



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Eribulin mesilate

Proprietary Product Name: Halaven

Sponsor: Eisai Australia Pty Ltd

October 2017

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- 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.
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- 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; it provides 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.

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Common abbreviations

| Abbreviation | Meaning |
|------------------|--|
| AE | Adverse Event |
| AESI | Adverse event of special interest |
| AJCC | American Joint Committee on Cancer |
| ALKP | Alkaline Phosphatase |
| ALT | Alanine Transaminase |
| ANC | Absolute neutrophil count |
| ARTG | Australian Register of Therapeutic Goods |
| AST | Aspartate Transaminase |
| AUC | Area under the curve |
| BIL | Bilirubin |
| BUN | Blood urea nitrogen |
| CBR | Clinical Benefit Rate |
| CI | Confidence interval |
| C _{max} | Maximum concentration |
| C _{min} | Minimum concentration |
| CMI | Consumer Medicines Information |
| CL | Clearance |
| CR | Complete Response |
| CrCl | Creatinine clearance |
| CT | X-Ray Computed Tomography |
| CTCAE | Common terminology criteria for adverse events |
| CV | Coefficient of variation |
| DCR | Disease Control Rate |
| dSD | Durable stable disease |
| ECG | Electrocardiograph |
| EMA | European Medicines Agency |

| Abbreviation | Meaning |
|--------------|--|
| EORTC | European Organisation for Research and Treatment of Cancer |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GIT | Gastrointestinal tract |
| ICH | International Conference on Harmonisation |
| L | Litre(s) |
| LDH | Lactate Dehydrogenase |
| LFTs | Liver function tests |
| MBC | Metastatic breast cancer |
| MEDRA | Medical dictionary for regulatory activities |
| MRI | Magnetic Resonance Imaging |
| NCCN | National Comprehensive Cancer Network |
| ORR | Objective response rate |
| OS | Overall Survival |
| PD | Pharmacodynamics |
| PFR12wks | Progression-free survival rate at 12 weeks |
| PFS | Progression free survival |
| PI | Product Information |
| PK | Pharmacokinetics |
| PR | Partial Response |
| PS | Performance status |
| QoL | Quality of Life |
| RECIST | Response evaluation criteria in solid tumours |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| STS | Soft Tissue Sarcoma |
| TGA | Therapeutic Goods Administration |

| Abbreviation | Meaning |
|--------------|-------------------------------|
| Tmax | Time of maximum concentration |
| WHO | World Health Organisation |

I. Introduction to product submission

Submission details

| | |
|------------------------------------|---|
| <i>Type of submission:</i> | Extension of Indications |
| <i>Decision:</i> | Approved |
| <i>Date of decision:</i> | 16 November 2016 |
| <i>Date of entry onto ARTG</i> | 18 November 2016 |
| <i>Active ingredient(s):</i> | Eribulin mesilate |
| <i>Product name(s):</i> | Halaven |
| <i>Sponsor's name and address:</i> | Eisai Australia Pty Ltd Level 2, 437 St. Kilda Road, Melbourne, VIC, 3004. |
| <i>Dose form(s):</i> | Solution for injection |
| <i>Strength(s):</i> | 1mg/2 mL |
| <i>Container(s):</i> | Glass vial |
| <i>Pack size(s):</i> | 1 or 6 |
| <i>Approved therapeutic use:</i> | <i>Halaven is indicated for the treatment of patients with unresectable liposarcoma who have received prior chemotherapy for advanced or metastatic disease.</i> |
| <i>Route(s) of administration:</i> | Intravenous (IV) |
| <i>Dosage:</i> | 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. See Attachment 1 for further details. |
| <i>ARTG number (s):</i> | 187136 |

Product background

This AusPAR describes the application by the sponsor to extend the indications for Halaven (eribulin mesilate; 1 mg/2 mL solution for injection) to include treatment of patients with unresectable soft tissue sarcoma (STS) who have received prior chemotherapy for advanced or metastatic disease.

Currently this product is registered for the following indications:

Halaven is indicated for the treatment of patients with locally advanced or metastatic breast cancer, who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless these are contraindicated.

The proposed dose and dosage regimen for the new indication are the same as the maximum daily dose for the currently approved anti-neoplastic indication of Halaven (1.4 mg/m² on Days 1 and 8 of every 21 day cycle).

Eribulin mesilate is in the halichondrin class of antineoplastic agents. It binds to tubulin, inhibiting microtubule formation and is cytotoxic, preventing mitosis and cell proliferation.

Soft-tissue sarcomas (STS) are a heterogeneous group of rare malignant tumours arising in tissues derived from embryonic mesoderm (for example, muscle and adipose tissue and blood vessels) and include about 1% of all malignancies in adults and 7 to 10% of malignancies in children.

Usually presenting as a painless enlarging mass, soft-tissue sarcomas most commonly occur in limbs, limb girdle and abdomen. Peripheral STSs commonly metastasise to lungs and those arising in the abdomen commonly spread to liver and peritoneum. The American Joint Committee on Cancer (AJCC) system used for grading and staging (Table 3, under *Clinical findings*, below) was used in the pivotal study in this submission. Adverse prognostic factors include large tumour size, high grade, advanced stage, older age and histological subtype. The mainstay of treatment is surgery, with radiotherapy for local control in resectable disease or where surgery is inappropriate. Systemic chemotherapy is used in subjects with unresectable disease.

STS comprises over fifty histologically distinct subtypes. The most common of these subtypes in adults are undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma and synovial sarcoma. Most are relatively resistant to systemic therapies. Systemic therapy is not considered curative for advanced or unresectable soft-tissue sarcoma. A subset of patients may have substantial long-term survival.

Currently available systemic treatments

Grandfathered products registered in Australia for the broad STS indication include doxorubicin, epirubicin, ifosfamide and dacarbazine. Doxorubicin (an anthracycline) alone or in combination with ifosfamide is recommended in the Australian Guideline as first-line treatment for unresectable/metastatic STS. See Table 1 for details.

Pazopanib (Votrient) was registered in Australia in 2010 for use as second or later line therapy of STS, excluding GIST and adipocytic sarcomas.

There is no standard second or later line treatment. Australian guidelines recommend ifosfamide (if not used in first-line) and then dacarbazine.¹

This submission is based on lack of established therapies for soft-tissue sarcomas after first-line failure and Phase III data showing efficacy in soft tissue sarcomas in Study 309.

Table 1: Approved medicines for treatment of soft-tissue sarcoma in Australia

| Generic | Tradename | Sponsor | TGA approved sarcoma indication |
|-------------|--------------------------------------|--|---|
| Doxorubicin | Adriamycin Plus multiple generics | Pfizer Australia multiple generics | 'Adriamycin has been used successfully to produce regression in neoplastic conditions such as: acute leukaemia, Wilms' tumour, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, lymphomas of both Hodgkin's and non-Hodgkin's type, bronchogenic |

¹ Cancer Council Australia Sarcoma Guidelines Working Party. Clinical practice guidelines for the management of adult onset sarcoma. Sydney: Cancer Council Australia.

| Generic | Tradename | Sponsor | TGA approved sarcoma indication |
|---------------|---------------------------------|-------------------|--|
| | | | (lung) carcinoma, thyroid carcinoma, hepatomas, ovarian carcinoma, etc.' The response rate provided for 'sarcoma' is '30%', median duration 4 months, first-line chemotherapy. |
| Epirubicin | Multiple generics | Multiple | 'Epirubicin hydrochloride has produced responses in a wide spectrum of neoplastic diseases and is indicated for the treatment of: breast cancer, gastric cancer, ovarian cancer, small cell lung cancer, lymphoma (non-Hodgkin's lymphoma), advanced/metastatic soft tissue sarcoma, superficial bladder cancer (Tis; Ta).' |
| Ifosfamide | Holoxan | Baxter Healthcare | 'Indications for the use of ifosfamide are tumours sensitive to ifosfamide either as a single agent or in combination with other chemotherapeutic agents. Tumour types that have been demonstrated to respond to ifosfamide single agent or in combination are germ cell tumours, sarcomas, lymphomas.' |
| Dacarbazine | Dacarbazine Sandoz plus generic | Sandoz, Hospira | 'Chemotherapy of metastatic malignant melanoma and various sarcomas. In other cancers, the available evidence shows dacarbazine to be ineffective or less effective than established regimens. Note. The use of dacarbazine is restricted to hospitals with an oncology service.' |
| Pazopanib HCl | Votrient Tablets | Novartis | 'VOTRIENT is indicated for the treatment of advanced (unresectable and/or metastatic) soft tissue sarcoma (STS) in patients who, unless otherwise contraindicated, have received prior chemotherapy including an anthracycline treatment. The Phase III trial population excluded patients with gastrointestinal stromal tumour (GIST) or adipocytic soft tissue sarcoma'. Votrient has a boxed warning: 'Severe and fatal hepatotoxicity has been observed in clinical studies.' |

| Generic | Tradename | Sponsor | TGA approved sarcoma indication |
|---------|-----------|---------|--|
| | | | Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. [See PRECAUTIONS.] |

Regulatory guidelines

- The TGA has adopted the EU Guideline on the evaluation of anticancer medicinal products in man, EMA/CHMP/205/95/Rev.4 (and relevant appendices).
- TGA-adopted EU Guidelines include 'Points to consider on application with 1) meta-analysis; 2) single pivotal study' (CPMP/EWP/2330/99).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on the 4 September 2012.

At the time of submission to the TGA, similar applications had been lodged in the European Union, the USA and in Switzerland (Table 2). The application in the USA was approved on 28 January 2016. The European Medicines Agency's (EMA's) advisory committee recommended approval of the application in Europe on 1 April 2016. In both cases the indication was restricted to subjects with liposarcoma.

Table 2: International regulatory status

| Country | Current Status | Approval date | Approved Indication |
|-----------------------|----------------|------------------|---|
| European Union | Approved | 06 May 2016 | Halaven is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease. |
| USA | Approved | 28 January 2016 | Halaven is indicated for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing treatment. |
| Russia | Approved | 15 May 2016 | Halaven is indicated for the treatment of patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease |
| Japan | Approved | 29 February 2016 | Soft tissue sarcoma |

The complete indications in the USA are:

Metastatic Breast Cancer

Halaven is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting [see Clinical Studies (14.1)].

Liposarcoma

Halaven is indicated for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen [see Clinical Studies (14.2)].

The full indications in the EU are:

Halaven is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.

Halaven is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (see section 5.1).

Thus FDA and EMA have approved the indication for patients with unresectable liposarcoma in patients who have received a prior anthracycline-containing regimen. The FDA and EMA approved indications include second-line therapy.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

The nonclinical studies submitted by the sponsor comprised only pharmacology and in vitro pharmacokinetic drug interaction studies (CYP 450 inhibition/induction and transporter interaction studies). The sponsor did not submit any new nonclinical data concerning the secondary pharmacology or toxicity of eribulin.

Pharmacology

In vitro studies showed that eribulin was active against the proliferation of soft tissue sarcoma (rhabdoid, rhabdomyosarcoma and Ewing's sarcoma) cell lines from paediatric patients (relative 50% inhibitory concentration (IC₅₀) < 1 nM). In previously evaluated studies provided in the original submission, eribulin inhibited the proliferation of a uterine sarcoma cell line from adult patients (IC₅₀ 1.99 nM) but it was not effective in the

inhibition of a multi-drug resistant uterine sarcoma cell line (with P-gp overexpression) (IC₅₀ 5.2 µM).

In animal xenograft models in athymic immunosuppressed mice, eribulin significantly inhibited human adult and paediatric soft tissue sarcoma tumour growth. Complete or almost complete tumour regression was observed in mice with xenografts of some rhabdoid, rhabdomyosarcoma and Ewing's sarcoma cell lines and tumour growth inhibition against leiomyosarcoma. The tumour inhibitory effect was observed at approximately 1 mg/kg (3 mg/m², IV weekly or IP every 4 days), slightly above the clinical dose (1.4 mg/m²). Treatment was generally well tolerated with usually no mortality or remarkable body weight loss.

The proposed new indication is supported by nonclinical data.

Pharmacokinetics

Protein binding

One new protein binding study showed that eribulin mesilate was moderately bound to human plasma proteins approximately 64%) independent of drug concentration (5 to 500 ng/mL). This finding is consistent with the reported protein binding values of approximately 49 to 65% (range tested, 100 to 1000 ng/mL) in human plasma in the original application for eribulin mesilate.

Pharmacokinetic Drug interactions

In vitro studies were conducted to evaluate potential pharmacokinetic drug interactions.

Eribulin was not an inhibitor of human liver microsomal cytochrome P450 (CYP) isozymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 (<46% inhibition and IC₅₀ > 200 µM). It inhibited CYP3A activity, with IC₅₀ of 50 µM (36.5 µg/mL) for 6β hydroxylation of testosterone, 3 µM (2.2 µg/mL) for midazolam 1' hydroxylation and 2 µM (1.46 µg/mL) for oxidation of nifedipine. The findings are consistent with two previously evaluated studies, which also showed no inhibition of CYP1A2, CYP2C9, CYP2C19 and CYP2D6 but significant inhibition of CYP3A4. The apparent K_i against CYP3A4 was approximately 3 to 6 µM for R-warfarin 10-hydroxylation, 5 to 17 µM for testosterone 6β-hydroxylation, and 3 to 11 µM for nifedipine dehydration. The IC₅₀ and K_i values were 7 to 182 fold higher than the free fraction clinical peak plasma concentration (C_{max}) (approximately 0.2 µg/mL based on the total C_{max} of 0.52 µg/mL and protein binding of ~60%). Based on the in vitro study results, eribulin may be considered as a weak to moderate CYP3A4 inhibitor. It may increase the plasma concentration of drugs that are predominantly metabolised by CYP3A4.

Eribulin did not induce CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in cultured human hepatocytes exposed to eribulin for 3 days at concentrations of 1 to 10 µM (0.73 to 7.3 µg/mL corresponding to 3.7-37-fold the free fraction clinical C_{max}). Instead, the activity of CYP1A2 (up to 70%), CYP2B6 (up to 56%), CYP2C9 (up to 78% in 2/3 donors) and CYP3A4 activity (up to 80%) was reduced, with corresponding decreases in mRNA expression, suggesting that the decreased enzyme activity was likely due to down-regulation of mRNA expression of these enzymes. The most significant mRNA down-regulation was CYP2B6 (by 52 to 85% at 1 µM and approximately 95% at 5 and 10 µM) and to a lesser extent, CYP1A2 (by 48 to 62% at 1 µM, 75 to 89% at 5 µM and 74 to 91% at 10 µM). Whilst the sponsor considers that it is unlikely that the down-regulation of Messenger Ribonucleic Acid (mRNA) expression is clinically relevant based on low therapeutic doses used in the clinic, the testing concentration of 1 µM (0.73 µg/mL) is in fact only 3.7 fold the free fraction clinical C_{max} (approximately 0.2 µg/mL). Despite the absence of significant inhibition of CYP1A2 and CYP2B6 in the in vitro hepatic microsome

assays, down-regulation of the expression of these enzymes may be clinically relevant. The down-regulation of CYP1A2 and CYP2B6 and potential clinical effects in terms of pharmacokinetic drug interactions should be further investigated.

In vitro transporter studies showed that eribulin was not a substrate of uptake (organic cation transporter (OCT) 1, OCT2, organic anion transporter (OAT1), OAT3, OATP1B1, OATP1B3) or efflux (breast cancer resistance protein transporter (BCRP), Bile Salt Export Pump (BSEP), Multidrug resistance-associated protein 2 (MRP) and MRP4) transporters. Similarly, eribulin was not an inhibitor of the above transporters and Multidrug and toxin extrusion protein 1 (MATE1). It displayed only weak inhibition of OATP1B1 and OATP1B3 (<30% at 10 μ M), which is not considered clinically relevant. A previously evaluated study indicated that eribulin is a substrate of P-gp but not an inhibitor at clinically relevant concentrations.

Nonclinical summary and conclusions

- Only nonclinical pharmacology and in vitro pharmacokinetic drug interaction studies (CYP 450 inhibition/induction and transporter interaction studies) were submitted.
- Primary pharmacology studies demonstrated anti-proliferative activity (cytotoxicity) against cancer cell lines (including STS) in vitro at therapeutically relevant concentrations and STS tumour growth inhibition in athymic mice bearing human rhabdoid, rhabdomyosarcoma, leiomyosarcoma, and Ewing's sarcoma xenografts.
- Eribulin was not an inhibitor of human liver microsomal CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1. It caused weak to moderate inhibition of the human CYP3A4 CYP450 isozyme at concentrations 7 to 182 fold the free fraction clinical C_{max} in human liver microsomes in vitro. A precautionary statement on potential effects on the metabolism of CYP3A4 substrates is suggested in the Product Information.
- Eribulin did not induce CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human hepatocytes at concentrations up to 10 μ M (37 fold the free fraction clinical C_{max}). Instead, it slightly reduced the activity of these enzymes, associated with down-regulation of mRNA expression (significant down-regulation of CYP1A2 and CYP2B6).
- Eribulin is not a substrate of the uptake transporters BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 or the efflux transporter pumps MRP2, MRP4 and BSEP.
- Eribulin is not an inhibitor of the uptake transporters BCRP, OCT1, OCT2, OAT1, OAT3 or the efflux transporters: MRP2, MRP4, BSEP and MATE1. Eribulin resulted in only slight inhibition of OATP1B1 and OATP1B3 at high concentrations.
- There are no nonclinical objections to the proposed extension of indications for eribulin mesilate (Halaven). It is recommended that the down-regulation of CYP1A2 and CYP2B6 and potential clinical effects in terms of pharmacokinetic drug interactions should be further investigated.
- The draft Product Information should be amended as directed (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

Clinical rationale

STS are a heterogeneous group of malignant tumours arising in tissues derived from the embryonic mesoderm (for example, skeletal muscle, smooth muscle, adipose tissue and blood vessels). The 2002 World Health Organization (WHO) classification of soft tissue tumours (both benign and malignant) lists over 50 separate soft tissue malignancies. The most common of these subtypes in adults are undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma and synovial sarcoma.²

The WHO classification system was revised in 2013. However, the 2002 system would have been current at the time the studies in this submission were conducted.

STS can develop anywhere in the body but most commonly occurs in the limbs and limb girdles and in the abdomen. They are rare, comprising about 1% of all malignancies in adults and 7 to 10% of paediatric cancers. The tumours usually present as a painless slowly enlarging mass.^{3,4} There are various systems used for the grading and staging of STS. A commonly used one is that produced by the American Joint Committee on Cancer (AJCC). The AJCC system used for the pivotal study in this submission is shown in Table 3. Peripheral STS most commonly metastasize to the lungs while those arising in the abdomen commonly spread to the liver and peritoneum.²

Adverse prognostic factors in subjects with STS include large tumour size, high grade, advanced stage, older age and histological subtype.⁴

Table 3: American Joint Committee on Cancer Staging of Soft Tissue Sarcoma

| Tumour Grade (G) | | |
|---|---|--------------------|
| GX | Grade cannot be assessed | |
| G1 | Well differentiated | |
| G2 | Moderately differentiated | |
| G3 | Poorly differentiated | |
| G4 | Poorly differentiated or undifferentiated | |
| Primary Tumour (T) | | |
| TX | Primary tumour cannot be assessed | |
| T0 | No evidence of primary tumour | |
| T1 | Tumour 5 cm or less in greatest dimension | |
| | T1a | Superficial tumour |
| | T1b | Deep tumour |
| T2 | Tumour 5 cm or larger in greatest dimension | |
| | T2a | Superficial tumour |
| | T2b | Deep tumour |
| [Note: Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumours.] | | |
| Regional lymph nodes (N)* | | |
| NX | Regional lymph nodes cannot be assessed | |

² National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Soft Tissue Sarcoma. Version 2.2016; 2016.

³ Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. *N Engl J Med*. 2005; 353 (7): 701-11.

⁴ Shiba S, Peach A Howard S. Diagnosis and management of soft tissue sarcoma *BMJ* 2010; 341: c717

| Tumour Grade (G) | | | | |
|---|---|-------|----|----|
| N0 | No regional lymph node metastases | | | |
| N1 | Regional lymph node metastasis [Note: Presence of positive nodes (N1) is considered stage IV.] | | | |
| Distant Metastasis (M) | | | | |
| MX | Distant metastasis cannot be assessed | | | |
| M0 | No distant metastasis | | | |
| M1 | Distant metastasis | | | |
| AJCC Stage Groupings | | | | |
| Stage I | G1 | T1a | N0 | M0 |
| | G1 | T1b | N0 | M0 |
| | G1 | T2a | N0 | M0 |
| | G1 | T2b | N0 | M0 |
| | G2 | T1a | N0 | M0 |
| | G2 | T1b | N0 | M0 |
| | G2 | T2a | N0 | M0 |
| | G2 | T2b | N0 | M0 |
| Stage II | G3 | T1a | N0 | M0 |
| | G3 | T1b | N0 | M0 |
| | G3 | T2a | N0 | M0 |
| | G4 | T1a | N0 | M0 |
| | G4 | T1b | N0 | M0 |
| | G4 | T2a | N0 | M0 |
| Stage III | G3 | T2b | N0 | M0 |
| | G4 | T2b | N0 | M0 |
| Stage IV | Any G | Any T | N1 | M0 |
| | Any G | Any T | N0 | M1 |
| AJCC, American Joint Committee on Cancer; TNM, tumour node metastasis. <i>*Laterality does not affect the N classification. If a lymph node dissection is performed, then pathologic evaluation would ordinarily include at least eight nodes.</i> | | | | |

Soft tissue sarcoma. In: American Joint Committee on Cancer: AJCC Cancer Staging Manual. 6th Ed. New York, NY: Springer, 2002, pp 193-197.

Treatment

A number of current clinical practice guidelines provide evidence-based recommendations regarding appropriate treatment of STS in adults. These include guidelines produced by:

- The National Comprehensive Cancer Network (NCCN) in the United States (2016)²;
- The Cancer Council of Australia in collaboration with the Australasian Sarcoma Study Group (2014)⁵.
- The European Society of Medical Oncology (2014)⁶;

⁵Cancer Council Australia Sarcoma Guidelines Working Party. Clinical practice guidelines for the management of adult onset sarcoma. Sydney: Cancer Council Australia. [Version URL: <http://wiki.cancer.org.au/australiawiki/index.php?oldid=106741>, cited 2016 Apr 13].

⁶ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25 Suppl 3: iii102-12

The mainstay of treatment for STS is surgery. Radiotherapy improves local control in subjects with resectable disease and can be used alone in subjects in whom surgery is considered inappropriate^{3,4}. Systemic chemotherapy is used in subjects with unresectable disease.

The current clinical practice guidelines generally recommend anthracycline based chemotherapy as first-line treatment for unresectable/ metastatic STS. The Australian guideline recommends doxorubicin, either alone or in combination with ifosfamide. There is no standard second or later line treatment. The various guidelines refer to a large number of agents that can be considered for second or later-line therapy. These include ifosfamide (if not used in first line), trabectedin (not registered in Australia), gemcitabine, dacarbazine and pazopanib (excluding subjects with adipocytic sarcomas). The Australian guidelines recommend ifosfamide (if not used in first-line) and then dacarbazine.

In Australia, agents registered for the treatment of STS include various grandfathered agents such as doxorubicin, epirubicin, ifosfamide and dacarbazine. These agents all have a broad STS indication, not restricted by line of therapy or histological subtype. The tyrosine kinase inhibitor pazopanib is registered for use as second or later line therapy of STS, excluding Gastrointestinal stromal tumors (GIST) and adipocytic sarcomas.

The rationale for the submission is based on the lack of established therapies for STS after failure of first line therapy.

Guidance

The following EMA guidelines which have been adopted by the TGA are considered relevant to the current submission:

- Guideline on the evaluation of anticancer medicinal products⁷;
- Points to consider on application with 1. Meta-analyses; 2. One pivotal study⁸.

Compliance with these guidelines will be considered in the relevant sections of this report.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- One pivotal Phase III randomised controlled trial in subjects with STS (Study 309);
- Two single-arm Phase II studies in subjects with STS (Studies 207 and 217);
- One single-arm Phase II study in subjects with breast cancer (Study 206). This study contained safety data not previously reviewed by the TGA.
- Two population pharmacokinetic analyses.
- Literature references.

Paediatric data

The submission did not include paediatric data. The sponsor has a paediatric investigation plan (PIP) agreed with the EMA which involves the conduct of three clinical studies in

⁷ European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95/Rev.4; (2012).

⁸ European Medicines Agency. Points to consider on application with 1. Meta-analyses; 2. One pivotal study; CPMP/EWP/2330/99 (2001).

children with STS. The plan is due to be completed by 2029⁹. According to the TGA submission, an initial report is due to be submitted by September 2017.

In the United States, the sponsor has a waiver from the FDA for paediatric data. The waiver was granted on the grounds that the FDA has designated eribulin as an orphan drug for the treatment of STS.

Good clinical practice

The clinical study reports included in the submission all included an assurance that the studies were conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included three clinical studies in STS: Studies 207, 217 and 309. In each of these studies sparse PK sampling was performed as follows:

- Study 207: a total of 7 samples were collected from each subject in Cycle 1 only. Time points for collection were: prior to eribulin administration, and then at any time within each of the following time windows after the end eribulin administration; 5 to 10 minutes, 15 to 90 minutes, 2 to 4 hours, 4 to 7 hours, 7 to 14 hours and 16 to 50 hours.
- Study 217: trough samples were collected prior to eribulin administration on Days 1 and 8 of Cycles 1 and 2.
- Study 309 (eribulin arm only): samples were collected on Cycle 1/day 1 (end of infusion, and at 0.5 to 6 hours and 24 to 120 hours after the end of the infusion), Cycle 1/Day 8 (pre-dose and at the end of the infusion), Cycle 2/Day 1 (end of infusion, and at 0.5 to 6 hours and 24 to 120 hours after the end of the infusion), and Cycle 2/Day 8 (pre-dose and at the end of the infusion).

Eribulin was quantified using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

The PK data collected were used in two population PK and PK/PD analyses:

- Report No CPMS-E7389-003R (dated 17 April 2013) combined data from Study 207 with data from eight previously evaluated Phase I and II studies.
- Report No CPMS-E7389-005R (dated 18 June 2015) combined data from Studies 207, 217 and 309 with data from seven other previously evaluated Phase I and II studies.

Evaluator's conclusions on pharmacokinetics

The PK properties of eribulin as described by the population PK analyses were consistent with those previously determined. Findings included the following:

- Typical clearance was estimated to be approximately 2.8 L/hour.
- Markers of impaired hepatic function (decreased albumin, increased liver function tests (LFTs)) were associated with increased exposure to eribulin.

⁹ European Medicines Agency. EMA decision P/0136/2015. 15 June 2015

- Tumour type (sarcoma versus other tumours) or type of sarcoma did not affect eribulin PK.
- Eribulin PK was not affected by age, gender, race, Eastern Cooperative Oncology Group (ECOG) status¹⁰ or creatinine clearance.

A number of population PK/PD analyses were also undertaken. Findings of these analyses included the following:

- No relationship was identified between eribulin exposure and efficacy endpoints (progression free survival (PFS), overall survival, overall response or reduction in tumour size);
- Subjects who developed certain adverse events (AEs) (neuropathy, fatigue) had higher eribulin exposure compared to other subjects;
- A model was developed that adequately described the effect of eribulin on absolute neutrophil count. Inhibition of neutrophil proliferation by eribulin was higher in Japanese subjects and in subjects receiving granulocyte colony stimulating factor (G-CSF) treatment.
- No relationship was identified between eribulin exposure and QT interval¹¹.

Pharmacodynamics

Studies providing pharmacodynamic data

Apart from the PK/PD analyses described above and in Attachment 2, no new clinical pharmacodynamic data were included in the submission.

Dosage selection for the pivotal studies

The dose of eribulin selected for all the STS studies was 1.4 mg/m² IV over 2 to 5 minutes on Days 1 and 8 of a 21 day cycle.

The choice was based on findings of Phase I and II studies conducted prior to the STS studies. The maximum tolerated dose (MTD) of eribulin was determined to be 1.4 mg/m² when administered as a bolus on Days 1, 8, and 15 of a 28 day cycle. However, in subsequent Phase II studies, the Day 15 dose in the 28 day cycle had to be omitted in more than 50% of cases due to hematologic toxicity. Efficacy was not affected by skipping the Day 15 dose. It was therefore concluded that 1.4 mg/m² on Days 1 and 8 of a 21 day cycle was likely to be the optimal dose and schedule. This was the dosage regimen approved for use in breast cancer.

¹⁰ECOG performance status:

| Scale | Performance Status |
|-------|---|
| 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 (eg, light house work, office work). |
| 2 | Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

¹¹In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

Efficacy

Studies providing efficacy data

The pivotal efficacy study was Study 309. Two single-arm Phase II studies in subjects with STS (Studies 207 and 217) were also submitted.

Evaluator's conclusions on efficacy for STS

The pivotal study in the submission was well designed and well executed. The design complied with the recommendations of the EMA guideline on anticancer agents⁷ that has been adopted by the TGA. The choice of dacarbazine as the comparator agent was reasonable.

The study demonstrated a statistically significant increase in survival with eribulin compared to dacarbazine (hazard ratio (HR) = 0.768 [95% confidence interval (CI): 0.618 – 0.954]; $p = 0.0169$). Median survival was increased by approximately 2 months. The magnitude of the survival benefit is clinically significant. The TGA has in recent years approved pazopanib for advanced STS and the pivotal study for this drug demonstrated a prolongation of PFS by approximately 3 months compared with placebo, with no demonstrated improvement in overall survival.

Eribulin was not associated with significant benefits on the other efficacy endpoints studied such as PFS or response rates. These endpoints are generally considered to be surrogates for the gold standard of overall survival. In the presence of a demonstrated overall survival benefit, the absence of a demonstrated effect of eribulin on these endpoints is not considered important. Eribulin treatment was not associated with any improvement or impairment of Quality of Life (QoL) compared to dacarbazine.

The indication proposed by the sponsor would permit use of eribulin in all forms of STS. Enrolment in the pivotal study was restricted to subjects with liposarcoma or leiomyosarcoma, as the Phase II study did not demonstrate convincing evidence of activity for eribulin in other histological subtypes. There is therefore no adequate evidence to support use of eribulin in histological subtypes other than liposarcoma or leiomyosarcoma. If a new STS indication is to be approved the other subtypes should be excluded.

Although a statistically significant effect on overall survival was demonstrated in the pivotal study, subgroup analysis indicated that there was a notable difference between the two STS subtypes. The overall survival benefit was driven by a marked survival benefit in the liposarcoma subgroup (HR = 0.511 [95%CI: 0.346 – 0.753]). In this subgroup median survival was prolonged by approximately 7 months (15.6 versus 8.4 months). In contrast, the HR in the leiomyosarcoma subgroup was 0.927 (95%CI: 0.714 to 1.203), with no increase in median survival. However, the study was not powered to demonstrate a significant effect on survival in the leiomyosarcoma subgroup. It might be concluded that the efficacy of eribulin in leiomyosarcoma is approximately comparable to that of dacarbazine. However, dacarbazine has not been demonstrated to produce a survival benefit in STS. Evidence of efficacy in liposarcoma is therefore convincing, while evidence for efficacy in leiomyosarcoma is uncertain.

The two Phase II studies used the novel endpoint of progression-free rate at 12 weeks (PFR12wks) and were single-arm, non-comparative studies. In both studies PFR12wks was higher among liposarcoma subjects than among leiomyosarcoma subjects, a finding that is consistent with the efficacy results of the pivotal study. According to the European Organisation for Research and Treatment of Cancer (EORTC) Sarcoma group a PFR12wks > 40% indicates activity of a drug in the second line STS setting. Using this criterion, activity in liposarcoma was demonstrated in both studies (46.9% in Study 207 and 81.3% in Study 217) and activity in leiomyosarcoma was demonstrated in one of the studies

(31.6% in Study 207 and 42.1% in Study 217). It should be noted that most subjects in these studies were receiving eribulin as third or later line therapy and therefore the cut-off of 40% may not be applicable.

The indication proposed by the sponsor would permit use of eribulin as second or later line therapy. In the pivotal study only 9.2% of eribulin-treated subjects had received only one line of prior treatment for their advanced disease. In Study 207 the proportion was 30.7% and in Study 217 it was 35.3%. Therefore the majority of patients in the clinical trial program received eribulin as third or later line therapy, and it could be argued that the proposed indication should be revised to reflect this. However, this evaluator would support an indication that does not exclude second line use for the following reasons:

- There is no generally agreed standard for second line therapy of STS;
- The current Australian clinical practice guideline for STS (4) recommends the use of dacarbazine after failure of doxorubicin and ifosfamide. Doxorubicin and ifosfamide are often used in combination as first-line therapy, and in this scenario dacarbazine would be recommended as second line therapy. The pivotal study would suggest that eribulin is clearly superior to dacarbazine, at least for liposarcoma;
- Cytotoxic agents generally have greater efficacy in less heavily pre-treated subjects.

The submission for the new indication is based on a single pivotal study and the TGA has adopted an EMA guideline that deals with this situation.¹² This guideline sets out certain 'prerequisites' that must be met for approval of such a submission. In the opinion of this evaluator, the design and results of the pivotal study allow the conclusion that these prerequisites have been met, at least for liposarcoma.

Overall the evidence submitted to support the efficacy of eribulin for liposarcoma is considered acceptable. Evidence for efficacy in leiomyosarcoma is uncertain. There is no adequate evidence for efficacy in other histological subtypes.

Safety

Studies providing safety data

Eribulin is known to be associated with the following toxicities, as described in the current PI:

- Myelosuppression, mainly manifesting as neutropaenia but also including anaemia, thrombocytopaenia and febrile neutropaenia;
- Peripheral neuropathy;
- QT prolongation;
- Gastrointestinal toxicity including anorexia, nausea, vomiting, diarrhoea, constipation, and stomatitis;
- Liver function test abnormalities;
- Fatigue, alopecia and musculoskeletal pain.

Studies providing evaluable safety data

The following studies provided evaluable safety data:

¹² U.S. Food and Drug Administration. FDA News Release. FDA approves first drug to show survival benefit in liposarcoma. 28 January 2016.

Pivotal efficacy study (Study 309)

In the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs) were recorded throughout the study. AEs were coded into standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA) and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.
- Comprehensive physical examinations were conducted at baseline, on Day 1 of each cycle and at the off-treatment visit. Symptom-directed examinations were conducted at other study visits.
- Laboratory tests were performed at baseline, Days 8 and 15 of Cycle 1, Days 1, 8 and 15 of Cycle 2, Days 1 and 8 of subsequent cycles and at the off-treatment visit. Parameters tested were:
 - Haematology: haematocrit, haemoglobin, red blood cells (RBC), platelet count, white blood cells (WBC) with differential count (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils, [ANC]), Haemoglobin amount per red blood cell (MCH), amount of haemoglobin relative to the size of the cell (MCHC) and red blood cell size (MCV).
 - Biochemistry: chloride, potassium, sodium, blood urea nitrogen (BUN) or urea, serum creatinine, magnesium, phosphorus, calcium, albumin, total protein, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), conjugated (direct) and total bilirubin, lactate dehydrogenase (LDH).
- Urinalysis (glucose, haemoglobin (or blood), ketones, pH, protein and specific gravity) was performed on day 1 of each cycle.
- ECGs were collected at baseline, Cycle 1/Day 1 pre-dose and end of infusion (Arm A and Arm B), Cycle 1/ Day 8 pre-dose and end of infusion (Arm A only), Cycle 2/Day 1 pre-dose and end of infusion (Arm A and Arm B), Cycle 2/Day 8 pre-dose and end of infusion (Arm A only), Cycle 3 and all subsequent cycles on Day 1 pre-dose (Arm A and Arm B), and Day 8 pre-dose (Arm A only) and at the off-treatment Visit (Arm A and Arm B).

Phase II efficacy studies (studies 207 and 217)

Safety data collected in the two Phase II studies was similar in nature and extent to that collected in the pivotal study.

Other safety data

The sponsor's Summary of Clinical Safety (SCS) presented safety data for the following populations:

- The pivotal study (Study 309: eribulin versus dacarbazine);
- A pooled population of sarcoma patients who received eribulin in Studies 207, 217 and 309 (n=404);
- A pooled population of metastatic breast cancer (MBC) patients who had received eribulin (n=1559). Most of these patients had participated in studies previously evaluated by the TGA. However the population included 56 subjects who had participated in a single-arm Phase II study (Study 206) that had not been reviewed previously by the TGA. The safety findings from this study are reviewed in Attachment 2 under *Safety*.
- A pooled population of sarcoma and MBC subjects (n=1963).

The data presented in the SCS has been used for the review of safety in this report. The SCS also analysed a collection of adverse events of special interest (AESI), based on MedDRA terms.

Patient exposure

Patient exposure is summarised in Table 4. A total of 404 subjects with STS were treated with eribulin in the submitted studies. The median duration of exposure was 12 weeks or 4 cycles. Median relative dose intensity was 93.4% of the planned dose. 40.8% of subjects require a dose delay and 25.7% required a dose reduction.

Table 4: Patient exposure

| | Study 309 | | STS Population ^a (N=404) | MBC Population ^b (N=1559) | Eribulin Integrated Safety Population ^c (N=1963) |
|--|------------------------|------------------------|--|---|--|
| | Eribulin (N=226) | Dacarbazine (N=224) | | | |
| Duration of exposure (week) | | | | | |
| N | 226 | 224 | 404 | 1559 | 1963 |
| Mean (SD) | 17.4 (18.65) | 13.7 (13.35) | 18.0 (20.58) | 21.2 (20.44) | 20.6 (20.50) |
| Median | 10.0 | 9.0 | 12.0 | 15.9 | 15.0 |
| Q1, Q3 | 6.0, 21.0 | 6.0, 16.6 | 6.0, 21.2 | 9.0, 27.0 | 7.0, 25.0 |
| Min, Max | 3, 112 | 3, 110 | 3, 178 | 3, 196 | 3, 196 |
| Total number of cycles administered per subject | | | | | |
| N | 226 | 224 | 404 | 1559 | 1963 |
| Mean (SD) | 5.5 (5.75) | 4.2 (3.88) | 5.7 (6.47) | 6.7 (6.47) | 6.5 (6.48) |
| Median | 3.0 | 3.0 | 4.0 | 5.0 | 5.0 |
| Q1, Q3 | 2.0, 7.0 | 2.0, 5.0 | 2.0, 7.0 | 3.0, 8.0 | 2.0, 8.0 |
| Min, Max | 1, 34 | 1, 30 | 1, 58 | 1, 65 | 1, 65 |
| Cumulative dose (mg/m²) per subject^d | | | | | |
| n | 226 | 224 | 404 | 1559 | 1963 |
| Mean (SD) | 13.44 (13.719) | 3993.28 (3860.853) | 14.09 (15.635) | 17.00 (16.709) | 16.40 (16.532) |
| Median | 8.03 | 2481.10 | 8.41 | 12.40 | 11.21 |
| Q1, Q3 | 5.56, 16.73 | 1990.48, 4748.65 | 5.58, 16.80 | 6.40, 20.83 | 5.63, 19.66 |
| Min, Max | 1.4, 84.7 | 849.6, 33914.5 | 1.3, 164.8 | 1.4, 182.3 | 1.3, 182.3 |
| Actual dose intensity (mg/m²/week) per subject^e | | | | | |
| N | 226 | 224 | 404 | 1558 | 1962 |
| Mean (SD) | 0.803 (0.1591) | 305.644 (50.7909) | 0.812 (0.1478) | 0.799 (0.1512) | 0.801 (0.1506) |
| Median | 0.873 | 315.737 | 0.872 | 0.855 | 0.858 |
| Q1, Q3 | 0.709, 0.932 | 280.801, 333.333 | 0.717, 0.930 | 0.702, 0.925 | 0.706, 0.927 |
| Min, Max | 0.32, 0.97 | 130.40, 405.18 | 0.32, 0.97 | 0.24, 1.04 | 0.24, 1.04 |
| Relative dose intensity per subject^f | | | | | |
| n | 226 | 224 | 404 | 1558 | 1962 |
| Mean (SD) | 0.861 (0.1705) | 0.919 (0.1202) | 0.870 (0.1585) | 0.856 (0.1621) | 0.859 (0.1614) |
| Median | 0.935 | 0.991 | 0.934 | 0.916 | 0.920 |
| Q1, Q3 | 0.759, 0.998 | 0.853, 1.000 | 0.768, 0.998 | 0.752, 0.991 | 0.757, 0.994 |
| Min, Max | 0.35, 1.04 | 0.39, 1.08 | 0.35, 1.04 | 0.25, 1.12 | 0.25, 1.12 |
| Any dose delay/reduction/omission | | | | | |
| Dose delay | 70 (31.0) | 79 (35.3) | 165 (40.8) | 632 (40.5) | 797 (40.6) |
| Dose omission | 28 (12.4) | - | 49 (12.1) | 209 (13.4) | 258 (13.1) |
| Dose reduction | 59 (26.1) ^g | - | 104 (25.7) | 475 (30.5) | 579 (29.5) |
| Reduced to 1.1 mg/m ² | 58 (25.7) | - | 103 (25.5) | - | - |
| Reduced to 0.7 mg/m ² | 24 (10.6) | - | 34 (8.4) | - | - |

Dose delay: Study medication was administered at least one week later than the scheduled dosing day per regular scheme of eribulin dosing on Day 1 and Day 8 of each cycle, and dacarbazine dosing on Day 1 of each cycle, over the consecutive 21-day treatment cycles.

Dose omission (applicable to eribulin Day 8): dose for Day 8 of a cycle was not administered while dose for Day 1 of the cycle had been administered.

Dose reduction (applicable to eribulin): eribulin dose was reduced to 1.1 mg/m² or 0.7 mg/m².

Max = maximum, MBC = metastatic breast cancer, Min = minimum, STS = soft tissue sarcoma.

a The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

d Cumulative dose (mg/m²) = the sum of doses received (mg/m²) during the entire study

e Actual dose intensity (mg/m²/week) = Cumulative dose (mg/m²) / Duration of exposure (week)

f Relative dose intensity = Actual dose intensity (mg/m²/week) / Planned dose intensity (mg/m²/week), where planned dose intensity is 1.4 mg/m² x 2/3 for subjects receiving eribulin mesilate and 850 (or 1000, 1200) mg/m² x 1/3 for subjects receiving dacarbazine.

g 58 of 59 subjects had dose reductions due to treatment-emergent adverse events (TEAEs). See Table 15

Safety issues with the potential for major regulatory impact

Liver toxicity

Eribulin is known to be associated with hepatic toxicity. In the pivotal study the incidence of LFT abnormalities was comparable to that observed with dacarbazine, another agent known to be associated with hepatotoxicity. In the STS studies there were no cases meeting the criteria for Hy's law, which is predictive of severe drug induced liver injury.

There was one case of serious hepatotoxicity in the eribulin arm of the pivotal study. This was found to be due to disease progression with biliary obstruction and was assessed as unrelated to study drug. There were no serious hepatic AEs in Study 206.

Haematological toxicity

Bone marrow suppression is a known adverse reaction with eribulin and was very common in the STS studies and Study 206. There were no cases of serious pancytopenia reported in the STS studies or Study 206.

Serious skin reactions

The current PI for eribulin lists Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) as adverse reactions that have been observed with eribulin in the post-market setting. There was no serious skin AEs reported in the STS studies or in Study 206.

Cardiovascular safety

The current PI for eribulin lists QT prolongation, tachycardia, hot flushes, deep venous thrombosis and pulmonary embolism as cardiovascular adverse reactions associated with eribulin.

Data from the STS studies on QT prolongation are described in Attachment 2. In the pivotal study serious cardiac disorders occurred in 0.9% of subjects in both arms. Serious cardiac events in the eribulin arm were atrial fibrillation (1) and pericardial effusion (1). In the Phase II studies there was one additional report of serious pericardial effusion and one of serious cardiac failure.

Serious vascular disorders were more common with dacarbazine (2.2% versus 0.9%). Serious vascular events in the eribulin arm were superior vena cava syndrome (1) and vena cava thrombosis (1). In the phase 2 studies there were two additional serious AEs of thrombosis.

Postmarketing data

No post-marketing data were included in the submission.

Evaluator's conclusions on safety

In STS subjects, the toxicity profile of eribulin was consistent with that previously documented in breast cancer subjects. No new safety issues were identified in the STS studies. Common adverse events observed in STS subjects treated with eribulin were haematological toxicities (especially neutropaenia), peripheral neuropathy, GIT events, fatigue and alopecia.

The drug was moderately more toxic than dacarbazine with a higher incidence of grade ≥ 3 AEs (67.3% versus 56.3%) and AEs leading to withdrawal (7.5% versus 4.9%). Also, there were 2 deaths in the pivotal study that appeared to be related to eribulin, compared to none related to dacarbazine. Both deaths followed the development of severe neutropaenia. However, the overall effect of eribulin on mortality is favourable compared to dacarbazine, at least in the subpopulation of patients with liposarcoma.

The relatively low incidence of discontinuation due to AEs (7.5%) suggests that the toxicity of eribulin was manageable.

Previously treated unresectable STS is a serious, life-threatening condition, as evidenced by a median survival of only 11.5 months with dacarbazine treatment in the pivotal study. For such a patient group the toxicity of eribulin, as described above, is considered acceptable.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of eribulin in subjects with liposarcoma are:

- A statistically and clinically significant reduction in the risk of death, with a HR of 0.511 (95%CI: 0.346 – 0.753) and a prolongation of median survival by approximately 7 months (15.6 versus 8.4 months), compared to dacarbazine treatment.

The benefits of eribulin in subjects with leiomyosarcoma are uncertain. The evidence to support a beneficial effect of eribulin in other histological subtypes of STS, compared to dacarbazine, is inadequate.

Eribulin is not associated with significant quality of life benefits compared to dacarbazine.

First round assessment of risks

The risks of eribulin in the treatment of soft tissue sarcoma are:

- Various risks previously documented with use of the drug. These include haematological toxicities, peripheral neuropathy, GIT events, fatigue and alopecia.

The overall risks with eribulin treatment for STS are moderately greater than those for dacarbazine.

First round assessment of benefit-risk balance

The benefit-risk balance of eribulin in the treatment of liposarcoma is favourable. Given the uncertainty of the drug's efficacy in leiomyosarcoma, a favourable benefit-risk balance for this indication cannot be concluded. The benefit-risk balance of eribulin for other subtypes of STS is unfavourable.

First Round Recommendation Regarding Authorisation

It is recommended that eribulin be approved for the following indication only:

For the treatment of patients with unresectable liposarcoma, who have received prior chemotherapy for advanced or metastatic disease.

Clinical Questions

Only one clinical question was raised (see Attachment 2) and no second round clinical evaluation was conducted.

V. Pharmacovigilance findings

Risk management plan

Summary

- The sponsor has submitted EU-RMP version 4.0 (dated 15 July 2015; DLP 14 May 2015) and ASA version 1.0 (November 2015) in support of the extended indications in this application. The most recently evaluated RMP was EU RMP version 1.0 (Data Lock Point (DLP) 12 May 2009) in the initial application for registration. Subsequently EU-RMP version 3.0 (dated 2 January 2014, DLP 14 November 2013) and ASA (no version, dated 29 September 2014) were received from the sponsor.

- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 5.
- Peripheral neuropathy is being investigated in a Phase III clinical trial.

Table 5: Summary of safety concerns

R=Routine and A=Additional

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|-----------------------------------|--|-------------------|---|-------------------|---|
| | | R | A | R | A |
| Important identified risks | Myelosuppression and associated infections | Ü | - | Ü | - |
| | Peripheral neuropathy | Ü | Ü | Ü | - |
| | Nausea/Vomiting | Ü | - | Ü | - |
| | Depression & Insomnia | Ü | - | Ü | - |
| | Tachycardia | Ü | - | Ü | - |
| | Disseminated intravascular coagulation | Ü | - | Ü | - |
| Important potential risks | Adverse Pregnancy Outcomes | Ü | - | Ü | - |
| | Male infertility | Ü | - | Ü | - |
| | Gastrointestinal perforation | Ü | - | Ü | - |
| | Pancreatitis | Ü | - | Ü | - |
| Missing information | Use in patients with hepatic impairment | Ü | - | Ü | - |
| | Use in patients with renal impairment | Ü | - | Ü | - |
| | Use in patients with cardiovascular impairment | Ü | - | Ü | - |
| | Use in the elderly | Ü | - | Ü | - |
| | Use in male patients | Ü | - | Ü | - |
| | Use in pregnant women | Ü | - | Ü | - |
| | Use in paediatric and adolescent population | Ü | - | Ü | - |

Recommendations

There are no outstanding issues.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The EU-RMP version 4.0 (dated 15 July 2015; DLP 14 May 2015) and ASA version 1.0 (November 2015), submitted with application PM-2015-04001-1-4, must be implemented.

VI. Overall conclusion and risk/benefit assessment

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

Quality

No new quality data were provided with this submission. There was no change to the registered formulation.

Nonclinical

Nonclinical pharmacology and in vitro pharmacokinetic drug interaction studies (CYP 450 inhibition/induction and transporter interaction studies) were submitted.

Primary pharmacology studies demonstrated anti-proliferative activity (cytotoxicity) against cancer cell lines (including STS) in vitro at therapeutically relevant concentrations and STS tumour growth inhibition in athymic mice bearing human rhabdoid, rhabdomyosarcoma, leiomyosarcoma, and Ewing's sarcoma xenografts.

Eribulin caused weak to moderate inhibition of the human CYP3A4 CYP450 isozyme at concentrations 7 to 182 fold the free fraction clinical C_{max} in human liver microsomes in vitro. A precautionary statement on potential effects on the metabolism of CYP3A4 substrates was suggested in the draft PI.

Eribulin was associated with significant down-regulation of CYP1A2 and CYP2B6. It was recommended that this down-regulation and potential clinical effects in terms of PK drug interactions be further investigated.

Recommendations for amending the draft PI were made. The amended PI included in the response to requests incorporated the changes to 'Interactions with other medicines' as recommended.

Use in Pregnancy: Category D (no change to current registration).

There were no nonclinical objections to the proposed extension of indications for eribulin mesilate.

Clinical

The clinical evaluator recommended that eribulin be approved for the following indication only:

For the treatment of patients with unresectable liposarcoma, who have received prior chemotherapy for advanced or metastatic disease.

The clinical dossier consisted of a clinical overview and summaries, a pivotal Phase III clinical trial and two Phase II trials in STS and a breast cancer Phase II study containing safety data not previously evaluated by TGA. There were also two population PK analyses.

Pharmacology

PK data were collected in 3 clinical studies (207, 217 and 309) and used in Population PK and PK/PD analyses. The evaluator considered the design, conduct, and analyses of the studies were satisfactory. The PK properties of eribulin were consistent with those previously determined. Impaired hepatic function, as indicated by decreased albumin and increased LFTs, was associated with increased eribulin exposure.

Findings from population PK/PD analyses included: no relationship between eribulin exposure and efficacy endpoints or between eribulin exposure and QT interval; subjects who developed neuropathy and fatigue had higher exposure compared to other subjects; inhibition of neutrophil proliferation by eribulin was higher in Japanese subjects and subjects receiving G-CSF treatment.

Drug-drug interactions

No clinical information was provided; see above for Nonclinical evaluation.

Efficacy

Study 309 was the pivotal efficacy Phase III study comparing eribulin treatment with dacarbazine in patients with advanced soft-tissue sarcoma (adipocytic or leiomyosarcoma). The submission also included Phase II open label Studies 207 and 217 which included additional types of STS. See Table 6 for summaries of the studies.

Table 6: Summaries of populations, key features and results from Studies 309 and 207

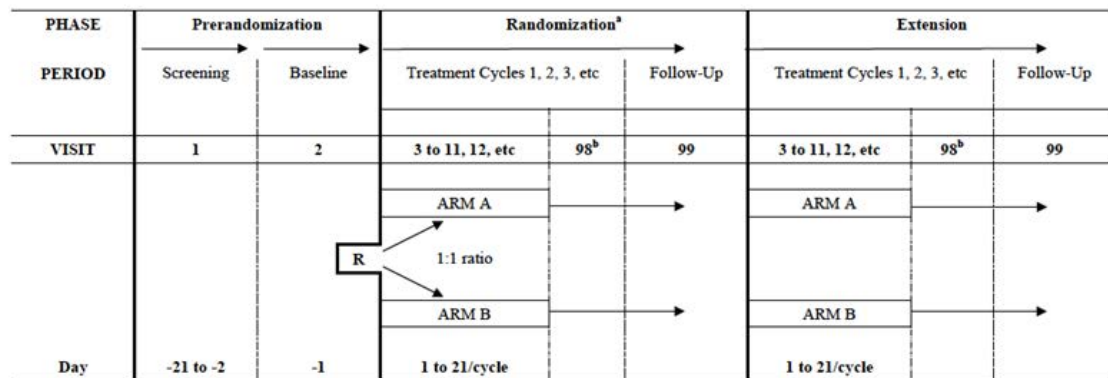
| Study ID, population | Key features | Comment |
|---|--|---|
| Phase III | | |
| Study 309 Randomised open label parallel groups eribulin versus dacarbazine | <u>Arm A</u> Eribulin days 1 and 8 of 21 day cycle n = 228 <u>Arm B</u> dacarbazine day 1 of 21 day cycle n = 224 | No difference in overall progression-free survival (months); Median (95% CI) 2.6(1.9, 2.8) versus 2.6(1.8, 2.7). |
| Subjects had at least 2 prior lines of therapy and advanced disease incurable by surgery/radiotherapy | Primary efficacy outcome OS; deaths eribulin 176 versus dacarbazine 181, HR 0.768 (95% CI 0.618-0.954); median OS months (95% CI) 13.5 (10.9, 15.6) versus 11.5 (9.6, 13.0). | OS median (months) by histology: ADI eribulin 15.6 versus dacarbazine 8.4 LMS eribulin 12.7 versus dacarbazine 13 |
| Phase II | | |
| Study 207 open label single arm | Eribulin Days 1 and 8 of 21 day cycle n = 127; 115 evaluable for efficacy | |
| Subjects had advanced or metastatic STS, disease progression in previous 6 months; | Primary outcome progression-free survival at 12 weeks (PFR12wks) using RECIST version 1.0 criteria; ADI 46.9%, LMS 31.6%, lower in other two | Predefined efficacy rate of > 30% reached only in adipocytic sarcoma (liposarcoma) and LMS strata. |

| Study ID, population | Key features | Comment |
|--|--|---|
| LMS, ADI, synovial, 'other'. | strata. | |
| Study 217 open label single arm | Eribulin Days 1 and 8 of 21 day cycle n =51; | |
| As for 207; LMS/ADI n = 35 or 'other' n = 16 | PFR12wks 81.3%% for ADI, 42% LMS, 31.3% for 'other' sarcoma type s | Median PFS for whole efficacy population 4.07 months. |
| Pop PK/PD | | |
| Data from above studies analysed | Hepatic impairment associated with increased exposure | Findings consistent with known profile; ; subjects who developed neuropathy and fatigue had higher exposure compared to other subjects; |

Pivotal efficacy study

Study 309 was a randomised, open-label, Phase III trial with two parallel groups, eribulin (Arm A, n =228) versus dacarbazine (Arm B, n = 224). See study schema at Figure 1 below. The study was conducted at 110 centres in 22 countries. The primary objective was to compare overall survival. Following screening and baseline visits subjects entered a randomisation phase receiving treatment in 21 day cycles until disease progression or unacceptable toxicity, with clinic visits at Days 1, 8, and 15 of the cycle.

Figure 1: Study 309 Study schema



R = randomization.

Arm A = Eribulin mesilate 1.4 mg/m² IV on Days 1 and 8, every 21 days.

Arm B = Dacarbazine IV on Day 1, every 21 days. The starting dose must be selected from one of the following doses: 850 mg/m² or 1,000 mg/m², or 1,200 mg/m².

a. The Randomization Phase will end at the time of data cut-off for the primary analysis when the target number of events has been observed. All subjects still on treatment with study treatment or are in survival follow-up will then enter the Extension Phase.

b. Off-treatment Visit.

Inclusion and exclusion criteria

Subjects had to have histologically confirmed diagnosis of advanced soft tissue sarcoma of high or intermediate grade, either adipocytic sarcoma or leiomyosarcoma, incurable by surgery or radiotherapy and having received at least 2 standard systemic regimens (one including anthracycline unless contra-indicated) for advanced STS. Measurable disease and radiographic evidence of disease progression by RECIST criteria¹³ were specified.

¹³ Response Evaluation Criteria In Solid Tumors (RECIST) is a set of published rules that define when tumors in cancer patients improve ('respond'), stay the same ('stabilize'), or worsen ('progress') during treatment.

Randomisation and interventions

Subjects were randomised 1:1 to receive Eribulin 1.4 mg/m² IV over 2 to 5 minutes on Days 1 and 8 of a 21 day cycle (n = 228), or Dacarbazine 850, 1000 or 1200 mg/m² IV over 15 to 60 minutes on Day 1 of 21 day cycle (n = 224). Doses could be delayed or reduced as pre-specified. Randomisation was stratified by histology, geographical region and number of prior regimens, 2 or >2.

The evaluator considered the choice of dacarbazine as comparator was acceptable in view of registration status and the Australian guidelines.

Demographic and baseline characteristics

The two groups were similar overall; mean age 55.7 years, 21% aged 65 or over, 73% White, mean body weight (BW) 75 kg. In the eribulin group 70% were female versus 63% for dacarbazine. Overall about 34% had adipocytic sarcoma and 66% had leiomyosarcoma. Baseline disease characteristics and prior treatments were similar; the eribulin group had slightly better ECOG performance status at baseline but overall the two arms were well balanced.

Efficacy assessment methodology

The primary analysis set was intent-to-treat (ITT), all subjects randomised. The primary efficacy outcome was overall survival (OS), measured from the date of randomisation until the date of death from any cause. Secondary outcomes were:

- progression-free survival
- PFR12wks; the proportion of subjects still alive without disease progression 12 weeks from randomisation. Subjects were considered to be progression-free if the tumour assessment performed during week 12 indicated stable disease (SD), partial response (PR) or complete response (CR).
- clinical benefit rate ('CBR' the proportion of subjects with best overall response of CR or PR or durable SD that is, SD ≥ 11 weeks)

Disease progression and response were assessed by the investigators using RECIST v 1.1. Tumour assessments (computed tomography (CT)/ Magnetic resonance imaging (MRI) of chest/abdomen/pelvis/other areas of known disease plus areas of newly suspected disease) were performed at 6 and 12 weeks then every 9 weeks, sooner if clinically indicated, until disease progression was confirmed. Subjects who discontinued without disease progression were assessed by the same schedule, until disease progression or commencement of another anticancer therapy. Subjects were followed up for survival every 12 weeks after the off-treatment visit.

The evaluator noted that PFR12wks was intended for use in Phase II studies to identify activity in new drugs. It was used as a primary endpoint in the Phase II studies of eribulin included in the submission.

Efficacy outcomes

The final analysis was conducted after a total of 357 deaths had occurred.

Overall survival

Results are summarised in Table 7 and Figure 2. Treatment with eribulin was associated with a statistically significant improvement in overall survival compared with dacarbazine treatment (Hazard Ratio, HR = 0.768 [95% CI: 0.618 – 0.954]; p = 0.0169). Median OS was improved by approximately 2 months (13.5 versus 11.5 months). The estimated

proportion of subjects alive after 12 months was 54.8% eribulin versus 47.5% dacarbazine.

Table 7: Overall survival (primary endpoint)

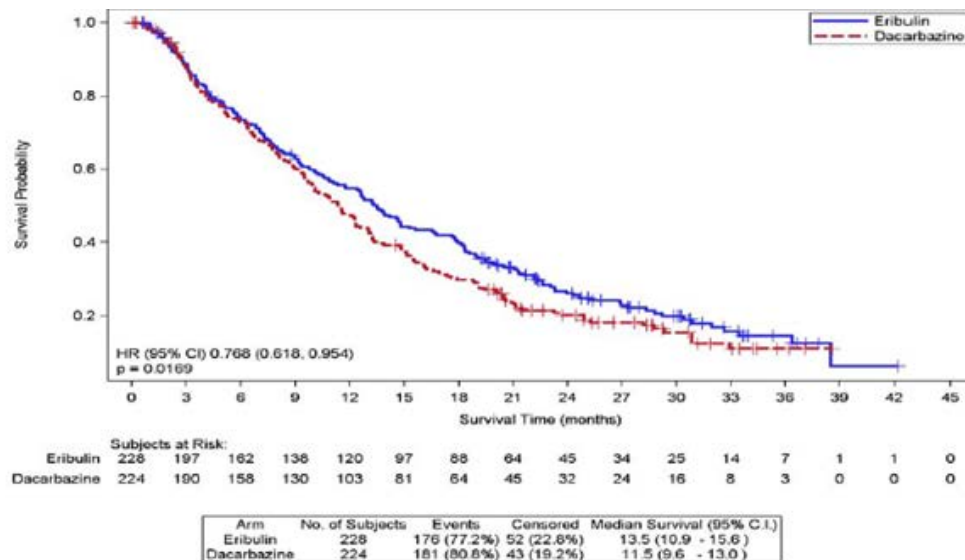
| | Eribulin (N=228) | Dacarbazine (N=224) |
|---|-----------------------------|--------------------------------|
| Deaths, n (%) | 176 (77.2) | 181 (80.8) |
| Censored, n (%) | 52 (22.8) | 43 (19.2) |
| Withdrew consent | 8 (3.5) | 8 (3.6) |
| Alive at database cut-off | 44 (19.3) | 35 (15.6) |
| Overall survival (months) ^a | | |
| Median (95% CI) | 13.5 (10.9, 15.6) | 11.5 (9.6, 13.0) |
| Q1 (95% CI) | 5.8 (4.2, 7.2) | 5.2 (4.0, 6.7) |
| Q3 (95% CI) | 24.7 (22.1, 30.9) | 20.5 (17.4, 24.9) |
| Stratified P-value ^b | 0.0169 | |
| Hazard ratio (95% CI) ^c | 0.768 (0.618, 0.954) | |
| Overall survival rate (95% CI) ^c | | |
| 3 months | 0.888 (0.838, 0.923) | 0.876 (0.825, 0.914) |
| 6 months | 0.734 (0.671, 0.787) | 0.729 (0.665, 0.783) |
| 12 months | 0.548 (0.481, 0.611) | 0.475 (0.407, 0.540) |
| 18 months | 0.402 (0.337, 0.466) | 0.299 (0.239, 0.361) |
| 24 months | 0.260 (0.202, 0.322) | 0.202 (0.150, 0.259) |

a: The median, first and third quartile of overall survival, the cumulative probability of overall survival at 3, 6, 12, 18, 24 months and the corresponding two-sided 95% CIs are based on Kaplan-Meier product-limit method and Greenwood formula, respectively, for each treatment arm.

b: P-value is calculated two-sided log-rank test, stratified by histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2). Significant level is alpha= 0.0455.

c: Hazard ratio is based on a stratified Cox regression model including treatment as covariate, and histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2) as strata

Figure 2: Study 309 - Overall survival (primary endpoint)



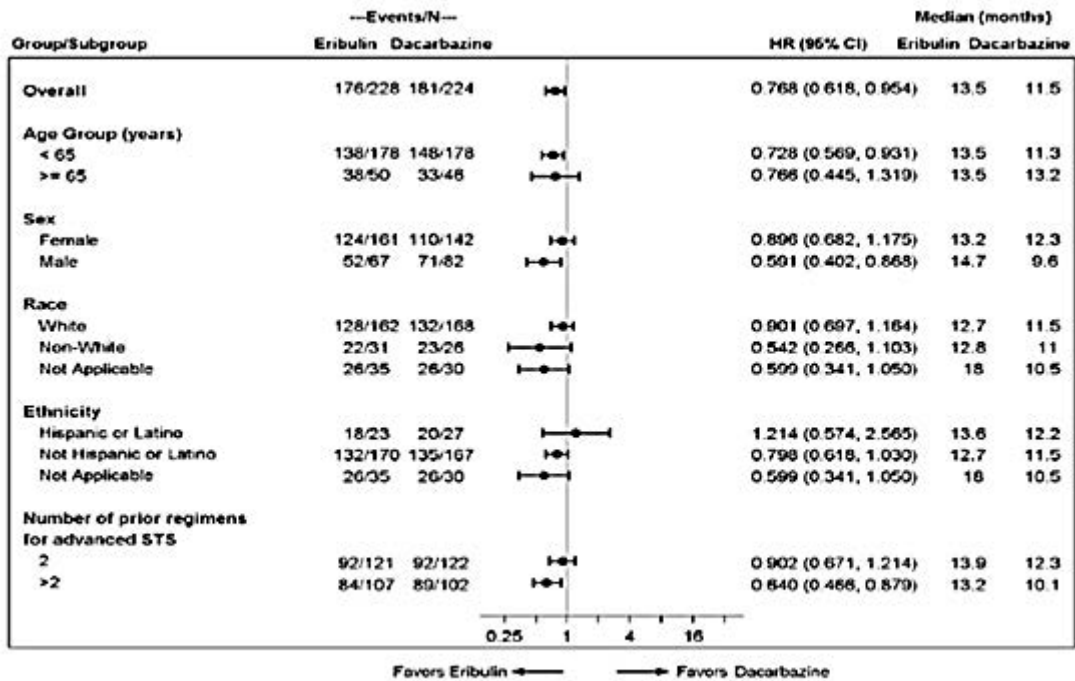
Kaplan-Meier Plot of Overall Survival: Full Analysis Set

HR = hazard ratio. HR is based on a stratified Cox regression model, including treatment as covariate, and histology, geographic region and number of prior regimens for advanced STS as data.

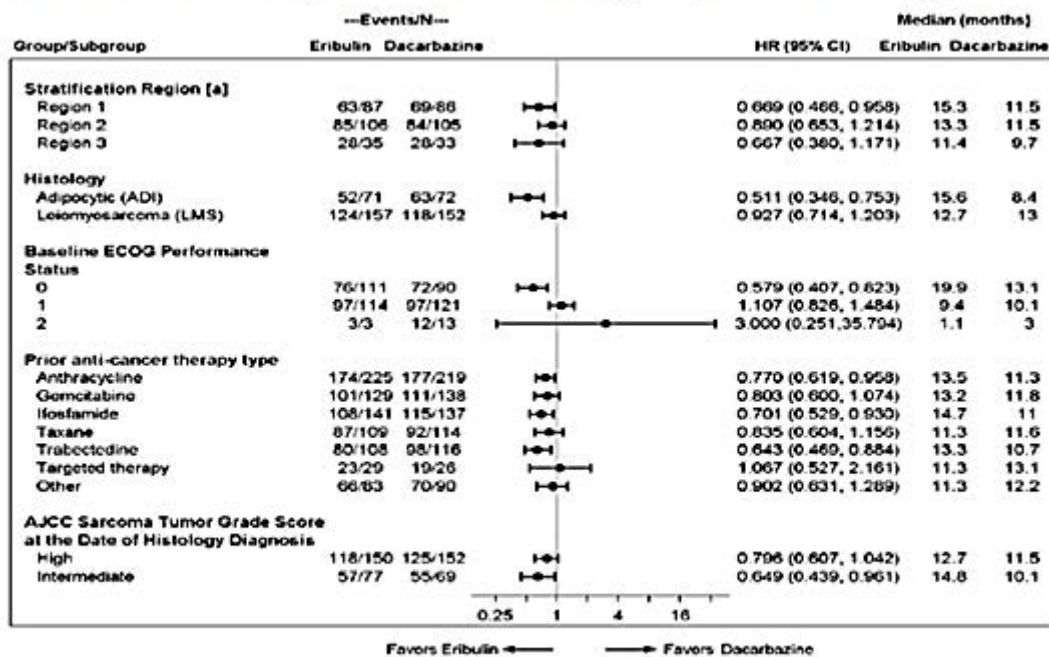
P-value is calculated by 2-sided log-rank test, stratified by histology (ADI or LMS), geographic region (1, 2 or 3) and number of prior regimens for advanced STS (2 or >2).

The pivotal trial enrolled only subjects with liposarcoma or leiomyosarcoma. Results of pre-planned subgroup analyses performed for descriptive purposes are shown in Figure 3.

Figure 3: Study 309 Subgroup analyses of overall survival



Note: Information on race or ethnicity is not collected in some countries (eg France) and is recorded as "Not applicable".



a: Region 1: USA and Canada; Region 2: Western Europe, Australia and Israel; Region 3: Eastern Europe, Latin America and Asia.

This included analysis of overall survival for liposarcoma (adipocytic, ADI) and leiomyosarcoma (LMS) histology subgroups, showing median survival of 15.6 months for eribulin versus 8.4 months for dacarbazine for liposarcoma, and 12.7 months for eribulin versus 13 months dacarbazine for leiomyosarcoma. This subgroup analysis suggested there was a notable difference between the two STS subtypes.

Progression-free survival

There were no significant differences between the two treatments. Analysis by histology subgroups suggested an effect of eribulin treatment in liposarcoma subjects, but not in

leiomyosarcoma subjects. PFR 12wks was 33.3% in eribulin group and 28.6% for dacarbazine. The CBR was 46.1% versus 47.8%.

Objective response rate

This was an exploratory outcome (proportion with CR or PR). Objective response rates were low in both groups (3.9% with eribulin and 4.9% with dacarbazine). All responses were partial responses.

Quality of life

The sponsor provided a separate report on the QoL variables, which contained a large number of analyses. Compliance rates were high with > 80% of subjects completing questionnaires during the first 9 cycles. No consistent differences were demonstrated between the treatment groups.

Evaluator's assessment

Overall the clinical evaluator considered that the pivotal study was well designed and executed and consistent with the TGA adopted EMA guideline on anti-cancer drugs. The evaluator considered that the magnitude of the OS improvement was clinically significant.

The evaluator asked '*In Study 309, what was the PFS rate at 12 weeks for the two histological groups included in the trial (for both eribulin and dacarbazine)?*'

The following information was provided:

In Study 309, the PFR12wks overall was 33.3% (27.2-39.9; 95%CI) and 28.6% (22.8-35.0; 95%CI) for eribulin and dacarbazine, respectively.

Study 309 CSR and D90Q7-1 were provided by the sponsor.

The PFS rates at 12 weeks for histology and histology subcategory groups were lower in the leiomyosarcoma group. In the LMS uterine histology subgroup the PFR12 weeks was 16.2% versus 34.9% for eribulin versus dacarbazine. In general the findings for the endpoint PFR12 weeks were consistent with the two Phase II studies as shown below.

Other studies

Study 207 was an open-label, single-arm, Phase II trial (n = 128 enrolled) in patients with histologically confirmed advanced or metastatic STS (leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and 'other') and evidence of disease progression in the previous 6 months. Subjects could have received only one prior combination regimen or two single agent cytotoxic drugs for metastatic disease. Mean age was 56 years, 52% were female and 56% had received 2 prior anti-cancer regimens.

The primary endpoint was PFR12wks; there were 115 subjects evaluable for efficacy. The predefined efficacy rate of >30% was reached in the adipocytic sarcoma (46.9%) and leiomyosarcoma (31.6%) strata. PFS rate was lower in the other two strata with low numbers of subjects. Median PFS for the whole efficacy population was 2.7 months and median OS was 11.8 months.

Study 217 was an open-label, single-arm, phase 2 trial (n = 51 enrolled) in subjects with advanced STS (2 strata; leiomyosarcoma n = 19/ adipocytic n =16 or 'other' n = 16) previously treated with chemotherapy. Overall median age was 52 years and 54.9% were female; 66.7% had received 2 prior anticancer regimens and 33.3% had received more than 2.

PFR12wks was 81.3% for adipocytic sarcoma, 42.1% for leiomyosarcoma and 31.3% for other sarcomas. Median PFS for the whole efficacy population was 4.07 months. Patients

with leiomyosarcoma or adipocytic sarcoma had longer PFS than those with other sarcomas. Median OS for the whole population was 13.17 months.

Efficacy evaluation conclusion

Treatment with eribulin was associated with a statistically significant improvement in overall survival compared with dacarbazine treatment (Hazard Ratio [HR] = 0.768 [95%CI: 0.618 – 0.954]; p = 0.0169). Median OS was improved by approximately 2 months (13.5 versus 11.5 months). The evaluator considered that the magnitude of the OS improvement was clinically significant.

Efficacy in liposarcoma

The pivotal trial enrolled subjects with liposarcoma or leiomyosarcoma; there was no evidence to support use in other sarcoma subtypes. Subgroup analysis indicated that there was a notable difference between the two STS histology subtypes. Median survival in the liposarcoma (adipocytic, ADI) subgroup was 15.6 months for eribulin versus 8.4 months for dacarbazine while in the leiomyosarcoma (LMS) subgroup median survival was 12.7 months for eribulin versus 13 months dacarbazine. The evaluator commented '*Even though the study was not powered to detect significant differences in subgroups, a significant effect was demonstrated for the subgroup of subjects with adipocytic sarcoma (HR = 0.511 [95%CI: 0.346 – 0.753]). In this subgroup median survival was prolonged by approximately 7 months (15.6 versus 8.4 months). In contrast, the HR in the leiomyosarcoma subgroup was 0.927 (95%CI: 0.714 – 1.203), with no increase in median survival.*'

Therefore it appears the increase in median overall survival was driven by outcomes in the liposarcoma subgroup. For treatment of the leiomyosarcoma histological type of STS the evidence for efficacy was uncertain.

Second line treatment

The evaluator supported the extension of indication for eribulin for second-line or later treatment for liposarcoma, setting out reasons (see *Evaluator's conclusions on efficacy*).

In the pivotal study, 9.2% of eribulin-treated subjects had received only one line of prior treatment for advanced disease.

In Australia it appears that there is no generally agreed standard second line therapy for STS. The current Australian clinical practice guideline for STS¹⁴ recommends dacarbazine after failure of doxorubicin and ifosfamide. Doxorubicin and ifosfamide are often used in combination as first-line therapy and in this scenario dacarbazine would be recommended as second line therapy. The evaluator noted that the pivotal study suggests eribulin is superior to dacarbazine, at least for liposarcoma, and that cytotoxic agents generally have greater efficacy in less heavily pre-treated subjects.

In summary, the clinical evaluator recommended that the proposed additional indication should be narrowed to patients with unresectable liposarcoma who have received prior chemotherapy for advanced or metastatic disease.

The sponsor provided an amended indication and PI, making changes as requested by the clinical evaluator. In addition the Clinical Trials section was focused on the liposarcoma subgroup results for pivotal Study 309.

The Delegate agrees with the clinical evaluator's overall conclusions.

¹⁴Cancer Council Australia Sarcoma Guidelines Working Party. Clinical practice guidelines for the management of adult onset sarcoma. Sydney: Cancer Council Australia.

Safety

Exposure

A total of 404 subjects with STS were treated with eribulin in the submitted studies. The median duration of exposure was 12 weeks or 4 cycles, about 40% requiring dose delay and 25% dose reduction.

Study 309

AEs that were notably more common in the eribulin arm included neutropaenia (43.8% versus 23.7%), peripheral neuropathy (36.7% versus 15.2%), alopecia (35.0% versus 2.7%), pyrexia (27.9% versus 13.8%), stomatitis (13.7% versus 4.9%) and headache (18.1% versus 9.4%). Thrombocytopaenia was notably more common with dacarbazine treatment (27.7% versus 5.8%).

The pattern of treatment-related AEs was very similar to that observed for all AEs. Two possibly treatment-related deaths in the eribulin arm were due to Grade 4 neutropenia and sepsis; none were assessed as related in the dacarbazine arm. Decreased calcium, decreased potassium and hyperglycaemia occurred more commonly in the eribulin arm.

In pooled study data the patterns were similar to the pivotal study.

Issues

In Study 309 neutropenia overall was more common with eribulin than dacarbazine; \geq Grade 3 severity 80/226 (35.4%) for eribulin versus 35/224 (15.6%) for dacarbazine. The incidence of febrile neutropenia was 2 cases in both arms.

Grade 3 or higher neutropenia was more common in Asian/Pacific Islander subjects (n=70) than in White subjects (n=161), 81.4% versus 41.0%.

Peripheral neuropathy treatment-related events occurred in 75/226 (33.2%) for eribulin versus 19/224 (8.5%) for dacarbazine.

Liver toxicity is known as a risk for eribulin. In pooled data provided no AEs met Hy's law criteria; one case of serious hepatotoxicity in the eribulin arm of the pivotal study was found to be due to disease progression with biliary obstruction and assessed as unrelated to study drug.

Hypocalcaemia was observed in the pivotal study but was not initially included in the PI.

The evaluator noted that eribulin was '*moderately more toxic than dacarbazine with a higher incidence of grade \geq 3 AEs (67.3% versus 56.3%) and AEs leading to withdrawal (7.5% versus 4.9%).*'

Safety evaluation conclusion

Overall the evaluator considered the toxicity of eribulin was acceptable in the context of treatment of unresectable previously treated STS. The sponsor added increased risk of neutropenia in Asian/Pacific Islander subjects to Precautions and 'Hypocalcaemia' to Adverse Effects.

- The Delegate considers that relevant Adverse Events from Study 309 for eribulin with dacarbazine as comparator should be included separately.

Risk management plan

The EU-RMP and ASA were aligned except for the Australian specific additional important potential risk 'pancreatitis'. An additional pharmacovigilance activity is ongoing for the identified risk 'peripheral neuropathy'.

The clinical evaluation report identified safety aspects in the PI that are not included in the RMP, specifically QT prolongation and hepatotoxicity. These aspects were addressed in the

RMP evaluation report. The RMP evaluator reviewed the data on QT prolongation and concluded that while the evidence indicates that eribulin is associated with QT prolongation, the PI recommendation for screening, monitoring and management of at-risk patients was adequate and no additional risk mitigation measures were required. Hepatotoxicity has a low incidence of severe reactions.

Overall, the PI statements and pharmacovigilance measures were considered acceptable.

Recommended wording for conditions of registration

The EU-RMP version 4.0 (dated 15 July 2015; DLP 14 May 2015) and ASA version 1.0 (November 2015), submitted with application PM-2015-04001-1-4, must be implemented.

Risk-benefit analysis

Delegate's considerations

Efficacy

The data were from patients with advanced (locally recurrent, locally advanced and/or metastatic) adipocytic sarcoma (subtypes dedifferentiated, myxoid, round cell, pleomorphic) or leiomyosarcoma, incurable by surgery or radiotherapy, who had at least two prior systemic treatments.

The Delegate requests advice from the advisory committee as to whether the data are sufficient to characterise a population for whom the benefit-risk balance is positive for eribulin in the second-line treatment of sarcoma. If so, is this adequately defined in the proposed additional Indication?

Anthracyclines are considered standard first-line treatments in Australia for soft tissue sarcoma. Advice is sought about the clinical relevance in specifying in the indication the type of previous chemotherapy as including anthracycline.

Safety

The additional indication for liposarcoma is supported by Study 309 comparing eribulin and dacarbazine. Dacarbazine is a relevant comparator for treatment of liposarcoma.

Although the overall toxicity profile was considered similar for eribulin in Study 309 compared to the breast cancer studies, some important AEs occurred with considerably greater frequency for eribulin than for dacarbazine.

The Delegate requests advice about inclusion of such comparative information in the PI.

Summary of issues

The initial proposal submitted with this application was for extension of indications to STS in general; the initial indication sought was:

'For the treatment of patients with unresectable soft tissue sarcoma (STS), who have received prior chemotherapy for advanced or metastatic disease. Efficacy and safety have been established primarily in patients with leiomyosarcoma and liposarcoma.'

- Pivotal Study 309 enrolled adult subjects with liposarcoma or leiomyosarcoma who had received at least two prior lines of therapy and had advanced disease incurable by surgery or radiotherapy. The clinical evaluator recommended restricting the indication to second or later line treatment of unresectable liposarcoma, based on subgroup analyses in Study 309. The sponsor amended the proposed indication.

The Clinical Trials section of the PI amended text is also largely in line with the latest EU Summary of Product Characteristics (SmPC). Some changes to this section and Adverse Effects might provide relevant information to prescribers.

- AE information from Study 309 has not been included separately in the amended PI. Proposed changes to the Adverse Effects section include comparison between neutropenia rates in sarcoma and breast cancer. The proposed text does not reflect eribulin compared to dacarbazine.

Proposed action

The Delegate had no reason to say, at this time, that the application for extension of indications for eribulin mesilate (Halaven) for *'the treatment of patients with unresectable liposarcoma who have received prior chemotherapy for advanced or metastatic disease'* should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following issues:

1. Please comment on whether the data are sufficient to characterise a population for which the benefit –risk balance is considered positive for eribulin in the treatment of sarcoma, and advise on whether this is adequately defined in the amended proposed additional indication.
2. Please comment on the adequacy of the proposed PI to provide relevant details on the outcomes of efficacy and safety from pivotal Study 309.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Delegate issue 1

Please comment on whether the data are sufficient to characterise a population for which the benefit –risk balance is considered positive for eribulin in the treatment of sarcoma, and advise on whether this is adequately defined in the amended proposed additional indication.

Response

The 309 study was a randomized, open-label, Phase III, multicenter, global study to compare overall survival of subjects with advanced sarcoma (one of two subtypes: adipocytic (ADI) (Note: adipocytic is now referred to as liposarcoma and the proposed indication reflect this current terminology) or leiomyosarcoma (LMS) treated with eribulin or dacarbazine. Subjects had prior chemotherapy with at least 2 standard systemic regimens for advanced STS, one of which must have been an anthracycline (unless contraindicated).

A total of 452 subjects from 110 sites were randomised in a 1:1 ratio to one of 2 arms, Arm A: Eribulin mesilate, administered at a dose of 1.4 mg/m² intravenously on Days 1 and 8 of every 21 day treatment cycle; or Arm B: Dacarbazine, administered at a dose of 850 mg/m², 1,000 mg/m², or 1,200 mg/m² (as selected by the treating physician) intravenously on Day 1 of every 21 day treatment cycle.

The primary efficacy endpoint was OS measured from the date of randomisation until date of death from any cause. Secondary efficacy endpoints were: PFS, PFR12wks, CBR (defined as the proportion of subjects who had best overall response of CR, PR or Durable stable disease (dSD), > 11 weeks), safety and population PK profile of eribulin in the subjects with STS.

The primary analysis was based on a stratified log-rank test. The randomisation for the study was stratified by histology (ADI or LMS), geographic region (Region 1: USA and

Canada; or Region 2: Western Europe, Australasia and Israel; or Region 3: Eastern Europe, Latin America and Asia), and number of prior regimens for advanced STS (2 or >2 prior regimens). It was pre-specified in the statistical plan that these strata variables (along with other groups) would be analysed and described in the study report.

Efficacy results

The primary endpoint for the pivotal study (Study 309) was met, with a statistically significant increase in OS in the eribulin arm, compared with the dacarbazine arm. The median OS in the eribulin arm was 13.5 months compared with 11.5 months for the dacarbazine arm; the HR of OS in favour of eribulin was 0.768 (95% CI 0.618, 0.954), $P=0.0169$. This is impressive considering that this study compared eribulin with an active control, rather than a placebo.

The significance of this result has to be judged in the context of the results obtained with other treatments for this disease. Doxorubicin is considered globally as the standard of care in first line treatment of metastatic sarcoma, however little progress has been achieved in this line of treatment over the past few decades. Overall survival rates of 8 to 14 months with doxorubicin have been reported in the literature.¹⁵ Multiple randomised trials in the past three decades have examined the addition of other agents to doxorubicin as initial therapy for metastatic sarcoma. These agents included vincristine, cyclophosphamide, actinomycin D, dacarbazine, mitomycin C, cisplatin and ifosfamide¹⁶. Several trials have demonstrated improved ORR or PFS but not improved OS compared with doxorubicin as a single agent nor have head-to-head studies of liposomal doxorubicin, ifosfamide or docetaxel against doxorubicin demonstrated superiority.¹⁷

In the past several years, 4 randomised trials have been completed in second or later line of therapy. Two trials, pazopanib and ridaforolimus were placebo controlled^{31,18} and two trials, trabectedin and eribulin (the study in this application) were compared with an active agent, dacarbazine.¹⁸ Three of the four trials showed improved PFS for the

¹⁵D'Adamo DR. Appraising the current role of chemotherapy for the treatment of sarcoma. *Semin Oncol* 2011;38(suppl 3):S19-29.

Skubitz KM, D'Adamo DM. *Sarcoma*. *Mayo Clin Proc* 2007;82(11):1409-32.

¹⁶Santoro A, Tursz T, Mouridsen H, Verweij J, Steward W, Somers R, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1995;13(7): 1537- 45

Antman K, Crowley J, Balcerzak SP, Rivkin SE, Weiss GR, Elias A, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol* 1993;11(7):1276-85.

Baker LH, Frank J, Fine G, Balcerzak SP, Stephens RL, Stuckey WJ, et al. Combination chemotherapy using Adriamycin, DTIC, cyclophosphamide, and actinomycin D for advanced soft tissue sarcomas: a randomized comparative trial. A Phase III, Southwest Oncology Group Study (7613). *J Clin Oncol* 1987;5(1):86-91.

Edmonson JH, Ryan LM, Blum RH, Brooks JS, Shiraki M, Frytak S, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol* 1993;11(7):1269/75.

¹⁷Judson I, Radford JA, Harris M, Blay JY, van Hoesel Q, Le Cesne A, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2001;37(7):870-7.

Lorigan P, Verweij J, Papai Z, Rodenhuis S, Le Cesne A, Leahy MG, et al. Phase III trial of two investigational schedules of ifosfamide with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J Clin Oncol* 2007;25(21):3144-50.

Verweij J, Lee SM, Ruka W, Buesa J, Coleman R, van Hoesel R, et al. Randomized phase II study of docetaxel versus doxorubicin in first- and second-line chemotherapy for locally advanced or metastatic soft tissue sarcoma in adults: a study of the European organization for research and treatment of cancer soft tissue and bone sarcoma group. *J Clin Oncol* 2000;18(10):2081-6.

¹⁸Demetri GD, Chawla SP, Ray-coquard I, Le Cesne A, Staddon AP, Milhem MM, et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. *J Clin Oncol* 2013;(31(9):2485-92.

experimental arm– 3 months (4.6 versus 1.6 months) for pazopanib, 2.7 months for trabectedin (4.2 versus 1.5 months), and 3 weeks (17.7 versus 14.6 weeks) for ridaforolimus, but none of those trials showed improvement in OS. Despite the absence of a survival benefit, these results were considered sufficient to lead to regulatory approval for pazopanib and trabectedin, but not for ridaforolimus.

In contrast to these data, the study of eribulin discussed herein, while not demonstrating an improvement in PFS, did convincingly improve OS by 2.0 months compared with dacarbazine. Eribulin, in this trial, therefore, is the only drug in later than first line treatment to demonstrate a survival advantage over the comparator. It is also noteworthy that this is an active-controlled trial. The trial presented in this submission of eribulin compared with dacarbazine is clinically significant and represents considerable therapeutic progress, as it is the first trial of one single agent compared with another (not placebo) to demonstrate improvement of the gold standard of efficacy, OS.

The observed discrepancy for OS and PFS in the overall population of Study 309 has been observed before with eribulin and is consistent with the results from previous studies of eribulin in metastatic breast cancer (MBC), which have shown greater effects in OS compared with PFS (Study E7389-G000-301 and Study E7389-G000-305). In Study 309, no significant difference in the median PFS was observed between the 2 study arms with a median of 2.6 months in both the eribulin arm and the dacarbazine arm although there was a numerical benefit in favour of eribulin for the hazard ratio (HR=0.877; 95% CI=0.710, 1.085; $P=0.2287$ stratified log-rank test). These results, with greater effects on OS than on PFS, may be related to mechanisms of action of eribulin that cause changes in the tumor microenvironment with important effects on tumor biology and phenotype in both MBC and STS resulting in more differentiated, less aggressive residual tumors.

Overall survival and PFS benefits in favour of eribulin were observed consistently in all liposarcoma subgroups. The subgroup analyses for the liposarcoma histology and within the liposarcoma histology subtypes (dedifferentiated, pleomorphic, myxoid/round cell liposarcoma) are consistent with the observed effect in the overall liposarcoma population. Results with LMS were more heterogeneous with PFS and OS outcomes favouring eribulin for subjects with non-uterine LMS but PFS and OS favouring dacarbazine for subjects with uterine LMS. The heterogeneous results of LMS patients and subgroups of LMS patients are difficult to interpret in the context of previous randomised sarcoma trials.¹⁹ As such it is the sponsor's opinion that the positive outcomes of Study 309 apply to the entire ITT population without regard to subgroups.

Individual published randomised chemotherapy trials in sarcoma patients have shown differences in response rates (RR) by histology to different chemotherapy regimens but no differences in OS. One trial of doxorubicin plus dacarbazine showed an increase in the relative risk (RR) from 20% for single agent doxorubicin to 30% with the combination for all sarcoma patients, and to 45% for patients with leiomyosarcoma.²⁰ This was one of the first trials to demonstrate that dacarbazine (or its oral equivalent, temozolomide) appeared to be more active in LMS than in other sarcomas. This observation has been

Schöffski P, Maki PG, Italiano A, Gelderblom H, Grignani G, De Camargo VP, et al. Randomized, open-label, multicenter, phase III study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipoctytic sarcoma (ADI). *J Clin Oncol* 2015;33(15 Suppl): abstract Abstract 10502.

¹⁹Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. *J Clin Oncol* 2007;25(19):2755-63.

Demetri GD, von Mehren M, Jones RL, Hensely ML, Schuetz S, Staddon AP, et al. A randomized phase III study of trabectedin (T) or dacarbazine (D) for the treatment of patients (pts) with advanced liposarcoma (LPS) or leiomyosarcoma (LMS). *J Clin Oncol* 2015;33(15 Suppl): Abstract 10503.

²⁰Borden EC, Amato DA, Rosenbaum C, Enterline HT, Shiraki MJ, Creech RH, et al. Randomized comparison of three Adriamycin regimens for metastatic soft tissue sarcomas. *J Clin Oncol* 1987;5(6):840-50.

reproduced in several other trials.²¹ Another report showed a higher RR for patients with synovial sarcoma treated with doxorubicin and ifosfamide than for other histologies.²² There is currently no data to support a biological rationale for a differential response effect of various chemotherapy agents by subtype, for example liposarcoma, LMS or synovial sarcoma. Importantly, none of these combination trials has demonstrated a statistically significant improvement in OS in either of these histologies compared with doxorubicin.

Up until about the year 2000 large sarcoma trials enrolled high grade sarcoma patients and did not stratify by separate histologies. Around then it became clear that Gastrointestinal Stromal Tumor was a distinct sarcoma subtype characterised by mutation and overexpression of the CKIT tyrosine kinase. This property made GIST uniquely sensitive to therapy with imatinib, a CKIT tyrosine kinase inhibitor.²³ This success led to many more subtype specific therapy trials and multi arm trials to separately evaluate certain histologies.

There have been some modest successes in very rare subtypes, use of angiogenesis inhibitors (sorafenib and bevacizumab) for angiosarcomas²⁴ imatinib (also a PDGFR inhibitor) for dermatofibrosarcoma protuberans and chordoma²⁵, mTOR inhibitors for malignant perivascular epithelioid cell tumors (PEComas)²⁶ and the RANK ligand agonist denosumab for giant cell tumors of bone.²⁷

In the past decade multiple trials of both cytotoxic and targeted therapy have been conducted trying to establish meaningful differences between various subtypes of sarcoma. Such studies included pazopanib (leiomyosarcoma, liposarcoma, synovial sarcoma and other)²⁸, ridaforolimus (bone sarcomas, leiomyosarcoma, liposarcoma and other sarcoma)²⁹ and eribulin (leiomyosarcoma, liposarcoma, synovial sarcoma and

²¹ Omura GA, Major FD, Blessing JA, Sedlacek YV, Thigpen JT, Creasman MD, et al. A Randomized Study of Adriamycin With and Without Dimethyl Triazenoimidazole Carboxamide in Advanced Uterine Sarcomas. *Cancer* 1983;52(4):626-32.

Ferriss JS, Atkins KA, Lachance JA, Modesitt SC, and Jazaeri AA. Temozolomide in advanced and recurrent uterine leiomyosarcoma and correlation with o6-methylguanine DNA methyltransferase expression: a case series. *Int J Gynecol Cancer* 2010;20(1):120-5.

Garcia del Muro X, Lopez-Pousa A, Martin J, Buesa JM, Martinez-Trufero J, Casado A, et al. A phase II trial of temozolomide as a 6-week, continuous, oral schedule in patients with advanced soft tissue sarcoma: a study by the Spanis Group for Research on Sarcomas. *Cancer* 2005;104(8):1706-12.

²² Edmonson JH, Ryan LM, Blum RH, Brooks JS, Shiraki M, Frytak S, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol* 1993;11(7):1269/75.

²³ D'Adamo D. Advance in the treatment of gastrointestinal stromal tumor. *Adv Ther* 2009;26(9):826-37.

²⁴ Maki RG, D'Adamo DR, Keohan ML, Saulle M, Schuetze SM, Undevia SM, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol* 2009;27(19):3133-40.

²⁵ McArthur GA, Demetri GD, van Oosterom A, Heinrich MC, Debiec-Rychter M, Corless CL, et al. Molecular and Clinical Analysis of Locally Advanced Dermatofibrosarcoma Protuberans Treated With Imatinib: Imatinib Target Exploration Consortium Study B2225. *J Clin Oncol* 2005;23(4):866-73.

Casali PG, Messina A, Stacchiotti S, Tamborini E, Crippa F, Gronchi A, et al. Imatinib mesylate in chordoma. *Cancer* 2004;101(9):2086-97.

²⁶ Wagner AJ, Malinowska-Kolodziej I, Morgan JA, Qin W, Fletcher CD, Vena N, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. *J Clin Oncol* 2010;28(5):835-40.

²⁷ Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol* 2010;11(3):275-80.

²⁸ Sleijfer S, Ray-Coquard I, Papai Z, Le Cesne A, Scurr M, Schöffski P, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancersoft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol* 2009;27(19):2126-32.

²⁹ Chawla SP, Staddon AP, Baker LH, Scheutze SM, Tolcher AW, D'Amato GZ, et al. Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. *J Clin Oncol* 2012;30(1):78-84.

other)³⁰. Each of these non-randomized Phase II studies led to randomised trials in histology subtypes deemed positive by PFR12wks or clinical benefit rate (CBR). Thus the pazopanib Phase III trial was conducted in leiomyosarcoma, synovial sarcoma and 'other' sarcoma patients and was positive for PFS but not for OS.³¹ The ridaforolimus trial conducted in all 4 subgroups, bone sarcomas, leiomyosarcoma, liposarcoma and other, was positive with a 3.1 week improvement in median PFS but without OS difference.³² The eribulin trial presented here was positive for OS but not for PFS. Interestingly these subgroup specific or subgroup stratified randomised trials did not identify significant differences in OS outcome by histology. The single exception to this was a trial of dacarbazine versus gemcitabine plus dacarbazine, where leiomyosarcoma patients experienced improved survival compared with non LMS patients. Median PFS and OS were 4.9 and 18.3 months, respectively for patients with leiomyosarcoma and 2.1 and 7.8 months respectively for non-leiomyosarcoma patients.³³ Of note all patients on both arms of this trial received dacarbazine reinforcing the observation that dacarbazine has selective activity in LMS.

Study 309 was designed to evaluate efficacy of eribulin in subjects with soft tissue sarcomas of liposarcoma and LMS histology. The results demonstrated a clinically relevant, unprecedented and convincing improvement in OS for patients treated with eribulin compared to dacarbazine. The outcomes observed in Study 309 with regards to the differential efficacy for OS versus PFS are consistent with results previously reported in studies for metastatic breast cancer, which led to the approval of the drug in this indication. These are possibly based on the specific mechanisms of action of the drug influencing multiple aspects of the tumor microenvironment.

The subgroup analyses for the liposarcoma histology and within the liposarcoma histology subtypes are consistent with the observed effect in the overall liposarcoma population. The results for LMS histology are more heterogeneous, with some clinically defined subgroups showing more benefit than others. Further subgroup analyses, including for organ of origin (uterine versus non-uterine) do not yield a consistent picture and are likely influenced by chance findings due to insufficient sample sizes. There are no clinical historical data reported for a differential survival efficacy of systemic therapies between liposarcoma and LMS histology and there is no evident explanation based on tumor biology.

Therefore the sponsor believes that eribulin should be indicated as in the Phase III Study 309 and for the entire ITT population.

However, during the evaluation of the application, the clinical evaluator expressed concerns with the heterogeneity of the LMS population and proposed approval of only the liposarcoma population. The sponsor accepted this proposal and amended the proposed indication accordingly. This also aligns the indication with the approved indications in the USA and the EU. Given the unique survival advantage demonstrated by eribulin in the entire ITT population, it is therefore reasonable that subjects with liposarcoma have access to eribulin in second or later lines, regardless of prior therapy.

³⁰Shöffski P, Ray-Coquard IL, Cioffi A, Bui NB, Bauer S, Hartmann JT, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. *Lancet Oncol* 2011;12:1045-52.

³¹van der Graaf WTA and Gelderblom H. (2012). New Systemic Therapy Options for Advanced Sarcomas. *Curr Treat Options Oncol*. 2012 Sep; 13(3): 306–317.

³²Demetri GD, Chawla SP, Ray-coquard I, Le Cesne A, Staddon AP, Milhem MM, et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. *J Clin Oncol* 2013;(31(9):2485- 92.

³³García del Muro X, López-Pousa A, Maurel J, Martín J, Martínez-Trufero J, casado A, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol* 2011;29(18):2528-33.

Delegate issue 2:

Please comment on the adequacy of the proposed PI to provide relevant details on the outcomes of efficacy and safety from pivotal Study 309.

Response

In terms of the safety profile of Halaven, there were no significant differences in the soft tissue sarcoma population compared to the metastatic breast cancer population and the proposed PI is considered adequate. However, in order to be consistent with safety information provided for previous studies (Study 305 and Study 301) included in the PI, a table of very common AEs occurring in the Halaven and dacarbazine arms of Study 309 has been included.

In Study 309, the following very common AEs occurred at a significantly higher incidence in the eribulin group compared with the dacarbazine group: neutropenia (43.8% for eribulin versus 23.7% for dacarbazine), peripheral neuropathy (combining the terms neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, polyneuropathy and paraesthesia, 33.1% versus 7.5%, respectively), alopecia (35.0% versus 2.7%, respectively), and pyrexia (27.9% versus 13.8%, respectively). Thrombocytopenia occurred at a significantly higher incidence in the in the dacarbazine group compared with the eribulin group (27.7% versus 5.8%, respectively). This is consistent with the known safety profile of each of these products.

Advisory Committee Considerations

The ACPM (now called Advisory Committee on Medicines (ACM)) resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Halaven Solution for injection containing 1mg/2 mL of Eribulin mesilate to have an overall positive benefit–risk profile for the proposed indication;

Halaven is indicated for the treatment of patients with unresectable liposarcoma who have received prior chemotherapy for advanced or metastatic disease.

In making this recommendation the ACPM

- was of the view that based on information provided eribulin mesilate showed clinically significant improvement in overall and progression free survival compared to conventional dacarbazine treatment.
- noted that Halaven demonstrated reasonable efficacy for the proposed indication without significant new safety concerns.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate regarding proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

The committee is requested to provide advice on the following issues:

1. *Please comment on whether the data are sufficient to characterise a population for which the benefit –risk balance is considered positive for eribulin in the treatment of sarcoma, and advise on whether this is adequately defined in the amended proposed additional indication.*

The committee was of the view that provided clinical evidence showed a positive risk-benefit balance in the treatment of patients with unresectable liposarcoma and this has been adequately defined in the amended additional indication.

2. *Please comment on the adequacy of the proposed PI to provide relevant details on the outcomes of efficacy and safety from pivotal Study 309.*

The ACPM noted that information contained in the updated PI is well documented and it provides sufficient information in regards to safety and efficacy outcomes from pivotal study.

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACPM supported the proposed inclusion of additional information about neutropenia and septic shock in the Product Information documents.

The ACPM advised that 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 containing eribulin mesilate 1 mg/2 mL solution for injection glass vial for the new indication:

Halaven is indicated for the treatment of patients with unresectable liposarcoma who have received prior chemotherapy for advanced or metastatic disease.

Attachment 1. Product Information

The PI for Halaven approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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