weekly intervals. The population PK study reported high inter-individual variance for both the clearance (CL) and volume of distribution (central compartment) of eribulin with the respective coefficients of variation (CV) being 45.6% and 42.3%. High intersubject variability in the PK of eribulin were also observed in those individual PK studies in which the proposed eribulin dose of 1.4 mg/m^2 was administered.

Following IV administration of ^{14}C-eribulin, unchanged eribulin accounted for over 90% of the entire drug-derived radioactivity in the plasma, indicating that only low levels of circulating metabolites are formed. No major metabolites were found in the plasma and metabolite concentrations represented ≤ 0.6% of parent eribulin. *In vitro* data demonstrated that cytochrome P450 isozyme CYP3A4 was the main enzyme responsible

for the metabolism of eribulin, and that the metabolites formed by this enzyme were mainly the isomeric monohydroxylates.

Following administration of ^{14}C-erubulin approximately 90% of the radioactivity was recovered (approximately 82% in the faeces and 9% in the urine). Unchanged eribulin accounted for approximately 88% and 91% of the total radioactivity excreted in the faeces and urine respectively. Overall, the results suggest that eribulin is primarily eliminated unchanged by biliary excretion. In the mass balance study, eribulin total clearance was 3.93 L/h, and the renal clearance of 0.301 L/h represented less than 10% of total clearance. The actual renal clearance of approximately 0.3 L/h is very low compared with the fraction of eribulin unbound in plasma times the glomerular filtration rate (that is, approximately 0.6 x 7.5 L/h = 4.5 L/h). This suggests that eribulin is reabsorbed in the kidneys and may be secreted (but to a lesser extent than it is reabsorbed). If it is assumed that the non-renal clearance of approximately 3.6 L/h approximates hepatic clearance (CL_H) then it can be estimated that the hepatic extraction ratio (EH) is 0.04 (that is, CL_H = QH x EH; where QH is hepatic blood flow of 90 L/hr). The low hepatic extraction ratio is consistent with the long terminal t½of eribulin.

The population PK study found that eribulin clearance increased with increasing body weight, and there was also a strong trend for increasing body weight to be associated with increasing volume of distribution. In addition, this study found that albumin, bilirubin and alkaline phosphatase levels were predictors of eribulin clearance. Clearance decreased with increasing levels of bilirubin and alkaline phosphatase and increased with increasing levels of albumin. The population PK study demonstrated that age, gender, race, and co-administration of CYP3A4 inducers and inhibitors were not important predictors of eribulin clearance.

Hepatic impairment increases exposure to eribulin with the $AUC_{0-\infty}$ being approximately 1.8 and 2.8 fold greater in patients with mild hepatic impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B), respectively, than in patients with normal hepatic function. Consequently, downward dose adjustments are recommended to 0.7 mg/m^2 for patients with moderate hepatic impairment and 1.1 mg/m^2 for patients with mild hepatic impairment. There are no satisfactory data on the PK of eribulin in patients with severe hepatic impairment.

Renal impairment increases exposure to eribulin, despite renal excretion of unchanged eribulin being less than 10% of an administered dose. Unconfirmed data are reported to show that the mean geometric dose normalised exposure increases 2 fold in patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 mL/min). Consequently, it is recommended that the dose be adjusted downwards to 1.1 mg/m^2 in patients with moderate renal impairment. No dose adjustment is recommended for patients with mild renal impairment (CrCL 50-80 mL/min). There are no data on the PK of eribulin in patients with severe renal impairment (that is, CrCL < 30 mL/min).

In a PK drug-drug interaction study, co-administration of eribulin and ketoconazole (a potent CYP3A4 inhibitor and a P-gp inhibitor) did not increase eribulin exposure compared with eribulin alone. The submitted data indicate that a drug-drug interaction study with the CYP3A4 inducer rifampicin commenced after the data cut-off date for the submission. *In vitro* studies have shown that eribulin is unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP 2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4, or induce CYP1A, CYP3A, CYP2C9, or CYP2C19 at clinically expected plasma concentrations. *In vitro* studies show that eribulin is a weak inhibitor of P-gp, but this effect is unlikely to be significant at clinically expected eribulin concentrations. The sponsor indicates that *in vivo* studies are being undertaken to investigate the uptake and inhibitory effects of eribulin in several protein transporter systems. These investigations are considered to be clinically important as it has been estimated that up to 70% of an administered dose of eribulin is eliminated through biliary excretion.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included four studies in patients with advanced solid tumours with PK/PD data, one of which also included secondary pharmacology data on the effect of eribulin on the QT interval. There was also a PK/PD (and PK/adverse event; PK/AE) report using pooled data from the Phase II Study [211].

None of the PD studies had deficiencies that excluded their results from consideration. There were no PD studies in healthy human volunteers. There were no studies in humans on the primary pharmacology of eribulin.

Evaluator's overall conclusions on pharmacodynamics

The dose-escalation Studies 101 and 102 demonstrated that reductions in the absolute neutrophil count (ANC) were related to increased exposure to eribulin, and the population PK study showed that the probability of experiencing a Grade 4 neutropenia was related to increased eribulin exposure (AUC) and increased AST levels. It is considered that the available PK/AE data suggest that the increased risk of experiencing reductions in the ANC and increases in Grade 4 neutropenia can be expected at clinically relevant eribulin exposures. The available PK/AE data do not establish a relationship between increasing eribulin exposure and fatigue or neuropathy. In addition, the exploratory PK/PD data do not establish a relationship between eribulin exposure and clinical outcomes such as OS and disease progression.

The data from the QT interval study is considered to give rise to "regulatory concern" as, following a dose of eribulin 1.4 mg/m^2 on Days 1 and 8, the Day 8 maximum post dose time-matched QTcF[16] prolongation was > 5 msec, and the maximum upper bound of the post dose time-matched 95% confidence interval (CI) was > 10 msec. Furthermore, the increase in QTcF on Day 8 was greater in women than in men (an expected finding). The PK of eribulin were almost identical on Day 1 and Day 8, and the PK/PD analysis showed that the increase in the QTc interval on Day 8 was unrelated to plasma eribulin concentration.

Efficacy and safety

Dosage selection for the pivotal study

The eribulin dose of 1.4 mg/m^2 (administered as an IV bolus over 2 to 5 minutes on Days 1 and 8 of each 21 Day Cycle) was selected from experience in the Phase I/II studies. In the first Phase I dose-finding study [NCI 5730], the MTD was determined to be 1.4 mg/m^2 in patients with advanced solid tumours when administered as a bolus on Days 1, 8, and 15 of a 28 Day cycle. Based on these results, an eribulin dose regimen of 1.4 mg/m^2 administered as an IV bolus on Days 1, 8, and 15 of a 28 Day cycle was chosen for further exploration in two Phase II, open-label, single-arm studies [201, 202]. Following these two studies, the eribulin dose regimen of 1.4 mg/m^2 IV bolus on Days 1 and 15 of a 21 Day Cycle was chosen for the [pivotal] Phase III study [305[17]].

[16] QTc is the QT interval adjusted for heart rate. QTc calculated using a correction factor developed by Louis Friderica is identified as QTcF.

[17] Also known as EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389). The results of the EMBRACE study have been published: 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;377:914-923.

Study 201 included patients with advanced metastatic breast cancer previously treated with chemotherapy including an anthracycline and a taxane. In the first cohort (n = 71), patients received eribulin 1.4 mg/m^2 IV bolus on Days 1, 8, and 15 of a 28 Day cycle. However, because of the high number of dose delays, reductions or omissions due to neutropenia on Day 15, a second cohort (n = 33) was added to receive 1.4 mg/m^2 IV bolus on Days 1 and 8 of a 21 Day Cycle. In this study the primary endpoint was the overall response rate (ORR; complete response [CR] or partial response [PR], confirmed 4 to 8 weeks after first observed). The efficacy analysis showed that in the 28 Day schedule cohort 11.5% (10/87) of patients were assessed with PR as best response compared with 14.3% (4/28) of patients in the 21 Day cohort. There were no patients in the study with CR. Dose interruptions, delays or omissions were reported in 76% of patients in the 28 Day schedule group and 42% of patients in the 21 Day schedule group. The 1.4 mg/m^2 dose regimen on Days 1 and 8 of a 21 Day cycle was considered to have an acceptable tolerability profile, with neutropenia, fatigue, and alopecia being the most common treatment related AEs.

Study 202 included patients with advanced non-small cell lung cancer (NSCLC) who had progressed during or after initial treatment with platinum-based doublet chemotherapy stratified for prior taxane therapy. In this study, it was initially planned to have a group of patients (taxane pre-treated and taxane-naïve patients) treated with eribulin 1.4 mg/m^2 IV bolus on Days 1, 8, and 15 of a 28 Day cycle. However, after a preliminary evaluation of data from the first 33 patients in the 28 Day cohort, it was noted that 17 patients had missed the Day 15 dose due to haematological toxicity. The haematological toxicity seemed to have recovered by Day 21 in most cases. Efficacy outcomes were similar between those patients who had received the Day 15 dose and those who had not received the Day 15 dose. These findings led to a protocol amendment resulting in the addition of a second dosing schedule cohort in which eribulin was administered as a 1.4 mg/m^2 IV bolus on Days 1 and 8 of a 21 Day cycle to evaluate the efficacy and safety of this alternate dose schedule. A total of 106 patients were enrolled, 78 patients (58 taxane pre-treated and 20 taxane-naïve patients) treated with eribulin 1.4 mg/m^2 IV bolus on Days 1, 8, and 15 of a 28 Day cycle, and 28 taxane pre-treated patients treated with eribulin 1.4 mg/m^2 IV bolus on Days 1 and 8 and of a 21 Day cycle. Differences in efficacy were observed between the two Cycles, with patients in the 28 Day cohort having a PR rate of 11.7% and a disease control rate of 59.7%, compared with a PR rate of 3.8% and a disease control rate of 42.3% in patients in the 21 Day cohort. Grade 3-4 haematological toxicity (anaemia, leukopenia, and neutropenia) was more frequently observed in patients in the 21 Day cohort compared with patients in the 28 Day cohort. However, Grade 3-4 nausea, fatigue, pyrexia, and dehydration were more frequently observed in the patients in the 28 Day cohort compared with the 21 Day cohort.

> **Evaluator's Comment**: The data from the two Phase II studies [201, 202] indicate that the 1.4 mg/m^2 IV bolus dose regimen administered on Days 1 and 8 of a 21 Day Cycle was appropriate for further investigation in the supportive Phase II study [211] and the pivotal Phase III study [305] in patients with locally recurrent or advanced or metastatic breast cancer previously treated with chemotherapy.

Evaluator's conclusions on clinical efficacy for the proposed indication.

The submission included one pivotal, Phase III, open-label study [305] that compared the effect of eribulin (n = 508) administered at the proposed dosing regimen with treatment of physician's choice (TPC) (n = 254) on the primary efficacy variable of OS, and the secondary efficacy variables of progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) in women with heavily pre-treated metastatic breast cancer. Overall, the patient population in the pivotal study is considered to reflect

both the patient population specified in the proposed indication and women in the Australian community who might be offered treatment with eribulin.

The submission also included two, Phase II, open-label, one-arm studies [201, 211] in which the primary efficacy endpoint was the ORR and the secondary efficacy endpoints were OS, PFS, and DoR. In addition, the submission included a descriptive analysis of the pooled efficacy data from the two Phase II studies [201, 211] and the single, pivotal Phase III study [305]. However, the two Phase II studies and the pooled Phase II/III analysis provide limited efficacy data which are difficult to interpret in the absence of a control comparator. In particular, data from the key efficacy endpoints of OS and PFS are not considered to be clinically meaningful in the absence of a suitable comparator. Consequently, it is considered that the efficacy data supporting the submission are dependent on the single, pivotal, Phase III study.

The pivotal study [305] showed that the primary efficacy endpoint of OS (intention to treat (ITT) population) in patients in the eribulin group (n = 508) was statistically significantly superior compared with patients in the TPC group (n = 254). In the original data, the median OS was 399 days [95% CI: 360, 434] in the eribulin group and 324 days [95% CI: 282, 380] in the TPC group: hazard ratio (HR) = 0.809 [95% CI: 0.660, 0.991]; p = 0.041, stratified log-rank test. Since there was an interim analysis, the adjusted significance level for the final log-rank test was 0.049. The OS analysis in the per protocol (PP) population showed a numerically similar HR to the OS analysis in the ITT population, but in contrast to the ITT analysis the PP analysis was not statistically significant. The failure of the PP analysis to demonstrate statistical significance was probably due to the small sample size.

The results for OS survival in the original analysis were confirmed in the updated analysis (ITT population) which included more mature data: that is, a total of 589 deaths (77.3% of enrolled patients) in the updated data compared with 422 deaths (55.4% of enrolled patients) in the original data. In the updated data, the median OS was 403 days [95% CI: 367, 438] in the eribulin group (n = 508) and 321 days [95% CI: 282, 365] in the TPC group (n = 254): HR = 0.805 [95% CI: 281, 365]; p = 0.014, stratified log-rank test. In the updated data, the OS analysis in the PP population was statistically significant.

In the original analysis, the median OS benefit in the ITT population in favour of eribulin compared with TPC was 75.0 days [95% CI: 21.4, 128.6]. This result is consistent with the updated analysis which showed a median OS benefit in favour of eribulin compared with TPC of 82 days [95% CI: 29.9, 134.1]. The median OS of benefits in favour of eribulin of 75 days and 82 days (that is, 2.5 months and 2.7 months) are considered to be clinically meaningful in the population of women studied in the pivotal study. However, it should be noted that the assumptions made to estimate the sample size included median OS of 9 months and 12 months in the TPC and eribulin groups, respectively (that is, a HR of 0.75). These assumptions suggest that the minimal clinically significant median OS benefit in favour of eribulin relative to TPC was considered by the sponsor to be 3 months. Neither the original nor the updated OS benefits for eribulin relative to TPC quite reached the 3 month value.

There were no updated PFS data and all results relate to the original data. Median PFS (ITT population) was 45 days longer in the eribulin group compared with the TPC group, although the difference did not reach statistical significance based on blinded Independent review (primary analysis): HR = 0.865 [95% CI: 0.714, 1.048]; p = 0.137, stratified log-rank test). In this analysis, the median PFS was 113 days and 68 days in the eribulin group and TPC group, respectively. However, in a sensitivity analysis based on Investigator review the median PFS (ITT population) was 44 days longer in the eribulin group compared with the TPC group, and the difference between the two treatment groups (110 and 66 days, eribulin and TPC, respectively) was statistically significant: HR = 0.757 [95% CI: 0.638, 0.900]; p = 0.002. The difference in statistical significance between the two

reviews relate to different censoring rules relating to disease progression in the Independent review compared with the Investigator review. However, despite the difference in statistical significance between the two reviews, the numerical median PFS benefits in the eribulin group compared with the TPC are considered to be clinically equivalent (that is, 45 and 44 days, Independent and Investigator, respectively).

There were no updated ORR data and the results relate to the original data. Based on the Independent review in the response evaluable population, the ORR was 12.2% [95% CI: 9.4, 15.5] in the eribulin group and 4.7% [95% CI: 2.3, 8.4] in the TPC group: p = 0.002, Fisher's exact test. The major contributor to the ORR in both treatment groups was PR (11.5% and 4.7%, eribulin and TPC groups, respectively), with CR being 0.6% in the eribulin group and 0% in the TPC group. There were no updated DoR data and the results relate to the original data. In the Independent review, there was no statistically significant difference between the two treatment groups, but the TPC group is considered to include too few patients to make the comparison meaningful.

There were a number of pre-specified and post hoc subgroup analyses of OS in the pivotal study. It is considered that these analyses are exploratory. The study was not designed to test the subgroup comparisons, none of the subgroup comparisons were specified as primary or secondary efficacy variables, the subgroup analyses were underpowered, and no statistical adjustments were made to account for the multiple pairwise comparisons.

In summary, the current submission is considered to provide relevant efficacy data from only one pivotal Phase III study [305], with the supportive efficacy data from the two Phase II studies [201, 211] and the pooled Phase II/III Studies [305, 201, 211] providing only limited information due to the lack of control comparator treatment (particularly relating to OS and PFS). The TGA has adopted an EU guideline which provides guidance on applications with one pivotal study [*Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal Study.* CPMP/EWP/2330/99; 31 May 2001]. The "Points to consider" document states that *'There is a general demand for replication of scientific results…'*, but notes that *'..clinical drug development differs from the situation with strictly experimental studies'*. However, the document states that *'..where the confirmatory evidence is provided by only one pivotal study, this study will have to be exceptionally compelling, and the regulatory evaluation will need to pay special attention to* [certain factors]*'*.

If the factors listed in the "Points to consider" document are applied to the pivotal Phase III study [305] in the current submission, then the following observations can be made:

- the study is considered to be internally valid and no significant potential biases have been identified even though the study is open-label and the comparator is a mixture primarily of chemotherapy TPC;
- the study is considered to be externally valid as the results can be reasonably extrapolated to an Australian population of women with locally recurrent or metastatic breast cancer previously treated with chemotherapy as defined by the proposed indication;
- the increase in median OS of 2.7 months (updated data) in the eribulin group compared with the TPC group is considered to be clinically relevant in the proposed patient population;
- the degree of statistical significance for the primary efficacy endpoint of OS for the comparison between eribulin and TPC is considered to be satisfactory for both the original and updated data; the data quality is considered to be good;
- there is internal consistency between the key efficacy endpoints of OS and PFS with both time-to-event efficacy variables being longer in the eribulin group compared with the TPC group;

- there were no reported centre effects although subgroup analysis based on geographical regions showed a statistically significant OS benefit in eribulin treated patients compared with TPC in Region 1 (North America/Western Europe/Australia) but not in Region 2 (Eastern Europe) or Region 3 (Latin America/South Africa); and
- the plausibility of the hypothesis tested is considered reasonable given that eribulin has in vivo activity against a range of tumour types including human breast cancer xenografts.

Safety

Studies providing evaluable safety data

The primary focus of the review of the safety data in the CER is on the comparison between eribulin and TPC from the pivotal Phase III study [305]. The data from the pivotal study are the only safety data in the submission which compared eribulin administered at the proposed dose regimen for the proposed indication with a comparator group. In the pivotal study, the safety population consisted of all randomised patients who received at least a partial dose of study treatment. It included a total of 750 patients of whom 503 were in the eribulin group and 247 were in the TPC group.

The primary safety data from the pivotal Phase III study [305] are supported by pooled safety data from 1222 eribulin treated patients from eleven completed Phase I/II/III studies [Studies 305, 201, 202, 204, 211, 201, 102, 103, 108, 109, 110]. The 1222 patients in the Phase I/II/III AETP included a BCP of 827 patients from 2 Phase II Studies [201, 211] and 1 pivotal Phase III Study [305] who had been treated with eribulin at the proposed dose. In addition to the 827 patients with breast cancer from the 3 Phase II/Phase III studies [201, 211, 305], the AETP included a total of 395 patients from 8 other completed Phase I/II studies in solid tumours, including 70 patients with breast cancer treated with eribulin according to the 28 Day schedule in Study 201. The 11 Phase I/II studies (apart from studies 201, 211, and 305) included: 2 completed Phase 1 dose-escalation studies [101, 102]; 4 completed Phase I clinical pharmacology studies [103, 108, 109, 110]; and 2 completed Phase II studies ([202 [NSCLC], 204 [advanced prostate cancer] with a data cut-off of 31 May 2009. In general, safety in each clinical study was assessed by treatment emergent adverse events (TEAEs), serious TEAEs, deaths, extent of exposure to study treatment, physical examination findings, vital sign measurements, ECGs, and clinical laboratory results.

There was considerable overlap among eribulin treated patients from the pivotal study (n = 503), the AETP group (n = 1222), and the BCP group (n = 827). Of the 1222 patients in the AETP group, 67.7% (n = 827) came from the BCP group, and of these 827 patients 60.8% (n = 503) came from eribulin treated patients in the pivotal study. Patient disposition in the relative eribulin treated groups are summarised below in Table 3.

Table 3. Patient disposition AETP (n = 1245), BCP (n = 840) and pivotal study (n = 752); all enrolled patients.

	Eribulin Treated Patients Phase I/II/III		Pivotal Phase III study 305	
	All (AETP)	Breast Cancer (BCP)	Eribulin	TPC
Enrolled	1245	840	508	254
Treated	1222 (98.2%)	827 (98.5%)	503 (99.0%)	247 (97.2%)
Treatment ongoing	77 (6.3%)	24 (2.9%)	19 (3.8%)	3 (1.2%)
Discontinued treatment	1145 (93.7%)	803 (97.1%)	484 (95.3%)	244 (96.1%)
Primary reason for discontinuation				
Adverse event (including death)	130 (10.6%)	77 (9.3%)	53 (10.4%)	26 (10.2%)
Patient withdrew consent	38 (3.1%)	38 (3.1%)	10 (2.0%)	7 (2.8%)
Progressive disease *RECIST criteria	787 (64.4%)	577 (69.8%)	336 (66.1%)	153 (60.2%)
Clinical progression	108 (8.8%)	90 (10.9%)	61 (12.0%)	36 (14.2%)
Physician's decision	60 (4.9%)	32 (3.9%)	18 (3.5%)	13 (5.1%)
Lost to follow-up	0	0	0	0
Other	22 (1.8%)	10 (1.2%	6 (1.2%)	9 (3.5%)
Died on study treatment or within 30 days of last treatment	57/1222 (4.7%)	34/827 (4.1%)	20/503 (4.0%)	19/147 (7.7%).

* Response Evaluation Criteria In Solid Tumours (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumour response with X-ray, computer tomography and magnetic resonance imaging.

In addition to the safety data outlined above, the submission also included safety data from the studies summarised below.

- Safety data on eribulin from 1136 subjects enrolled in 5 ongoing clinical studies not completed at the cut-off date for the submission: Phase Ib study of eribulin in combination with carboplatin [104]; Phase II study of eribulin for soft-tissue sarcoma [207]; randomised Phase II study of neuropathy in breast cancer subjects comparing eribulin with ixabepilone [209]; Phase II study of eribulin for advanced breast cancer in Japan [221]; and Phase III study in advanced breast cancer comparing eribulin with capecitabine [301]. Safety data from the submitted progress reports from these 5 studies have been examined and are considered to be consistent with the pooled safety data from the AETP group.
- Safety data on eribulin from 9 Phase I and II studies in patients with solid tumours sponsored by the NCI (1 completed phase I study [NCI 5730] and 8 ongoing studies). None of these NCI studies involve the proposed indication. The submission included a safety summary for completed study 5730 (n = 40), and progress reports for the other 8 NCI studies [7427 (n = 16); 7444 (n = 21); 7431 (n = 70), 7435 (n = 56), 7437 (n = 41), 7448 (n = 15), E805 (n = 112), and S0168 (n = 42)]. The safety data from these studies have been examined and are considered to be consistent with the pooled safety data from the AETP group.

Evaluator's Comment: The safety database is considered to include an adequate number of patients for the assessment of eribulin at the proposed dose for the proposed indication. The major focus on the safety of eribulin in the CER is on the original comparative data from the pivotal study [305] (eribulin versus TPC), supplemented by the safety data from the AETP group from the 11 Phase I/II/III studies. Patient disposition was similar in the AETP group, the BCP group, and the eribulin safety group from the pivotal study. This was not unexpected given the significant overlapping of patients among the three safety populations.

In the pivotal study, the majority of randomised patients had discontinued treatment at the time of the cut-off date (484 [95.3%] and 244 [96.1%], eribulin and TPC groups, respectively). The primary reason for discontinuation in both treatment groups was progressive disease according to RECIST criteria, and the percentage of patients discontinuing for this reason was higher in the eribulin group than in the TPC group (336 [66.1%] and 153 [60.2%], respectively). Clinical progression not according to RECIST criteria resulted in 61 (12.0%) discontinuations in the eribulin group and 36 (14.2%) in the TPC group. In both the eribulin and the TPC groups, discontinuations due to AEs occurred in a similar proportion of randomised patients (50 [9.8%] and 24 [9.4%], respectively).

Evaluator's overall conclusion on clinical safety

- The primary focus on safety in the CER has been on the data from the safety population in the pivotal Phase III study [305] consisting of 750 patients (n = 503, eribulin; n = 247, TPC). The safety data in the pivotal study in eribulin treated patients (n = 503) is consistent with the pooled safety data in the AETP group (n = 1222) from 11 Phase I/II/III studies, and the pooled safety data in the BCP group (n = 827) from the pivotal Phase III study [305] and 2 Phase II supportive studies [201, 211]. This observation is not surprising, given the considerable overlapping of patients among the three safety populations.
- In the pivotal study, nearly all patients in both the eribulin (98.8%, n = 487) and the TPC (93.1%, n = 230) groups experienced at least one AE (irrespective of relationship to treatment). The most frequently reported AEs (≥ 20%) in patients in either treatment group (eribulin versus TPC) were asthenia/fatigue (53.7%, n = 270 versus 39.7%, n = 98), neutropenia (51.7%, n = 260 versus 29.6%, n = 73) alopecia (44.5%, n = 224 versus 9.7%, n = 24), peripheral neuropathy (34.6%, n = 174 versus 16.2%, n = 40), nausea (34.6%, n = 174 versus 28.3%, n = 70), constipation (24.7%, n = 124 versus 20.6%, n = 51), leukopenia (23.1%, n = 116 versus 11.3%, n = 28), arthralgia/myalgia (21.7%, n = 109 versus 11.7%, n = 29), weight decreased (21.3%, n = 107 versus 14.2%, n = 35), pyrexia (20.9%, n = 105 versus 12.6%, n = 31), and anaemia (18.7%, n = 94 versus 22.7%, n = 56).
- The majority of the commonly reported AEs (≥ 20%) in either treatment group were National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2. However, in the eribulin group (versus TPC), there were four CTCAE Grade 3 events reported with an incidence of ≥ 5% (neutropenia 21.1%, n = 106 versus 14.2%, n = 35; leukopenia 11.7%, n = 59 versus 4.9%, n = 12; asthenia/fatigue 8.2%, n = 41 versus 10.1%, n = 25; peripheral neuropathy 7.8%, n = 39 versus 2.0%, n = 5), and one CTCAE Grade 4 event reported with an incidence of ≥ 5% (neutropenia 24.1%, n = 121 versus 6.9%, n = 17).
- Adverse events occurring with an incidence of ≥ 10% but < 20% in patients in the eribulin group, and ≥ 2% more commonly than in patients in the TPC group were anorexia (19.5%, n = 98 versus 13.0%, n = 32), headache (19.3%, n = 97 versus 11.7%, n = 29), dyspnoea (15.7%, n = 79 versus 12.6%, n = 31), back pain (15.7%, n = 79

versus 7.3%, n = 18), arthralgia (13.7%, n = 69 versus 5.3%, n = 13), peripheral sensory neuropathy (12.3%, n = 62 versus 4.0%, n = 10), bone pain (11.9%, n = 60 versus 9.3%, n = 23), paraesthesia (11.1%, n = 56 versus 6.5%, n = 16), and myalgia (10.7%, n = 54 versus 6.9%, n = 17).

- The frequent AEs (any) in both treatment groups (eribulin versus TPC) appear to have been managed by dose delays (35.2%, n = 177 versus 32.4%, n = 80), dose reductions (16.9%, n = 85 versus 15.8%, n = 39), and dose interruptions (5.0%, n = 25 versus 10.1%, n = 25), rather than treatment discontinuation (13.3%, n = 67 versus 15.4%, n = 38). The two most common AEs (≥ 1%) leading to treatment discontinuation in the eribulin group (versus TPC) were peripheral neuropathy (4.8%, n = 24 versus 1.2%, n = 3), and asthenia/fatigue (1.8%, n = 9 versus 1.6%, n = 4). All other AEs in the eribulin group leading to discontinuation occurred with an incidence of < 1%.
- In the pivotal study, each of the two haematological AEs of special interest (neutropenia and febrile neutropenia) and the four non-haematological AEs of special interest (asthenia/fatigue, alopecia, peripheral neuropathy, and arthralgia/myalgia) occurred notably more frequently in patients in the eribulin group compared with the TPC group.
- Serious AEs leading to death during the study or within 30 days of last study treatment occurred in 4.0% (n = 20) of patients in the eribulin group and 7.3% (n = 18) of patients in the TPC group. SAEs (fatal and others) were reported in 25.0% (n = 126) of eribulin-treated patients and 25.9% (n = 64) of patients in the TPC group. The most frequently reported SAEs in the eribulin group (versus the TPC group) was febrile neutropenia (4.2%, n = 21 versus 1.2%, n = 3). Fatal SAEs were reported as treatment related in 5 (1.0%) patients in the eribulin group and 2 (0.8%) patients in the TPC group.
- The most commonly reported haematological AE in both treatment groups was neutropenia, and this AE was reported more frequently in patients in the eribulin group (51.7%, n = 260) than in the TPC group (29.6%, n = 73). Furthermore, in both the eribulin and the TPC groups, neutropenia was the most frequently reported CTCAE Grade 3 event (21.1%, n = 106 and 14.2%, n = 35, respectively) and CTCAE 4 event (24.1%, n = 121 and 6.9%, n = 17, respectively). Febrile neutropenia was reported less frequently than neutropenia in both the eribulin group (4.6%, n = 23) and the TPC group (1.6%, n = 4), but all cases were CTCAE Grade 3, 4, or 5 events. The two most common SAEs in patients in the eribulin group (versus TPC group) were febrile neutropenia (4.2%, n = 21 versus 1.2%, n = 3), and neutropenia (1.8%, n = 9 versus 0%). There were 2 fatal serious TEAEs due to febrile neutropenia reported as being treatment related occurring within 30 days of the last dose (1 in each treatment group).
- Neutropenia leading to discontinuation occurred in only 3 patients (0.6%) in the eribulin group and no patients in the TPC group. However, neutropenia resulting in discontinuation, delay or dose reduction occurred in 114 (27.2%) patients in the eribulin group and 46 (18.6%) patients in TPC group. These results indicate that neutropenia in both treatment groups was primarily managed by dose delays or reductions rather than treatment discontinuation. In addition, neutropenia appears to have been commonly managed with granulocyte colony stimulating factor (G-CSF). In the eribulin group G-CSF, pegfilgastrim, and granulocyte/macrophage (GM)-CSF were administered to 17.7% (n = 89), 2.4% (n = 12), and 0.2% (n = 1) of patients, respectively, and the corresponding values in the TPC group were 7.7% (n = 19), 3.2% (n = 8), and 0 (0%).
- During the pivotal study, 82.5% (n = 415) of eribulin treated patients had a laboratory test ANC of CTCAE Grade 1 or above. In eribulin treated patients, the ANC shifted from

baseline CTCAE Grade 0 (95.8%, n = 482) to worst CTCAE Grade 3 in 27.4% (n = 138) of patients, and worst CTCAE Grade 4 in 26.8% (n = 135) of patients. In eribulin treated patients (n = 503), worst Grade CTCAE ANC Grade 3 and 4 occurred in 28.4% (n = 143) and 28.6% (n = 144) of patients, respectively, in the eribulin group, 287 (57.1%) patients had a nadir ANC (CTCAE Grade 3 or 4). The mean time to CTCAE Grade 3/4 nadir within a cycle was approximately 13 days, and the majority of patients recovered from the nadir (93.7%, n = 269) with a median time to recovery to ≤ CTCAE Grade 2 of about 8 days.

- In the pivotal study, the AE of anaemia was reported in 18.7% (n = 94) of patients in the eribulin group and 22.7% (n = 56) of patients in the TPC group, with more than 80% of patients in both groups experiencing CTCAE Grade 1 or 2 events. Discontinuation due to anaemia AEs occurred in 1 (0.2%) patient in the eribulin group and no patients in the TPC group. In the pooled BCP data, of the 509 patients with baseline laboratory haemoglobin CTCAE Grade 0, 340 (66.9%) experienced a post baseline shift to CTCAE Grade 1 or above with the majority of patients shifting only to CTCAE Grade 1 (296/340 [87.1%]). The AE of thrombocytopenia was reported infrequently in both the eribulin (2.6%, n = 13) and the TPC (4.9%, n = 12) groups, and discontinuations due to this AE occurred in only 1 (0.2%) patient in the eribulin group and 2 (0.8%) patients in the TPC group. In the pooled BCP data, of the 787 patients with baseline laboratory platelets CTCAE Grade 0, 128 (16.3%) experienced a post baseline shift to CTCAE Grade 1 or above with nearly all of these patients (86.7%, 111/128) shifting to CTCAE Grade 1. The AE of pancytopenia was reported in only 1 (0.2%) eribulin treated patient (CTCAE Grade 4 event), but did not result in treatment discontinuation.
- The major non-haematological safety concern associated with eribulin is the development of peripheral neuropathy. In the pivotal study, patients with pre-existing neuropathy > CTCAE Grade 2 were excluded from the study. Peripheral neuropathy was reported in 34.6% (n = 174) of patients in the eribulin group and 16.2% (n = 40) of patients in the TPC group. In both treatment groups, the majority of patients with peripheral neuropathy experienced CTCAE Grade 1 or 2 events. Peripheral neuropathy was the most commonly reported AE leading to treatment discontinuation in eribulin treated patients (4.8%, n = 24 versus 1.2%, n = 3 [TPC]), and discontinuations, delays or dose reductions due to this events occurred in 8.5% (n = 43) of eribulin treated patients. Overall, the data suggest that treatment continued in about 90% of eribulin treated patients who developed peripheral neuropathy, and that most of these patients did not require dose reductions or delays.
- Kaplan-Meier analysis in the pivotal study estimated that the risk of peripheral neuropathy developing or progressing to ≥ Grade 2 during treatment in patients without baseline disease or set to Grade 1 in patients with missing baseline data was 2.3 fold higher in the eribulin group than in the TPC group. In this analysis, the 1 year rate for development/progression of peripheral neuropathy was higher in patients in the eribulin group (21.4%) compared with the TPC group (9.5%), and the respective 2 year rates were 23.1% and 9.5%.
- In the BCP group, there were 288 (34.8%) patients with treatment emergent peripheral neuropathy (any), and at the time of follow-up after last treatment resolution had occurred in only 14.2% (n = 41) with a median time to resolution of 8.1 weeks. In this patient population the median time to onset of peripheral neuropathy was 23.4 weeks. In a sub-group analysis in the BCP group, the incidence of peripheral neuropathy was similar in eribulin treated patients without pre-existing neuropathy, with Grade 1 pre-existing neuropathy, and with Grade ≥ 2 pre-existing neuropathy (31.5% [197/625], 34.5% [49/142], and 29.6% [8/27], respectively).

- In the pivotal study, each of the two haematological AEs of special interest (neutropenia, febrile neutropenia) and the four non-haematological AEs of special interest (asthenia/fatigue, alopecia, peripheral neuropathy, arthralgia/myalgia) occurred notably more commonly in patients in the eribulin group compared with the TPC group. Cardiovascular AEs (cardiac disorders and vascular disorders) occurred marginally more commonly in patients in the eribulin group than in the TPC group. However, there does not appear to be an increased risk of hepatic, renal or immune system toxicity with eribulin compared with TPC.
- In the pivotal study, exposure to both treatments is considered adequate to allow for satisfactory comparative evaluation of the safety profiles of the two treatments in the proposed patient population. However, the median duration of exposure in the eribulin group (118.0 days) was longer than in the TPC group (n = 64.0 days). This difference in exposure duration might have, at least in part, accounted for the higher incidence of TEAEs in the eribulin group than in the TPC group. However, post hoc analyses provided in the sponsor's Summary of Clinical Safety to evaluate the effect of the difference in median duration of exposure between the two treatment groups on selected subgroups are considered to confirm the greater risk associated with eribulin compared with TPC. In both post hoc analyses (100 subject days of treatment exposure and first 8 weeks of the treatment period), the incidence of neutropenia, febrile neutropenia, peripheral anaemia, and alopecia was greater in the eribulin treated group than in the TPC group. In addition, the incidence of asthenia/fatigue and nausea was greater in the eribulin group in the first 8 weeks of treatment than in the TPC group.
- The TPC group included 238 chemotherapy treated patients and 9 hormonal treated patients. The pivotal study included post hoc subgroup analyses comparing the safety of eribulin and the 5 most commonly used chemotherapy agents in the TPC group. The comparative safety data from these subgroup analyses are considered to be exploratory rather than definitive as the study was specifically designed to compare eribulin with the total TPC population.

List of questions

Pharmacokinetics

1. In a public document, the sponsor has stated that 'the geometric mean dose-normalised systemic exposure increased two-fold compared to patients with normal renal function. A lower starting dose of 1.1 mg/m2 is recommended for patients with moderate renal impairment' [Eisai FDA Advisory Subcommittee Briefing Document; October 25, 2010]. However, the data supporting this statement relating to the "two-fold" increase could not be located in the submission. Please provide the data supporting the statement.

Efficacy

1. Why was prior chemotherapy with capecitabine not a specific inclusion criteria for the pivotal Phase III Study 305, although it had been for the Phase II study 211?
2. In the pivotal study [305], are the two patients in the eribulin group listed as having Stage 0 breast cancer at diagnosis those with identification numbers ID 14011002 and ID 14011008? Did these 2 patients have Stage 0 breast cancer, and if so why were they included in the study?
3. In the protocol (pivotal Study 305), it was stated that patients in the OS analysis were to be censored at the date last known to be alive, but in the OS analysis provided in

the CSR (pivotal Study 305) patients were censored at the data cut-off date (that is, 12 May 2009). Why was the OS censoring rule used in the CSR changed from that specified in the protocol, and did the different censoring rules influence the results of the provided OS analysis?

4. *In the CSR (pivotal Study 305), it is stated that "in addition to the PFS analyses as detailed in the Statistical Analysis Plan (SAP), following unblinding, discussion surrounding the interpretation of the [FDA Guideline] "Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" led to the formulation of a new set of PFS rules for censoring/progression. As such, this approach represents a post hoc analysis, as the methods used to define and interpret the results were not part of the pre-specified analysis. This analysis is based upon the Independent review of the radiological assessments. The main difference from this analysis as opposed to the PFS detailed in the SAP is that it takes into account progressions from non-target lesions (that is, unequivocal progressions) in addition to new lesion and target lesion progression events".*

   The sponsor is requested to respond to the following questions related to this matter.

- Were FDA (and/or EMA) officials participants in the "discussion" in addition to representatives of the sponsor?
- If representatives of the FDA (and/or EMA) were present, were the changes to the PFS censoring/progression rules after unblinding of the data driven primarily by regulatory officials?
- What were the specific issues relating to interpretation of the Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics which resulted in the changes to the censoring/progression rules for the PFS?
- Did the results for PFS differ for the analysis using the post hoc censoring/progression rules and the analysis using the protocol specified censoring/progression rules?

The evaluator also requested revisions to the PI and consumer medicines information (CMI) documents; details of these are beyond the scope of this AusPAR.

First round clinical summary and conclusions

First round benefit risk assessment

First round assessment of benefits

In the pivotal study [305], eribulin (n = 508 patients) at the proposed dose showed a clinically meaningful and statistically significant median OS benefit of 2.5 months [95% CI: 0.7, 4.3] compared with TPC (n = 254) in the original data, and 2.7 months [95% CI: 1.0, 4.5] in the updated (more mature) data. However, the OS benefit observed with eribulin relative to TPC is small and is considered to be at the lower limit of meaningful clinical benefit. The study was powered to detect a difference in median OS of 3 months in favour of eribulin (OS estimated to be 12 months) compared with TPC (OS estimated to be 9 months). Consequently, it can be inferred that the sponsor considered a median OS benefit of 3 months in favour of eribulin relative to TPC to be the minimum clinically meaningful difference.

In the pivotal study [305], in the original data (ITT population) median OS (primary efficacy variable) was 399 days [95% CI: 360, 434] in patients in the eribulin group and 324 days [95% CI: 282, 380] in the TPC group: HR [eribulin:TPC] = 0.809 [95% CI: 0.660, 0.991], p = 0.041 (stratified log-rank test). Median OS was 75.0 days [95% CI: 21.4, 128.6] longer in patients in the eribulin group compared with the TPC group. In the updated data

(ITT population), median OS was 403 days [95% CI: 367, 438] in patients in the eribulin group and 321 days [95% CI: 281, 365] in the TPC group: HR [eribulin:TPC] = 0.805 [95% CI: 0.667, 0.958], p = 0.014 (stratified log-rank test). Median OS was 82 [95% CI: 29.9, 134.1] days longer in patients in the eribulin group compared with the TPC group. In both the original and updated OS analyses, the HR was based on a Cox model stratified for Human Epidermal Growth Factor Receptor 2 (HER2, also known as *neu*) status, prior capecitabine treatment, and geographical region.

In the pivotal study [305], death occurred in 53.9% (n = 274) patients in the eribulin group and 58.3% (n = 148) of patients in the TPC group in the original data (that is, 55.4% [422/762] of all enrolled patients), and the corresponding figures were 76.0% (n = 386) and 79.9% (n = 203) in the updated patients (that is, 77.3% [589/762] of all enrolled patients).

In the pivotal study [305], in the primary analysis (Independent review) the median PFS (secondary efficacy variable) in the ITT population was 45 days longer in patients in the eribulin group compared with patients in the TPC group: 113 [95% CI: 101, 118] and 68 [95% CI: 63, 103] days, respectively). However, the difference in median PFS between the two treatment groups was not statistically significant: HR [eribulin:TPC] = 0.865 [95% CI: 0.714, 1.048]; p = 0.137 (stratified log-rank test). In a sensitivity analysis (Investigator review) using different censoring rules for disease progression, the median difference in PFS between the two groups was 44 days in favour of patients in the eribulin group compared with the TPC group: HR = 0.788 [95% CI: 0.644, 0.964]; p = 0.020 (stratified log-rank test). The median PFS benefits can be considered to be clinically equivalent for the two analyses even though the statistical results were inconsistent (that is, 45 days [not statistically significant], primary analysis and 44 days [statistically significant], sensitivity analysis). Overall, the median PFS benefit can be considered to be consistent with the median OS benefit (that is, both in favour of eribulin).

In the pivotal study, the ORR (secondary efficacy variable) was statistically significantly higher in the eribulin group compared with the TPC group based on Independent review (12.2% [95% CI: 9.4, 12.5] and 4.7% [95% CI: 2.3, 8.4]; p = 0.002 (Fisher's exact test). The major contributor to the ORR in both treatment groups was the PR (11.5% and 4.7%, eribulin and TPC groups respectively) with CR being 0.6% in the eribulin group and 0% in the TPC group. The sensitivity analysis of the ORR based on Investigator review was consistent with the primary analysis based on Independent review. Overall, the ORR is considered to support the OS and PFS analyses.

In the pivotal study [305], there was no statistically significant difference in the median DoR (secondary efficacy variable) between the eribulin and TPC treatment groups. However, the number of patients included in the TPC group is considered too small to provide a meaningful comparison for DoR between the two treatment groups.

The submission did not include any studies specifically comparing the benefits (efficacy) of eribulin with those of capecitabine and/or vinorelbine. In Australia, the approved indications of both capecitabine and vinorelbine can support their use as third-line monotherapy for patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens (which should have included an anthracycline and a taxane). Therefore, in the absence of pivotal efficacy data comparing eribulin with capecitabine/and or vinorelbine an argument can be made for relegating eribulin from third-line to fourth-line (or fifth-line) treatment for the proposed indication behind taxanes, anthracyclines and capecitabine and/or vinorelbine. However, there is no evidence from the published data that either capecitabine or vinorelbine as monotherapy offer an OS benefit for the proposed usage. Consequently, it is considered that the observed OS benefit of eribulin compared with TPC in the pivotal study is enough to support the approval of the drug as an alternative monotherapy to capecitabine and/or

vinorelbine, without the need for pivotal efficacy data comparing eribulin with capecitabine and/or vinorelbine.

First round assessment of risks

Overall, the safety data from the pivotal study [305] are considered to show that the risk to women in the proposed patient population treated with eribulin is greater than the risk to women treated with TPC. The assessment of the risks associated with eribulin described below are based on assessment of the pivotal study [305], unless otherwise stated. The safety profile of eribulin in the pivotal study is consistent with that seen with eribulin in other submitted studies.

In the pivotal study, nearly all patients in both the eribulin group (98.8%, n = 487) and the TPC group (93.1%, n = 230) experienced at least one AE (irrespective of relationship to treatment). However, patients in the eribulin group (n = 503) were at greater risk than patients in the TPC group (n = 247) for the following most commonly reported AEs (that is, events occurring with a frequency of ≥ 20% in either treatment group): asthenia/fatigue (53.7%, n = 270 versus 39.7%, n = 98); neutropenia (51.7%, n = 260 versus 29.6%, n = 73); alopecia (44.5%, n = 224 versus 9.7%, n = 24); peripheral neuropathy (34.6%, n = 174 versus 16.2%, n = 40); nausea (34.6%, n =1 74 versus 28.3%, n = 70); constipation (24.7%, n = 124 versus 20.6%, n = 51); leukopenia (23.1%, n = 116 versus 11.3%, n = 28), arthralgia/myalgia (21.7%, n = 109 versus 11.7%, n = 29); weight decreased (21.3%, n = 107 versus 14.2%, n = 35), and pyrexia (20.9%, n = 105 versus 12.6%, n = 31). The only AE reported with a frequency of ≥ 20% in either treatment group that occurred more frequently in TPC treated patients than in eribulin treated patients was anaemia (22.7%, n = 56 versus 18.7%, n = 94, respectively).

Furthermore, AEs occurring with an incidence of ≥ 10% but < 20% in patients in the eribulin group, and ≥ 2% more commonly than in patients in the TPC group were: anorexia (19.5%, n = 98 versus 13.0%, n = 32); headache (19.3%, n = 97 versus 11.7%, n = 29); dyspnoea (15.7%, n = 79 versus 12.6%, n = 31); back pain (15.7%, n = 79 versus 7.3%, n = 18); arthralgia 13.7%, n = 69 versus 5.3%, n = 13); peripheral sensory neuropathy (12.3%, n = 62 versus 4.0%, n = 10); bone pain (11.9%, n = 60 versus 9.3%, n = 23); paraesthesia (11.1%, n = 56 versus 6.5%, n = 16); and myalgia (10.7%, n = 54 versus 6.9%, n = 17).

The majority of the most commonly reported AEs (that is, events occurring with a frequency of ≥ 20% in either treatment group) were CTCAE Grade 1 or 2. However, in the eribulin group (versus TPC) there were four CTCAE Grade 3 events reported with an incidence of ≥ 5% (neutropenia 21.1%, n = 106 versus 14.2%, n = 35; leukopenia 11.7%, n = 59 versus 4.9%, n = 12; asthenia/fatigue 8.2%, n = 41 versus 10.1%, n = 25; peripheral neuropathy 7.8%, n = 39 versus 2.0%, n = 5), and one CTCAE Grade 4 event reported with an incidence of ≥ 5% (neutropenia 24.1%, n = 121 versus 6.9%, n = 17).

The frequent AEs (any) in both treatment groups (eribulin versus TPC) appear to be able to be managed by dose delays (35.2%, n = 177 versus 32.4%, n = 80), dose reductions (16.9%, n = 85 versus 15.8%, n = 39), and dose interruptions (5.0%, n = 25 versus 10.1%, n = 25), rather than treatment discontinuation (13.3%, n = 67 versus 15.4%, n = 38). In addition, the use of symptomatic medication to manage specific AEs such as nausea and vomiting also appears to have been high in both treatment groups (eribulin versus TPC): for example., dexamethasone 38.2%, n = 192 versus 34.0%, n = 84; ondansetron 31.4%, n = 158 versus 23.5%, n = 58; metoclopramide 15.9%, n = 80 versus 17.4%, n = 43; granisetron 13.5%, n = 68 versus 8.1%, n = 20; and palonosetron 4.6%, n = 23 versus 2.8%, n = 7. The two most common AEs (≥ 1%) leading to treatment discontinuation in the eribulin group (versus TPC) were peripheral neuropathy (4.8%, n = 24 versus 1.2%, n = 3), and asthenia/fatigue (1.8%, n = 9 versus 1.6%, n = 4). All other AEs in the eribulin group leading to discontinuation occurred with an incidence of < 1%.

At the data cut-off date of 12 May 2009 (original data), in the safety population there had been 271 (53.9%) deaths in the eribulin group and 143 (57.9%) deaths in the TPC group. The primary reason for death was progressive disease in both the eribulin group (50.5%, n = 254) and the TPC group (54.7%, n = 135). SAEs leading to death during the study or within 30 days of last study treatment occurred less commonly in patients in the eribulin group (4.0%, n = 20) than in the TPC group (7.3%, n = 18). Fatal SAE was reported as treatment related in 5 (1.0%) patients in the eribulin group (2 x dyspnoea, febrile neutropenia lung infection bronchopneumonia) and 2 (0.8%) patients in the TPC group (aspergillosis, febrile neutropenia). SAEs (fatal and others) were reported in 25.0% (n = 126) of eribulin-treated patients and 25.9% (n = 64) of patients in the TPC group. The most frequently reported SAEs in the eribulin group (versus the TPC group) was febrile neutropenia (4.2%, n = 21 versus 1.2%, n = 3).

Neutropenia was the most commonly reported haematological AE in both treatment groups, and was reported more frequently in patients in the eribulin group (51.7%, n = 260) than in the TPC group (29.6%, n = 73). Furthermore, in both the eribulin and the TPC groups, neutropenia was the most commonly reported CTCAE Grade 3 event (21.1%, n = 106 and 14.2%, n = 35, respectively) and CTCAE 4 event (24.1%, n = 121 and 6.9%, n = 17, respectively). Febrile neutropenia was reported less frequently than neutropenia in both the eribulin group (4.6%, n = 23) and the TPC group (1.6%, n = 4), but all cases were CTCAE Grade 3, 4, or 5 events. The two most common SAEs in patients in the eribulin group (versus TPC group) were febrile neutropenia (4.2%, n = 21 versus 1.2%, n = 3), and neutropenia (1.8%, n = 9 versus 0%)). There were 2 fatal serious TEAEs due to febrile neutropenia reported as being treatment related (1 in each treatment group) occurring within 30 days of the last dose.

Neutropenia leading to discontinuation occurred in only 3 patients (0.6%) in the eribulin group and no patients in the TPC group. However, neutropenia resulting in discontinuation, delay or dose reduction occurred more commonly in patients in the eribulin group (27.2%, n = 114) than in the TPC group (18.6%, n = 46). These results indicate that neutropenia in both treatment groups was primarily managed by dose delays or reductions rather than treatment discontinuation. In addition, the data indicate that neutropenia was also managed with CSF. In the eribulin group G-CSF, pegfilgastrim, and GM-CSF were received by 17.7% (n = 89), 2.4% (n = 12), and 0.2% (n = 1) of patients, respectively, and the corresponding values in the TPC group were 7.7% (n = 19), 3.2% (n = 8), and 0 (0%).

During the pivotal study, 82.5% (n = 415) of eribulin treated patients had a laboratory test ANC of CTCAE Grade 1 or above. In eribulin treated patients, the ANC shifted from baseline CTCAE Grade 0 (95.8%, n = 482) to worst CTCAE Grade 3 in 27.4% (n = 138) of patients and worst CTCAE Grade 4 in 26.8% (n = 135) of patients. In eribulin treated patients (n = 503), worst Grade CTCAE ANC Grade 3 and 4 occurred in 28.4% (n = 143) and 28.6% (n = 144) of patients, respectively. In the eribulin group, 287 (57.1%) patients had a nadir ANC (CTCAE Grade 3 or 4). The mean time to CTCAE Grade 3/4 nadir within a Cycle was approximately 13 days, and the majority of patients recovered from the nadir (93.7%, n = 269), with a median time to recovery to ≤ CTCAE Grade 2 of about 8 days.

In the pivotal study, the AE of anaemia was reported in 18.7% (n = 94) of patients in the eribulin group and 22.7% (n = 56) of patients in the TPC group, with more than 80% of patients both groups experiencing CTCAE Grade 1 or 2 events. Discontinuation due to anaemia AEs occurred in 1 (0.2%) patient in the eribulin group and no patients in the TPC group. Discontinuations, delay or dose reduction occurred in 10 (2.0%) patients with anaemia in the eribulin group and in 3 (1.2%) patients in the TPC group. In the pooled BCP data, of the 509 patients with baseline laboratory haemoglobin CTCAE Grade 0, 340 (66.9%) experienced a post baseline shift to CTCAE Grade 1 or above with the majority of patients shifting only to CTCAE Grade 1 (296/340 [87.1%]). Overall, the data suggest that

most patients who develop anaemia while being treated with eribulin do not require dose modification. Treatments used to manage anaemia during the study included (eribulin versus TPC): darbepoetin alfa (n = 24, 4.8% versus n = 11, 4.5%); erythropoietin human (n = 14, 2.8% versus n = 7, 2.8%); erythropoietin (n = 3, 0.6% versus n = 3, 1.2%); and red blood cells (n = 11, 2.2% versus n = 7, 2.8%).

The AE of thrombocytopenia was reported infrequently in both the eribulin (2.6%, n = 13) and the TPC (4.9%, n = 12) groups. Discontinuations due to this AE occurred in 1 (0.2%) patient in the eribulin group and 2 (0.8%) patients in the TPC group, and the corresponding patient numbers for discontinuation, delay, or dose reduction were 5 (1.0%) and 5 (2.0%). In the pooled BCP data, of the 787 patients with baseline laboratory platelets CTCAE Grade 0, 128 (16.3%) experienced a post baseline shift to CTCAE Grade 1 or above with nearly all patients (n = 111) shifting to CTCAE Grade 1. The AE of pancytopenia was reported in 1 (0.2%) eribulin treated patient only (CTCAE Grade 4 event), but did not result in treatment discontinuation.

The major non-haematological safety concern associated with eribulin is the development of peripheral neuropathy. In the pivotal study, peripheral neuropathy was identified as one of the four non-haematological AEs of special interest. In the pivotal study, patients with pre-existing neuropathy > CTCAE Grade 2 were excluded from the study. Peripheral neuropathy was reported in 34.6% (n = 174) of patients in the eribulin group and 16.2% (n = 40) of patients in the TPC group. In both treatment groups, the majority of patients with peripheral neuropathy experienced CTCAE Grade 1 or 2 events. Peripheral neuropathy was the most commonly reported AE leading to treatment discontinuation in eribulin treated patients (4.8%, n = 24 versus 1.2%, n = 3 [TPC]) and discontinuations, delays or dose reductions occurred in 8.5% (n = 43) of eribulin treated patients. Overall, the data suggest that treatment continued in about 90% of eribulin treated patients who developed peripheral neuropathy, and that most of these patients did not require dose reductions or delays despite ongoing peripheral neuropathy.

Kaplan-Meier analysis of peripheral neuropathy in the pivotal study estimated that the risk of this event developing or progressing during treatment (≥ Grade 2) was 2.3-fold higher in the eribulin group than in the TPC group in patients with no baseline peripheral neuropathy or baseline set to Grade 1 when data were missing. In this analysis, the estimated 1-year rate for development/progression of peripheral neuropathy was greater in patients in the eribulin group (21.4%) than in the TPC group (9.5%), and the corresponding figures for the estimated 2-year rates were 23.1% and 9.5%. In the BCP group, there were 288 (34.8%) patients with any treatment emergent peripheral neuropathy, and resolution at the time of follow-up after last treatment had occurred in only 14.2% (n = 41) with a median time to resolution of 8.1 weeks. In this patient population the median time to onset of peripheral neuropathy was 23.4 weeks. In a sub-group analysis in the pooled BCP group, the incidence of neuropathy related to eribulin treatment was similar in patients without pre-existing neuropathy, with Grade 1 pre-existing neuropathy, and with Grade ≥ 2 pre-existing neuropathy (31.5% [197/625], 34.5% [49/142], and 29.6% [8/27], respectively).

The risk of infections and infestations (any) were more common in the eribulin group (41.9%, n = 211) than in the TPC group (26.3%, n = TPC). This most likely reflects the higher incidence of neutropenia in the eribulin group compared with the TPC group. Infection/infestations (preferred terms) which occurred with a frequency of ≥ 2.0% in the eribulin group and more commonly than in the TPC group were: urinary tract infection (9.7%, n = 49 versus 5.3%, n = 13); nasopharyngitis (4.8%, n = 24 versus 2.8%, n = 7); upper respiratory tract infection (5.2%, n = 26 versus 2.0%, n = 5); rhinitis (4.4%, n = 22 versus 1.2%, n = 3); influenza (4.4%, n = 22 versus 0.8%, n = 2); cystitis (2.4%, n = 12 versus 1.2%, n = 3); pharyngitis (2.4%, n = 12 versus 0.4%, n = 1); bronchitis (2.2%, n = 11 versus 0.8%, n = 2); and sinusitis (2.2%, n = 11 versus 0.8%, n = 2). Infections/infestations

leading to discontinuation in the eribulin group occurred in 5 (1.0%) patients (2 x pneumonia, 1x lung infection, 1 x pyelonephritis, 1 x septic shock) and in 1 (0.4%) patient in the TPC group (aspergillosis).

The risk of cardiovascular AEs occurred more commonly in patients in the eribulin group than in the TPC group: cardiac disorders (6.6%, n = 33 versus 4.0%, n = 33, respectively); and vascular disorders (16.3%, n = 92 versus 13.0%, n = 32, respectively). Both tachycardia and palpitations occurred more frequently in the eribulin group than in the TPC group: tachycardia 3.6%, n = 18 versus 1.2%, n = 3, respectively, and palpitations 1.6%, n = 8 versus 0.4%, n = 1, respectively. Arrhythmia was reported in 1 (0.2%) patient in the eribulin group and 1 (0.4%) patient in the TPC group, and atrial fibrillation and atrial tachycardia were both reported in 1 (0.2%) patient in the eribulin group and no patients in the TPC group. There were no reports of Torsade de pointes in either treatment group. There were 3 patients with treatment-emergent serious AEs in the eribulin group (2 x pericardial effusion, 1 x cardiac failure) compared with no patients in the TPC group. There were no patients in either treatment group with cardiac disorders leading to discontinuation.

In the eribulin group (versus the TPC group), there were higher incidences of hypertension (3.6%, n = 18 versus 1.6%, n = 4), hot flush (2.8%, n = 14 versus 2.0%, n = 5), and hypotension (2.6%, n = 13 versus 1.6%, n = 4). There were 2 (0.4%) patients with deep vein thrombosis in the eribulin group compared with 3 (1.2%) in the TPC group, and the respective figures for embolism were 1 (0.2%) and 2 (0.8%) patients. Discontinuations due to vascular disorders were reported in 1 (0.2%) patient in the eribulin group (1 x deep vein thrombosis) and no patients in the TPC group. Fatal treatment-emergent vascular disorders (any term) were reported in 1 (0.2%) patient in the eribulin group (cardiovascular insufficiency) and 2 patients in the TPC group (1 x cardiovascular insufficiency; 1 x embolism).

Skin and subcutaneous tissue disorders (any) occurred more frequently in patients in the eribulin group (52.9%, n = 266) compared with the TPC group (32.0%, n = 79), due primarily to the greater number of patients with alopecia. However, palmar plantar erythrodysesthesia syndrome occurred notably more frequently in patients in the TPC group (5.7%, n = 14) than in patients in the eribulin group (1.4%, n = 7).

There does not appear to be an increased risk of hepatic, renal or immune system toxicity associated with eribulin compared with TPC.

First round assessment of benefit-risk balance

It is considered that the benefit-risk balance for eribulin, given the proposed usage, hinges on whether the small, but clinically meaningful and statistically significant OS benefit of 2.7 months [95% CI: 1.0, 4.5] (updated analysis, pivotal study) observed with eribulin compared with TPC outweighs the increased risks of eribulin compared with TPC (in particular neutropenia and peripheral neuropathy).

On balance, it is considered that the benefit-risk balance is marginally favourable for eribulin, given the proposed usage. The OS benefit observed with eribulin is small but clinically meaningful for the proposed patient population for whom other treatment options are limited and appear to offer no OS benefit. The risks of eribulin treatment are similar in type to those known to be associated with other chemotherapy agents used to treat advanced metastatic breast cancer. The risks appear to be manageable by dose delays, dose reductions, and symptomatic therapy rather than treatment discontinuation. The risk-benefit balance can only be considered to be favourable in patients with a life expectancy of at least 3 months as this was an inclusion criterion for the pivotal study.

First round recommendation regarding authorisation

- It is recommended that eribulin be approved as monotherapy 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.
- It is recommended that the proposed eribulin treatment regimen for the proposed indication be approved.

Sponsor's response to the list of questions

The sponsor's responses to the clinical questions raised following the first round clinical evaluation (see *List of Questions,* above) were evaluated in a second round CER, which provides comments on the sponsor's responses, the second round benefit-risk assessment, the second round recommendation regarding authorisation and second round comments on the PI documentation (not included in this AusPAR). The first and second round CERs were prepared by the same clinical evaluator. Summary details from the second round CER are provided below.

Second round clinical evaluation report

Clinical pharmacokinetics (Question 1)

Sponsor's response

The sponsor provided the source of the relevant data. In addition to the data provided in the text of these responses, the sponsor also provided individual patient information relating to the renal impairment status and dose-normalised AUC results for each patient from the relevant 6, Phase I studies identified in the responses.

Clinical evaluator's comment

The sponsor has satisfactorily identified and summarised the source data supporting the statement that geometric mean dose-normalised systemic exposure was 2 fold higher in patients with moderate renal impairment compared with subjects with normal renal function.

Clinical efficacy (Question 1)

Sponsor's response

Study 211 required having prior chemotherapy with capecitabine, and Study 305 did not. Prior capecitabine therapy was not mandated in Study 305 but was not excluded. To ensure balance across treatment arms, it was included as a randomisation stratification factor. The subgroup analysis of Study 305 showed a benefit for eribulin in both capecitabine pretreated and naïve subgroups. This was discussed with EMA prior to study start. EMA's position was if the results were consistent between the subgroups of patients treated and not previously with capecitabine in Study 305 and consistent with the 211 results, then 211 would be supportive of the 305 study.

Clinical evaluator's comment

No explanation has been provided for why the sponsor decided not to specify prior treatment with capecitabine as an inclusion criterion for the pivotal study. The clinical issues relating to the sub-group analyses of OS and PFS in capecitabine-pretreated and capecitabine-naïve patients in the pivotal study has been discussed in the first round CER.

Furthermore, the results of the sub-group analyses in capecitabine-pretreated and capecitabine-naïve patients are considered in the second round CER.

Clinical efficacy (Question 2)

Sponsor's response

- Two patients were initially diagnosed with Stage 0 however at study entry both patients were locally advanced or had metastatic disease.
- One patient was Stage IIa at initial diagnoses. In 2002 the patient had recurrence of disease and reassessed to locally advanced/ metastatic disease and received multiple lines of therapy (6), in January 2007 (study entry) patient was stage IV.
- One patient was diagnosed in February 2002 with ductal adenocarcinoma of the breast Stage 0. Approximately in July 2004 she was diagnosed with locally advance/metastatic carcinoma and received multiple lines (4) of chemotherapy before she was selected to participate in this study.
- One patient (also included under first dot point above) was diagnosed in May 1999 with ductal adenocarcinoma of the breast Stage 0. Approximately in November 2005 she was diagnosed with locally advance/metastatic carcinoma and received multiple lines (4) of chemotherapy before she was selected to participate in this study.

Clinical evaluator's comment

The sponsor's response is satisfactory.

Clinical efficacy (Question 3)

Sponsor's response

Within two weeks of the data cut-off date (12 May 2009), the sponsor followed up the status of all study subjects who were known to be still remaining in the study (not dead, not lost to follow up, not withdrawn consent) and confirmed whether the subject was alive on 12 May 2009 or if the subject had died, the date last known to be alive, was included in the clinical database. If the subject was alive on 12 May 2009, the sponsor censored the subject in OS analysis. This approach is in agreement with the plan outlined in the protocol. The protocol stated that patients in the OS analysis were censored at the date last known to be alive.

Clinical evaluator's comment

The sponsor's response is satisfactory.

Clinical efficacy (Question 4)

Sponsor's response

The primary analysis of PFS was done according to the SAP using the censoring rules in the SAP. Additional PFS calculations were done as sensitivity analysis using different censoring rules including when death or progression occurred after two or more missed assessments. This analysis was based on a recommendation from FDA in the pre-meeting minutes from the End of Phase (EOP) II meeting received on 21 March 2008. Additional analysis using the FDA guidance and the Clinical Trials Endpoint guidance were also done, without advice from FDA or EMA. Results were similar in all analyses, however statistical significance was lost in those analysis where censoring was more extensive. The censoring rules for the primary analysis are listed (below in Table 4).

Table 4: Censoring rules for PFS based on Independent review data.

Situation	End Date	Censored
Documented PD during the study	Date of the first assessment of the series of the tests that determined PD	No[a]
Death during the study before PD	Date of death	No[a]
Discontinued due to PD, but no documented PD	Date of last tumour assessment before discontinuation	Yes
Discontinued due to clinical progression per investigator	Date of last tumour assessment before discontinuation	Yes
No baseline assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death, and no post-baseline tumour assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death with post-baseline tumour assessments	Date of last tumour assessment	Yes
New anticancer treatment started prior to disease progression	Date of last tumour assessment before start of new treatment	Yes
Death or PD after one or more missed tumor assessments	Date of the last assessment before missed assessments	No[a]
Patients still on treatment without PD as of data cut-off	Date of last tumour assessment	Yes

a - Earliest date among the three dates is used in calculating the progression free survival.

The censoring according to FDA guidance is listed below (Table 5).

Table 5. PFS using FDA guidance document: sensitivity analysis.

Situation	End Date	Censored
Documented PD during the study	Earliest of • Date of radiological assessment showing new lesion (if progression is based on new lesion); • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	No[a]
Death during the study before PD	Date of death	No[a]
Discontinued due to PD, but no documented PD	Date of last tumour assessment before discontinuation	Yes
Discontinued due to clinical progression per investigator	Date of last tumour assessment before discontinuation	Yes
No baseline assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death, and no post-baseline tumour assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death with post-baseline tumour assessments	Date of last tumour assessment	Yes
New anticancer treatment started prior to disease progression	Date of last tumour assessment before start of new treatment	Yes
Death or PD after two or more missed tumor assessments	Date of the last assessment before missed assessments	Yes
Patients still on treatment without PD as of data cut-off	Date of last tumour assessment	Yes

The estimated HRs for PFS range from 0.819 to 0.868 (see Table 6, below), which is similar to the planned analysis (HR = 0.865, 95% CI = 0.714, 1.048) (see Table 7, below).

Table 6: PFS Forest plot of HR – Independent review summary; ITT population.

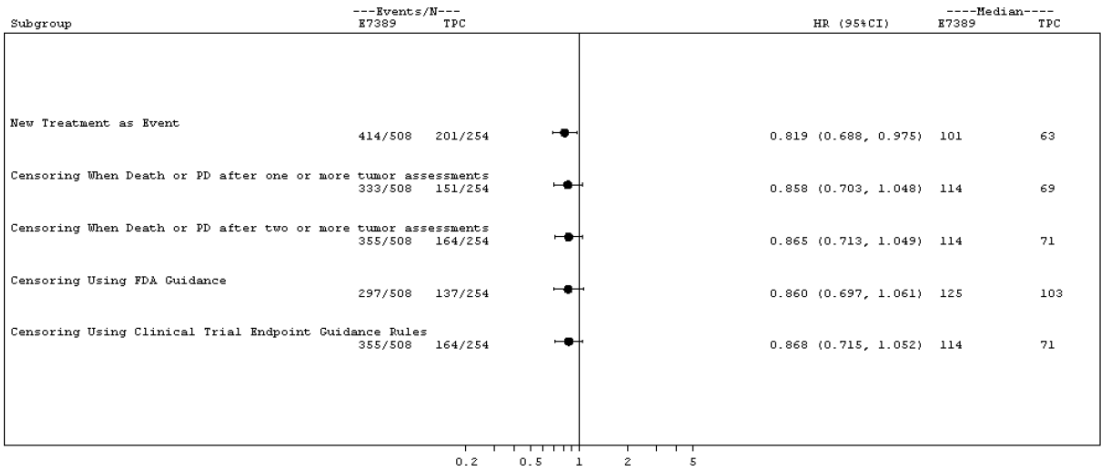


Table 7. PFS – Independent review summary; ITT population.

		Treatment Group	
		E7389 (N=508)	TPC (N=254)
Number of patients	Progressed or died	357 (70.3%)	164 (64.6%)
	Censored	151 (29.7%)	90 (35.4%)
Kaplan-Meier estimate of PFS (days)	1st Quartile (95% CI)	57.0 (55.0, 58.0)	54.0 (49.0, 57.0)
	Median (95% CI)	113.0 (101.0, 118.0)	68.0 (63.0, 103.0)
	3rd Quartile (95% CI)	187.0 (174.0, 205.0)	194.0 (147.0, 239.0)
Stratified log-rank test	p-value	0.137	
Hazard Ratio (E7389/TPC)*	Estimate	0.865	
	95% CI	(0.714, 1.048)	
Kaplan-Meier estimate of PFS at 3 months	3-month PFS rate (95% CI)	0.571 (0.526, 0.617)	0.449 (0.381, 0.517)
Kaplan-Meier estimate of PFS at 6 months	6-month PFS rate (95% CI)	0.263 (0.219, 0.307)	0.276 (0.210, 0.342)
Kaplan-Meier estimate of PFS at 9 months	9-month PFS rate (95% CI)	0.123 (0.085, 0.161)	0.113 (0.054, 0.172)
Kaplan-Meier estimate of PFS at 12 months	12-month PFS rate (95% CI)	0.088 (0.051, 0.125)	0.073 (0.020, 0.126)

Source: Listing 16.2.6.1.2 and Statistical Analysis Appendix 3.1
Note: * Hazard ratio based on a Cox model including HER2/neu status, prior capecitabine treatment and geographical region as strata.
Note: NE = Not Estimable due to insufficient events.

Clinical evaluator's comment

The sponsor's response is acceptable. The primary analysis of the PFS was by Independent review (HR = 0.865 [95% CI: 0.714, 1.048]; p = 0.137) (see Table 7, above). PFS was defined as the time from randomisation until progressive disease or death due to any cause. PFS was censored for patients who did not have an event (that is, those who were lost to follow-up or who had not progressed at the date of data cut-off). The primary analysis of PFS was based on the Independent review of tumor assessment in the ITT population, with the date of objective disease progression being based on the date of radiological disease progression as assessed by the Independent review of imaging data using RECIST criteria. Patients without disease progression were censored on the date of their last radiological assessment preceding the start of any additional anti-cancer therapy. Patients were also censored if they discontinued randomised treatment and began any alternative anti-cancer therapy prior to disease progression. The result of the primary PFS analysis was generally consistent with the results of the sensitivity analyses based on different censoring rules.

Second round benefit-risk assessment

Second round assessment of benefit

No new clinical information was submitted in response to the clinical questions. Accordingly the benefits of eribulin for the proposed indication are unchanged from those identified above in the initial (first round) assessment of benefits (see above).

Second round assessment of risks

No new clinical information was submitted in response to the clinical questions. Accordingly the risks of eribulin for the proposed indication are unchanged from those identified above in the initial (first round) assessment of risks (see above).

Second round assessment of benefit-risk balance

The benefit-risk balance of eribulin for the proposed indication remains favourable.

Second round recommendation regarding authorisation

- It is recommended that eribulin be approved as monotherapy 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.

- It is recommended that the proposed eribulin treatment regimen for the proposed indication be approved but with a downward dose adjustment for patients with moderate renal impairment.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR) (see Table 8 below).

Table 8. Summary of the EU RMP (extracted from the EU RMP version 1):

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Myelosuppression and associated infections	Neutropenia and myelosuppression included in all local/regional labels. Frequent monitoring of complete blood counts should be performed on all patients receiving eribulin. Patients should only be retreated with eribulin when ANC is ≥ 1000 cells/mm^3, platelets are ≥ 75,000 cells/mm^3, and any other toxicity of a previous Cycle has recovered to Grade ≤ 2 (except anaemia). Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia, may require a subsequent reduction of the dose or eribulin. Such events, and severity, to be monitored in post marketing environment. Cumulative experience will be described in any Periodic Safety Update Report (PSUR) as standard practice.	None required.
Peripheral neuropathy	Described in all local/regional labels. Neuropathy has been further evaluated in clinical studies. Such events, and severity, to be monitored in post marketing environment. Cumulative experience will be described in any PSUR as standard practice.	None required.

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA's Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the Ongoing Safety Concerns as specified by in the RMP are:

Important identified risks:

- Myelosuppression and associated infections
- Peripheral neuropathy

Important potential risk:

- Adverse pregnancy outcomes

OPR reviewer's comments:

It is noted that QT prolongation and effects on fertility are highlighted under the *Precautions* section of the proposed Australian PI but are not included as ongoing safety concerns in the RMP for close monitoring. Further clarification was sought from the sponsor and in the response to a TGA request for information, the sponsor stated that male infertility was discussed in the RMP and PI, and QT prolongation was discussed in the PI. The sponsor also confirmed that no additional risk minimisation activities are proposed for QT prolongation or male infertility. The possible inclusion of 'male infertility' as a SS of the RMP may need to be reconsidered in the future, in the event that the indications will be broaden to include the treatment of other cancers that may not predominantly affect women.

It appeared that 'patients with renal impairment' has been identified as an area requiring further monitoring and characterisation, as suggested by the commissioning of Study E7389-A001-106 specifically to evaluate this risk. It is recommended that 'patients with renal impairment' be added to the SS of the RMP as an area of Important missing information, either in the future update to the EU RMP or the Australian-specific Annex. Pursuant to the evaluation of the nonclinical and clinical aspects of the SS, the above summary of the Ongoing Safety Concerns is otherwise considered acceptable, unless additional safety concerns including but not limited to QT prolongation and effects on fertility are recommended for inclusion in the SS of the RMP by the non-clinical or clinical evaluator(s).

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed for all Ongoing Safety Concerns.

Risk minimisation activities

It is proposed that routine risk minimisation activities are sufficient for all ongoing safety concerns.

Summary of recommendations

As the final clinical and nonclinical evaluation reports are not available at the time of finalising this report, the final RMP may need to be updated to take into account any additional risk(s) and/or safety concerns identified in these final reports. Pending the finalisation of the clinical and nonclinical evaluation reports, the OPR offers the conclusion based on the currently available information that the submitted RMP is supportive to the application; the implementation of the RMP identified as EU Risk Management Plan (RMP) version 1 with data lock point of 12 May 2009, and any subsequent versions, is imposed as a condition of registration with the following qualifications:

If this application is approved, it is recommended that the Delegate considers the following proposed amendments to the RMP in context of the overall submission as to whether they are necessary and appropriate for implementation in Australia:

Safety specifications

The addition of the following to the SS of the RMP is recommended:

- 'patients with renal impairment' as an area of Missing information.

An amendment can be made to the future update of the EU RMP and/or provided in the form of an Australian-specific Annex to the EU RMP, which can be submitted to the TGA post registration.

Pharmacovigilance activities

The inclusions of the following studies as part of the additional pharmacovigilance activities of the RMP are recommended:

- Study E7389-G000-209 is designed to specifically evaluate the important identified risk 'peripheral neuropathy'. A brief description on how this study is appropriately designed to monitor and evaluate this risk and what the expected milestone for study reporting should also be provided.
- Study E7389-A001-106 is designed to evaluate the safety and PK in patients with moderate to severe renal impairment. The expected milestone for this study report should also be provided.

An amendment can be made to the future update of the EU RMP and/or provided in the form of an Australian-specific Annex to the EU RMP, which can be submitted to the TGA post registration.

Risk minimisation activities

- The inclusion of a risk minimisation strategy for the safety concern 'patients with renal impairment', by adding a recommendation in the Dosage and Administration section of the PI to reduce the dose of Halaven to 1.1 mg/m2 for patients with moderate renal impairment (defined as those with CrCL of 30-50 mL/min) may be considered as appropriate.
- The update to the information in the RMP is recommended to reflect the sponsor's commitment to implement routine risk minimisation activities in Australia for all relevant safety concerns, provided as an Australian specific Annex. This can be submitted to the TGA post registration.

Information presented in the Product Information

Details of recommended revisions to the PI are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The chemistry and quality control aspects are considered acceptable. Impurity limits were tightened following consideration by the PSC at its 143rd meeting (2012/1).

An issue remaining is the labelling of the dosage amount. Doses in this overview are based on the amount of eribulin mesilate since this is how they were presented in the application and the evaluation reports. The current practice is to label according to the amount of the active moiety, that is, eribulin 0.88 mg per vial; however, there is no international standard.

Nonclinical

Eribulin was significantly toxic to lymphoid, haematopoietic, peripheral nervous and male reproductive tissues in rats and dogs. Toxic effects were also seen in the liver, kidney,

gastrointestinal tract and skeletal muscle. There were deaths due to toxicity. The toxic effects occurred at exposure levels below or only marginally higher than the anticipated clinical exposure. The toxicity profile was similar to that of the taxanes.

Eribulin was clastogenic in mice and rats. This was expected for an anti-microtubule agent. Eribulin was also teratogenic and caused embryofetal deaths in rats at exposure levels below the anticipated clinical exposure. Carcinogenicity studies were not performed and there was no assessment of excretion of eribulin in breast milk.

The sponsor requested changes to the evaluation report. The nonclinical evaluator did not agree to most of the changes. None of the changes affected the overall assessment.

The nonclinical evaluator had reservations about approval of eribulin due to its toxicity and deferred to the clinical data.

Clinical

Pharmacology

- Using the proposed regimen of dosing on Days 1 and 8 of a 21 Day cycle, the maximum tolerated dose of eribulin in patients with advanced solid tumours was 2.0 mg/m2 (Study 105). At this dose, 3/3 patients experienced dose-limiting toxicity compared with 2/6 at 1.4 mg/m2. The later dose was chosen for the efficacy studies. The dose limiting toxicity was neutropenia.
- The relationship between QTcF and eribulin plasma concentration was assessed in 26 patients with advanced solid tumours (Study 110). The dose of eribulin was the same as the proposed dose for one cycle; 1.4 mg/m2 IV on Days 1 and 8 of the first 21 Day cycle. QT prolongation was seen on Day 8 and it was unrelated to eribulin plasma concentration which was the same on Days 1 and 8. On Day 8, the maximum post dose time-matched QTcF prolongation was > 5 ms and the upper bound of the 95% CI > 10 ms. There were no AEs related to the ECG. A precautionary statement is proposed for the PI.
- The PK studies were done in patients with advanced solid tumours. Eribulin had a large volume of distribution, ranging from mean 41 to 114 L/m2 in the studies. This suggests extensive distribution to tissues. Metabolism was minimal and most of the drug (90%) was excreted unchanged in faeces. Clearance was low, ranging from mean 1.1 to 2.4 L/h/m2 in the studies. The mean terminal plasma elimination t½ was 42 h. Biliary excretion was the main route of elimination. Renal excretion accounted for less than 10% of the dose. Based on pooled data from the three dose escalation studies, the PK of eribulin were linear for IV doses of 0.25 to 4.0 mg/m2. There was no accumulation with weekly dosing.
- Based on Study 108 and population PK analysis, eribulin exposure was increased in mild to moderate hepatic impairment and dose reduction to 1.1 mg/m2 in mild impairment and 0.7 mg/m2 in moderate impairment is recommended. There were limited data for severe hepatic impairment.
- Based on Study 110, Synold et al., 201018 and population PK analysis, eribulin exposure was also increased in mild to moderate renal impairment. The clinical evaluator recommended a reduced dose of 0.7 mg/m2 in moderate renal impairment;

[18] Synold TW, Tsao-Wei DD, Quinn DI *et al*. Phase I and pharmacokinetic (PK) study of eribulin (E7389) in patients (pts) with renal dysfunction (RD) and advanced urothelial cancer (UC) – A California Cancer Consortium trial. *J Clin Oncol* 2010;28:15s (suppl; abstract 2527).

however, the sponsor, in its response to the clinical evaluator's request for further information, disagreed. There were limited data in severe renal impairment.

- Since eribulin is mainly eliminated through biliary excretion, co-administration of eribulin and inhibitors of hepatic transporting proteins may increase eribulin exposure. Studies are underway to investigate this. The PI recommends against co-administration.

Efficacy

- The efficacy of eribulin in the proposed indication was assessed in three trials: a controlled trial (Study 305) and two uncontrolled trials (Studies 211 and 201). Patients were to have received prior anthracycline and taxane treatment but were not required to be refractory to this treatment. Patients were required to have progressed within 6 months of their last chemotherapeutic regimen.
- Study 305 (also called EMBRACE) was a randomised 2:1, open-label trial comparing eribulin with a single agent TPC. The trial was multinational including Australia. Patients received either eribulin IV injection 1.4 mg/m2 on Days 1 and 8 of a 21 Day Cycle (n = 508) or TPC (n = 254). The most common TPC were vinorelbine (24%), gemcitabine (18%), capecitabine (17%), taxane (15%) and anthracycline (9%). There is no standard third line treatment after an anthracycline and a taxane. Patients had received a median of 4 previous chemotherapy regimens for advanced breast cancer. The median age of patients was 55 years (range 27-85 years). The majority (91%) had Eastern Cooperative Oncology Group (ECOG) performance status[19] 0 or 1. Treatment was continued until disease progression or unacceptable toxicity. The median duration (range) of treatment was 3.9 months (0.7-16.3 months) with eribulin and 2.1 months (0.03-21.2 months) with TPC.
- Eribulin significantly increased OS, the primary endpoint, by a median 2.5 months compared with TPC (see Table 9). The analysis was done after 55% of patients had died. An updated analysis after 77% of patients had died achieved a similar result. Eribulin also significantly increased overall tumour response rate but not independently assessed PFS. The duration of response was short. The results have been published.[20]

	Eribulin **1.4 mg/m^2 Day 1 & 8 IV; n=508**	**TPC** **n = 254**	**Hazard Ratio [95% CI] or p-value of difference**
After 55% died Survival median *months*	13.1	10.6	0.81 [0.66, 0.99][2] p=0.041[3]

[19] ECOG has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction; 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 – Dead

[20] 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;377:914-923.

<u>After 77% died</u> Survival median *months*	13.2	10.6	0.81 [0.67, 0.96][2] p=0.014[3]
PFS[1] median *months*	3.7	2.2	0.87 [0.71, 1.05][2] p=0.137[3]
ORR[1] Complete Response Partial Response	12.2% (n=468) 0.6% 11.5%	4.7% (n=214) 0% 4.7%	p=0.002[4]
Duration of Response[1] median *months*	4.2	6.7	p=0.159[3]

- Table 9. Efficacy in advanced breast cancer after progression following at least two prior therapies including anthracycline and taxane (Study 305) – *intent-to-treat*

[1] Independently assessed (RECIST criteria). [2] Kaplan-Meier analysis and Cox regression. [3] Log-Rank Test – significance level adjusted to 0.049 in the first analysis. [4] Fisher's Exact Test. TPC: Treatment of Physician Choice. PFS: Progression-Free Survival. ORR: Overall Response Rate (complete response + partial response).

- The results of the uncontrolled trials were generally consistent with those of the pivotal trial 305. Trial 211 used the same 21 Day regimen as the pivotal trial. Trial 201 had 2 cohorts: cohort 1 received a 28 Day regimen of eribulin 1.4 mg/m2 IV on Days 1, 8 and 15 and cohort 2 received the 21 Day regimen of the pivotal trial. Response rates were assessed independently in both trials. The assessment method was not specified for trial 211. RECIST criteria were used in trial 201.
- In trial 211, outcomes were assessed in the "eligible population" which was representative of a refractory population that had received standard breast cancer treatment and was validated independently. The ORR was 9.3% (25/269), the median duration of response 4.1 months and median survival 10.4 months. The median duration of treatment was 2.8 months and median number of treatment cycles was 4.
- In trial 201, outcomes were assessed in the per protocol population. In the 28 Day cohort, the ORR was 10.2% (6/59), the median duration of response 5.0 months and median survival 7.9 months. In the 21 Day cohort, the ORR was 14.3% (4/28); median duration of response and survival were not reached. The median number of treatment cycles was 2.5 for the 28 Day regimen and 4 for the 21 Day regimen.

Safety

- There were safety data from the pivotal trial 305 (n = 503 eribulin, 247 TPC) and pooled data from AETP (n = 1,222) and the BCP (n = 827). The pooled data was consistent with the pivotal trial data. Unless otherwise stated, the data below are from the pivotal trial.
- Adverse events occurring frequently with eribulin and of considerably greater incidence (at least 10 percentage points) than TPC were asthenia/fatigue 54%, neutropenia 52%, alopecia 45%, peripheral neuropathy 35%, leukopenia 23% and arthralgia/myalgia 22%. Most of these events were considered treatment related by the investigator. Four events were frequently severe (CTCAE Grade 3-4) with eribulin: neutropenia 45%, leukopenia 14%, asthenia/fatigue 9% and peripheral neuropathy 8%. For eribulin patients with severe neutropenia, the median time to nadir ANC within a treatment Cycle was 12-14 days, the majority of patients (94%) recovered to Grade ≤ 2 with median recovery time of 8 days.
- Peripheral neuropathy was the most frequent AE leading to treatment discontinuation (4.8% with eribulin versus 1.2% with TPC). Based on the pooled eribulin data, the median time of onset of peripheral neuropathy was 5 months, the neuropathy resolved

in only 13-14% of patients and the median time to resolution was 2 months. The data were heavily censored due to lack of patient follow-up.

- There was a greater incidence of severe AEs with eribulin than TPC – 61% eribulin versus 46% TPC for Grade 3 events and 29% eribulin versus 13% TPC for Grade 4 events. Serious AEs reported as treatment related were also of greater incidence with eribulin (11.7%) than TPC (6.9%). Febrile neutropenia was the most common serious adverse reaction (4.2% eribulin versus 0.4% TPC). There were 5 deaths (1.0%) reported as treatment related in the eribulin group and 2 (0.8%) in the TPC group. The 5 eribulin deaths were due to febrile neutropenia, lung infection, bronchopneumonia and dyspnoea (2).
- Cardiac AEs occurred in 6.6% of eribulin patients and 4.0% of TPC patients. Tachycardia and palpitations were the commonest cardiac events: 3.6% with eribulin versus 1.2% with TPC for tachycardia and 1.6% with eribulin versus 0.4% with TPC for palpitations. There were no instances of Torsade de pointes.
- The median duration of exposure in the eribulin group (3.9 months) was higher than that in the TPC group (2.1 months) which may explain some of the differences in incidence of AEs. However, post hoc adjustments for duration of exposure confirmed the greater risk of eribulin than TPC.

Clinical evaluator's recommendation

The clinical evaluator supported registration.

Risk management plan

- Based on the nonclinical and clinical data, the SS is adequate.
- The EU RMP version 1 with data lock point 12 May 2009 was considered acceptable with amendments recommended by the RMP evaluator. The Delegate proposed to recommend the amendments be included as an Australian-specific Annex.

Risk-benefit analysis

Delegate considerations

In the pivotal trial 305 in patients with locally advanced or metastatic breast cancer who had progressed after at least two chemotherapeutic regimens including an anthracycline and a taxane, eribulin significantly increased OS by a median of 2.7 months compared with TPC in the updated analysis. Tumour response was also significantly increased but not PFS. There was support from two uncontrolled trials.

Eribulin had significant toxicity in particular neutropenia, leukopenia, peripheral neuropathy, alopecia and arthralgia/myalgia. Toxicity was managed by dose delays and/or reductions in most instances. Colony stimulating factors were also used to manage neutropenia. Symptomatic medication was used for nausea and vomiting. Based on a PD sub-study, ECG QT prolongation was a possible risk.

The increased survival with eribulin is clinically relevant in the context of last-resort treatment. However, it needs to be balanced against significant toxicity. The benefit-risk balance is marginally favourable. Eribulin is the first of a new drug class for advanced breast cancer and provides an alternative third line treatment for patients with this disease. Other third line options are capecitabine and vinorelbine.

Although the data are limited, the Delegate recommended the dose of eribulin be reduced to 1.1 mg/m^2 (a 21% reduction) in patients with moderate renal impairment (CrCL

30-50 mL/min) in line with the USA, rather than 0.7 mg/m^2 (a 50% reduction) recommended by the clinical evaluator. In the pooled results of the Phase I trials, in which there were 62 patients with normal renal function and 5 patients with moderate renal impairment, the dose-normalised mean AUC was 1.7 fold higher and the dose-normalised geometric mean AUC 1.5 fold higher in patients with moderate renal impairment than in patients with normal renal function. Therefore, a dose reduction of up to one-third is appropriate. This can be reviewed when the results of an ongoing study of eribulin in renal impairment are known.

Proposed action

The Delegate proposed to approve eribulin mesilate injection (Halaven) for the indication:

> *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.*

Approval will be subject to finalisation of the PI.

Proposed condition of registration:

Implementation of the EU RMP version 1.0 dated 12 May 2009 and subsequent revisions and an Australian-Specific Annex as agreed with the TGA's OPR.

Advice requested from ACPM

The Delegate sought general advice on this application from the ACPM.

Response from sponsor

The sponsor supports the Delegate's decision to approve Halaven for *"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."*

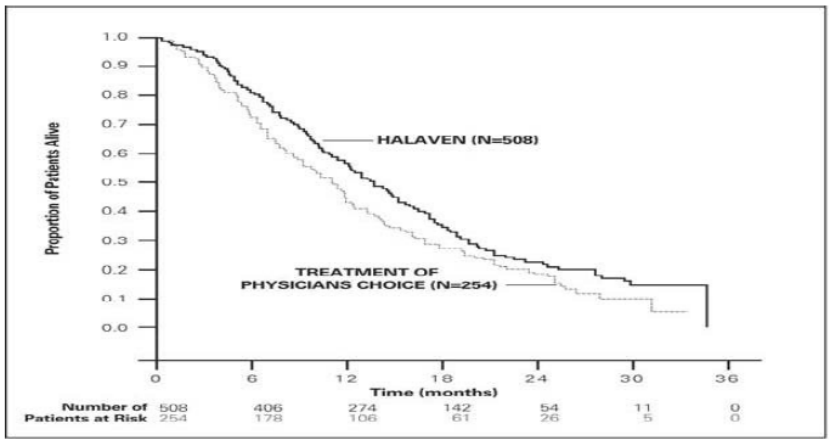
Halaven is approved in 37 countries, including the US, EU and Canada. The indication recommended by the TGA Delegate is aligned with the indication approved in the US, EU and Canada.

1. Statistical and clinical significant efficacy benefit has been demonstrated for Halaven versus TPC

In the pre-specified primary analysis (ITT population), OS was statistically significantly longer in the eribulin group compared to TPC (median 399 days [approximately 14 months] versus 324 days [approximately 11.5 months]; p = 0.041, stratified log-rank test). Based on a Cox proportional hazards model employing pre-specified stratification factors, the HR for OS was 0.809 (95% CI: 0.660, 0.991). The observed improvement in median survival of 75 days (approximately 2.5 months) compared to TPC is clinically relevant in this late-line setting.

An additional analysis was performed at the request of the EMA when approximately 75% to 85% of pre-specified events had accrued (cut-off date of March 2010), providing a more comprehensive analysis of OS data than the pre-specified primary analysis. A total of 588 deaths (77.2% of planned) were actually observed in the updated analysis data sweep. Kaplan-Meier survival curves were generated for OS as shown in the following figure:

Figure 2. Kaplan-Meier survival curves - OS.



In the updated analysis, OS was significantly extended for patients receiving eribulin compared to TPC (HR 0.805; 95% CI: 0.677, 0.958) with a nominal p = 0.014. Median values of OS were 403 days for eribulin and 321 days for TPC (a difference of 82 days). Notably, the OS curve for eribulin remained above that for TPC over the entire observation period (up to 1000 days in this data sweep).

The primary analysis of PFS was done according to the SAP using the censoring rules in the SAP. Additional PFS calculations were done as sensitivity analysis using different censoring rules including when death or progression occurred after two or more missed assessments. This analysis was based on a recommendation from FDA in the pre-meeting minutes from the EOP II meeting received on 21 March 2008. Additional analysis using the FDA guidance and the Clinical Trials Endpoint guidance were also done, without advice from FDA or EMA. Median PFS as determined by Independent review of the ITT population was 113 days in the eribulin arm and 68 days in the TPC arm. This difference did not reach statistical significance (HR 0.865; p = 0.137). In contrast, both the investigator assessment and per-protocol analysis showed a statistically significant PFS benefit compared to TPC. Results were similar in all analyses, however statistical significance was lost in those analysis where censoring was more extensive.

2. The safety profile of Halaven has been well defined and can be appropriately clinical managed.

Eisai has a robust signal detection process involving regular review of all ADRs reported. Ongoing signal detection including two submitted Periodic Safety Update Reports (PSURs) have not shown any change in incidence or severity of listed adverse reactions, including neutropenia, leukopenia, peripheral neuropathy, alopecia and arthralgia. All of these reactions are listed on the Company Core Data Sheet for Halaven and therefore appear in all labels in all countries globally, including the proposed PI for Australia. Prescribers are also informed of appropriate dose delays or dose reductions to manage adverse reactions at Grade 3 or 4 as shown in the *Dosage and Administration* section of the proposed Halaven PI.

3. Halaven has a favourable risk benefit assessment

The clinical benefit of eribulin has been demonstrated in the primary, randomised, active controlled Phase III study (Study 305). The results of this study provide clear evidence of a clinically meaningful improvement in OS in patients with locally advanced breast cancer (LABC) or metastatic breast cancer (MBC), a patient population with few treatment options and an unmet medical need. Eribulin is easy to administer, has an acceptable safety profile, and can be used in patients with pre-existing peripheral neuropathy.

Study 305 evaluated eribulin compared to TPC in 762 patients with LABC or MBC who had previously received two to five prior chemotherapy regimens (including an anthracycline and a taxane). The primary efficacy endpoint in Study 305 was OS, a robust endpoint for

studies in advanced cancer. The OS result was statistically significantly longer in the eribulin arm compared to the TPC arm (p = 0.041, HR 0.809, 95% CI: 0.660, 0.991). Median OS was 399 days in the eribulin arm and 324 days in the TPC arm, a 75 day (2.5 months) improvement. This OS benefit for patients with this stage of disease was confirmed by the updated analysis and is clinically meaningful.

The secondary endpoints in Study 305 (PFS, ORR, clinical benefit rate (CBR) and DoR) are supportive of the primary endpoint result, with the improved efficacy of eribulin compared to TPC confirmed. Median PFS with eribulin is longer than with TPC (113 days versus 68 days as assessed by Independent review, and 110 days versus 66 days as assessed by Investigator review); ORR is improved (12.2% versus 4.7%); and CBR is improved (22.6% versus 16.8%). The median DoR with eribulin was also clinically relevant (128 days by Independent review). Data for ORR and DoR from Study 305 are consistent with the data from the Phase II studies of eribulin in LABC and MBC.

Eribulin administration is simple and convenient. The ready-to-use presentation is given at a dose of 1.4 mg/m^2 administered over only 2 to 5 minutes on Days 1 and 8 in a 21 Day Cycle. No premedication with corticosteroids and antihistamines is necessary to prevent hypersensitivity.

Eribulin does not inhibit or induce CYP enzymes at relevant clinical concentrations, and no effect of CYP3A4 inhibitors or inducers on eribulin exposure was observed. This lack of drug–drug interaction provides greater flexibility and less risk in this patient population who often receive concomitant medications to control the effects of their advanced disease or to manage concomitant diseases, which are common in this population.

The safety of eribulin has been examined in 827 patients at the proposed dose regimen (including 503 patients from Study 305). The majority of the common TEAEs with eribulin were CTCAE Grade 1 or 2, and relatively few patients discontinued therapy because of AEs (13% of patients treated at the proposed dose).

The haematological toxicity with eribulin is frequent and sometimes severe but proved to be manageable with dose delays, dose reductions and the use of growth factors. Myelosuppression is related to eribulin exposure and primarily manifests as neutropenia. Notably, febrile neutropenia and thrombocytopenia were infrequent, and neutropenia led to eribulin discontinuation for < 0.6% of patients treated at the proposed dose. To manage haematological toxicity, patients should only be re-treated with eribulin when neutrophils recover to a level of ≥ 1 x 10^9/L and platelets are ≥ 75 x 10^9/L. Patients experiencing febrile neutropenia, severe and persistent neutropenia, or severe thrombocytopenia require a reduction of the dose of eribulin.

Subgroup analyses of TEAEs showed that Grade 4 neutropenia and febrile neutropenia were more likely to develop in patients with AST/ALT > 3 × upper limit of normal (ULN) or bilirubin > 1.5 × ULN. A precaution is proposed for the PI that reduction of the starting dose should be considered and these patients should be monitored closely for toxicity.

Common non-haematological TEAEs during eribulin therapy included asthenia/fatigue, and in some cases this was severe. Another common non-haematological TEAE was peripheral neuropathy. Most of the peripheral neuropathy events with eribulin were Grade 1 or Grade 2; development of Grade 3 and 4 TEAEs was not frequent (< 8% of patients treated with the proposed dose regimen). Peripheral neuropathy led to discontinuation of treatment in < 5% of patients treated with eribulin at the proposed dose and about half of the patients with Grade 3/4 peripheral neuropathy were able to continue treatment; thus, peripheral neuropathy was manageable. Patients with pre-existing neuropathy were no more likely to develop new or worsening symptoms than those who entered the study without the condition. These non-haematological TEAEs were usually manageable with dose delays, dose reductions, or supportive therapies. Guidance for dose delays and reductions are proposed in the PI.

4. Recommended dosage instructions for renally impaired patients

Eisai agrees with the Delegate's suggested dose reduction to 1.1 mg/m^2 in moderate renal impairment and has amended the text in the PI in alignment with the US PI.

Conclusion

Eribulin provides clear clinical benefit for the treatment of patients with LABC and MBC previously treated with at least two prior chemotherapy regimens. Eribulin is the only agent proven to extend survival in this patient population. Eribulin has an acceptable safety profile. The risk of toxicity with eribulin is comparable or less than that for other agents currently used in this population. Proposed precautions and dose adjustments will allow the toxicity of eribulin to be managed appropriately. Eribulin is provided as a ready-to-use formulation that is easily administered as a 2 to 5 minute IV infusion without the need for premedication to prevent hypersensitivity. Therefore, eribulin will be an important and clinically useful addition to the currently available therapies in this patient population with few remaining treatment options.

Product Information

The PI has been amended as recommended by the TGA. Details of revisions to the PI are beyond the scope of this AusPAR.

Risk Management Plan

The sponsor agrees to comply with the Delegate's recommendation that an RMP and Australian Specific Annex will be required to be submitted as a post approval condition of registration.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit–risk profile for the following indication**;**

> *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 making this recommendation the ACPM noted the absence of data to support any dosing guidelines for use in patients with renal dysfunction and expressed concern that guidance is required.

The ACPM agreed with the Delegate to the proposed amendments to the PI and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the *Dosage and Administration, Clinical Trials, Precautions* and *Contraindications* sections of the PI to ensure guidance to prescribers for dosing in patients with renal impairment, while highlighting the absence of evidence for use in this patient population.

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically encouraged the sponsor to conduct additional PK studies to inform robust dosage guidelines.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Halaven solution for injection, containing eribulin mesilate 1 mg/mL for the following indication:

Halaven 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.

Specific conditions of registration applying to these goods

The implementation in Australia of the EU eribulin mesilate RMP, version 1.0 dated 12 May 2009, and any subsequent revisions, as agreed with the TGA and its OPR.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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