

## 5.11 TRABECTEDIN, Powder for I.V. infusion 0.25mg, 1mg Yondelis<sup>®</sup>, Specialised Therapeutics Pharma Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100, Authority Required (STREAMLINED) listing for trabectedin for the treatment of advanced (unresectable and/or metastatic) leiomyosarcoma (LMS) in patients who have received prior chemotherapy treatment including an anthracycline.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus pazopanib. The key components of the clinical issues addressed by the submission are summarised below. The submission's key components table did not make a claim regarding safety, however its therapeutic conclusion was that trabectedin is non-inferior in terms of safety compared with pazopanib for the treatment of LMS.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients with unresectable or metastatic leiomyosarcoma following a prior anthracycline-containing regimen.
Intervention	Trabectedin ((Yondelis); ET-743) with a recommended dose of 1.5mg/m <sup>2</sup> via infusion in a 21-day treatment cycle
Comparator	Pazopanib with a recommended dose of 800mg orally once daily
Outcomes	PFS, ORR, OS, TTP, duration of response, HRQoL (MD Anderson Symptom Index), safety
Clinical claim	In patients with unresectable or metastatic leiomyosarcoma following a prior anthracycline-containing regimen, trabectedin is as effective as pazopanib at improving progression-free survival.

Source: Table 1 of the submission.

HRQoL = health related quality of life; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTP = time to progression.

### 2 Background

#### **Registration status**

- 2.1 **TGA status at time of PBAC consideration:** A TGA application for the treatment of soft tissue sarcoma was lodged in March 2020. The Delegate's Overview was provided with the Pre-Sub-Committee Response (PSCR). Trabectedin was approved on the 21 April 2021 for the treatment of patients with unresectable or metastatic LPS or LMS who had received a prior anthracycline-containing regimen. The ESC noted that trabectedin was designated as an orphan drug by the TGA.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

### 3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts	Dispensed price for maximum amount
TRABECTEDIN Powder for I.V. infusion, 0.25mg Powder for I.V. infusion, 1 mg	NEW (Public) NEW (Private)	3.25mg	2 3	Published: \$8,962.05 ( <i>Public hospital</i> ) \$9,126.95 (Private hospital) Effective: \$ [REDACTED] ( <i>Public hospital</i> ) \$ [REDACTED] (Private hospital)
<b>Available brands</b>				
Yondelis®				
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>				
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]				
<b>Administrative Advice:</b> <i>This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital.</i>				
<b>Administrative Advice:</b> <i>Special Pricing Arrangements apply.</i>				
<b>Episodicity:</b> <del>Soft tissue sarcoma is a progressive disease that is not episodic in nature</del> [not repeated again]				
<b>Severity:</b> Advanced (unresectable and/or metastatic)				
<b>Condition:</b> <del>Leiomyosarcoma</del> <i>Soft Tissue Sarcoma</i>				
<b>Indication:</b> Advanced (unresectable and/or metastatic) leiomyosarcoma				
<b>Treatment Phase:</b> Initial treatment				
<b>Clinical criteria:</b>				
<del>Patient must have leiomyosarcoma</del>				
<b>AND</b>				
<b>Clinical criteria:</b>				
Patient must have an ECOG performance status of 2 or less				
<b>AND</b>				
<b>Clinical criteria:</b>				
Patient must have received prior chemotherapy treatment including an anthracycline				
<b>AND</b>				
<b>Clinical criteria:</b>				
The treatment must be the sole PBS-subsidised therapy for this condition.				
<b>AND</b>				
<b>Population criteria:</b>				
Patient must be aged 18 years or older.				

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MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts	Dispensed price for maximum amount
TRABECTEDIN Powder for I.V. infusion, 0.25mg Powder for I.V. infusion, 1 mg	NEW (Public) NEW (Private)	3.25mg	5 7	Published: \$8,962.05 (Public hospital) \$9,126.95 (Private hospital) Effective: \$ [REDACTED] (Public hospital) \$ [REDACTED] (Private hospital)
<b>Available brands</b>				
Yondelis®				
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>				
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]				
<b>Administrative Advice:</b> This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital.				
<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
<b>Episodicity:</b>				
<b>Severity:</b> Advanced (unresectable and/or metastatic)				
<b>Condition:</b> <del>Leiomyosarcoma</del> Soft Tissue Sarcoma				
<b>Indication:</b> Advanced (unresectable and/or metastatic) leiomyosarcoma				
<b>Treatment Phase:</b> Continuing treatment				
<b>Clinical criteria:</b>				
Patient must have previously received PBS-subsidised therapy with this drug for this condition				
<b>AND</b>				
<b>Clinical criteria:</b>				
Patient must not develop progressive disease while being treated with this drug for this condition,				
<b>AND</b>				
<b>Clinical criteria:</b>				
The treatment must be the sole PBS-subsidised therapy for this condition.				
<b>AND</b>				
<b>Population criteria:</b>				
Patient must be aged 18 years or older.				

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts	Dispensed price for maximum amount
TRABECTEDIN Powder for I.V. infusion, 0.25mg Powder for I.V. infusion, 1 mg	NEW (Public) NEW (Private)	3.25mg	7	Published: \$8,962.05 (Public hospital) \$9,126.95 (Private hospital) Effective: \$ [REDACTED] (Public hospital) \$ [REDACTED] (Private hospital)
<b>Available brands</b>				
Yondelis®				
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>				
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
<b>Restriction type:</b>				

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<input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
<b>Administrative Advice:</b> <i>This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital.</i>
<b>Administrative Advice:</b> <i>Special Pricing Arrangements apply.</i>
<b>Episodicity:</b>
<b>Severity:</b> <i>Advanced (unresectable and/or metastatic)</i>
<b>Condition:</b> <i>Leiomyosarcoma</i>
<b>Indication:</b> <i>Advanced (unresectable and/or metastatic) leiomyosarcoma</i>
<b>Treatment Phase:</b> <i>Grandfather treatment (transition from non-PBS-subsidised to PBS-subsidised treatment)</i>
<b>Clinical criteria:</b>
<i>Patient must have been receiving treatment with this drug for this condition prior to &lt;PBS listing date&gt;</i>
<b>AND</b>
<b>Clinical criteria:</b>
<i>Patient must have an ECOG performance status of 2 or less prior to initiating non-PBS subsidised treatment</i>
<b>AND</b>
<b>Clinical criteria:</b>
<i>Patient must have received chemotherapy treatment including an anthracycline prior to initiating non-PBS subsidised treatment</i>
<b>AND</b>
<b>Clinical criteria:</b>
<i>Patient must not develop progressive disease while being treated with this drug for this condition,</i>
<b>AND</b>
<b>Clinical criteria:</b>
<i>The treatment must be the sole PBS-subsidised therapy for this condition.</i>
<b>AND</b>
<b>Population criteria:</b>
<i>Patient must be aged 18 years or older.</i>

- 3.2 The sponsor was aware of a Special Pricing Arrangement (SPA) for pazopanib, and indicated a willingness to negotiate an SPA for trabectedin based on this arrangement. The proposed published and effective ex-manufacturer price per 1 mg vial of trabectedin was \$2,731.16 and \$ [REDACTED], respectively. The proposed published and effective ex-manufacturer price per 0.25 mg vial of trabectedin was \$682.79 and \$ [REDACTED], respectively.
- 3.3 The PBAC noted the number of repeats was increased to 3 for initial therapy and 7 for continuing therapy to reflect the durations of therapy requested in the submission (three months and six months respectively).
- 3.4 The requested restriction was within the proposed indication in the draft Product Information (PI), however it allowed for second-line use, which was inconsistent with the proposed treatment algorithm presented in the submission. Inclusion criteria for Study 3007 specified (i) a prior anthracycline- and ifosfamide-containing regimen, or (ii) a prior anthracycline and at least one additional cytotoxic agent. The majority (88.3%) of patients in Study 3007 had received two or more lines of prior chemotherapy. The PSCR argued there was no clinical rationale for positioning trabectedin after pazopanib as international treatment guidelines, clinical trial data and usage data from international markets do not support such an additional restriction. The ESC agreed with the PSCR and considered the proposed restriction and placement of trabectedin in the treatment algorithm was reasonable. The PBAC

considered a restriction that allowed sequential therapy of pazopanib and trabectedin appropriate.

- 3.5 The PBAC noted an ECOG performance status of two or less was consistent with the current pazopanib restriction and considered it appropriate for a trabectedin listing.
- 3.6 The PBAC advised the age restriction be removed from the restriction to allow clinical judgment to guide the use of trabectedin in patients under 18 years of age.
- 3.7 The submission stated that a paid access program was introduced in November 2019 with 29 patients with LMS or LPS in the program at March 2021. The submission did not present a grandfather restriction. The PBAC considered a grandfather restriction appropriate.

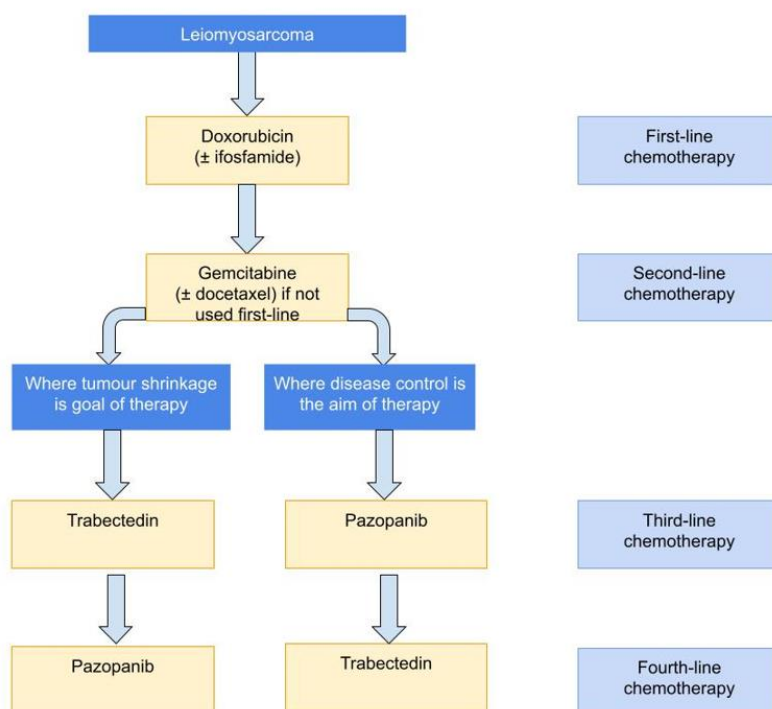
*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Soft tissue sarcomas (STS) are a rare, heterogeneous group of malignant tumours of mesenchymal origin that comprise less than 1% of all adult malignancies, and 12% of paediatric cancers. LMS and LPS are among the most common mesenchymal sarcomas, accounting for 20% and 10% of all STS, respectively (Bessen et al, 2016).
- 4.2 Leiomyosarcoma is an aggressive soft tissue sarcoma derived from smooth muscle cells typically of uterine, gastrointestinal or soft tissue origin. Women are affected more than men (2:1), with the disease typically occurring in the 5th and 6th decades of life. Prognosis and treatment vary on the location, stage and grade of the primary tumour as well as the presence of metastatic disease.
- 4.3 Many patients present with advanced disease. Unresectable or metastatic LMS has a poor prognosis. The median overall survival (OS) for LMS ranges from approximately 17 months for those on second-line therapy to 9 months for those on fourth-line therapy.
- 4.4 Pazopanib is currently available as a later line treatment for patients with LMS who have received prior chemotherapy treatment including an anthracycline. The submission proposed trabectedin as an alternative to pazopanib in the treatment algorithm. However, the treatment algorithm (Figure 1 below) and the clinical evidence presented in the submission indicated that pazopanib and trabectedin can be used sequentially. The trabectedin arm of Study 3007 had substantial prior (9.8%) and subsequent (28.6%) pazopanib use, and the pazopanib arm of the PALETTE trial had 16% and 34% of patients who had received prior and subsequent trabectedin respectively. The proportion of patients who may receive both trabectedin and pazopanib in Australian clinical practice is likely to be higher, as patients in Study 3007 had access to therapies not commonly used in Australia; for example, 26.6% of patients in the trabectedin arm went on to receive dacarbazine, which is not a PBS-listed treatment option in Australia. Sequential use suggests placebo/best supportive care may be the appropriate comparator in the population anticipated to receive

pazopanib, then trabectedin. The ESC considered that guidelines are consistent in recommending a doxorubicin containing regimen first-line (NCCN 2018, Casali 2018) but were broad in their recommendations on subsequent lines of therapy with optimal sequencing of chemotherapies not clearly established in clinical practice.

**Figure 1: Proposed treatment algorithm for patients with leiomyosarcoma treated with palliative intent following the listing of trabectedin**



Source: Figure 9, p 26 of the submission.

4.5 The clinical role of trabectedin in the target population is uncertain. The submission proposed trabectedin as either third- or fourth-line therapy in the treatment algorithm but the requested restriction did not preclude use as second-line therapy. Trabectedin treatment requires the insertion of a central venous catheter and connection of a 24-hour infusion once every 21 days, with steroid pre-treatment and observation in the outpatient setting. Pazopanib is a single tablet taken orally once per day. If patients were offered a choice between these two therapies in the third-line setting and told they had similar efficacy, the ESC considered it is conceivable that many patients would prefer the simpler tablet regime.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## 5 Comparator

5.1 The submission nominated pazopanib as the main comparator. The main argument provided in support of this nomination was that the current treatment guidelines from the Australia and New Zealand Sarcoma Association (ANZSA) place both pazopanib and trabectedin as a second-line, or beyond second-line, treatment options.

- 5.2 In patients where trabectedin is to be used after pazopanib, placebo may have been a more appropriate comparator. In the PALETTE trial, 49% of pazopanib-treated patients went on to receive subsequent chemotherapy and the submission used this figure to calculate the number of Australian patients who would receive pazopanib and then trabectedin.
- 5.3 The PSCR argued that data in international markets where both pazopanib and trabectedin are available indicate that trabectedin is widely used and that the difference in administration routes would likely not be a major issue as patients in this line of therapy would usually have a central line. The ESC considered that while some patients may elect to use an oral therapy such as pazopanib, the nominated comparator and justification of the proposed place in therapy was reasonable.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals (7) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the need for additional treatment options for LMS (and also LPS, for which PBS subsidy was not specifically sought) and highlighted that trabectedin is currently being used in clinical practice through the TGA Special Access Scheme at a great financial cost to patients.
- 6.3 The PBAC noted the advice received from Rare Cancers Australia, which highlighted the often poor prognosis associated with LMS and the need for additional therapeutic options for treating this rare condition.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the trabectedin submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for trabectedin, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>[1]</sup>, based on a comparison with various comparators.

### ***Clinical studies***

- 6.5 The submission was based on two studies. The first was a head-to-head, open-label trial comparing trabectedin with dacarbazine in patients with histologically proven LPS or LMS who have received prior treatment with either (i) a prior anthracycline- and ifosfamide-containing regimen, or (ii) a prior anthracycline and at least one additional cytotoxic agent (n= 577, Study 3007). The second was another head-to-head, double-

blinded randomised trial comparing pazopanib with placebo in a similar population (n =369, PALETTE). The PBAC reviewed PALETTE when considering pazopanib for the PBS listing in November 2012. The submission claimed that an indirect treatment comparison (ITC) could not be performed, as the trials were too heterogeneous. Despite this, a matching-adjusted ITC published as a conference abstract based on the same trials was presented in the submission to support its claim of the non-inferiority of trabectedin to pazopanib in terms of clinical efficacy and safety.

6.6 The submission also presented one additional trial, the TSAR study, which compared trabectedin with best supportive care (BSC), however only an abstract was available. The limited information presented in the abstract precluded an adequate evaluation of this study.

6.7 The table below presents the details of the key studies.

**Table 2: Studies and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Trabectedin v Dacarbazine</b>		
Study 3007	Janssen Research & Development. A Randomized Controlled Study of YONDELIS® (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma. Clinical Study Report ET743-SAR-3007	October 2014
	Janssen Research & Development. A Randomized Controlled Study of YONDELIS® (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma. Final Clinical Study Report Addendum ET743-SAR-3007	November 2015
	Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, Milhem M, Elias A, Ganjoo K, Tawbi H, Van Tine BA, Spira A, Dean A, Khokhar NZ, Park YC, Knoblauch RE, Parekh TV, Maki RG, Patel SR Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial.	<i>Journal of Clinical Oncology</i> 2016; 34(8):786-93.
<b>Trabectedin v Placebo</b>		
TSAR	NCT02672527 Trial Comparing Trabectedin to the Best Supportive Care in Patients With Sarcoma (TSAR). <a href="https://clinicaltrials.gov/ct2/show/NCT02672527">https://clinicaltrials.gov/ct2/show/NCT02672527</a>	Last updated 2018.
	Le Cesne A, Kapso Kapnang R, Foulon S, Bonastre J. Health-related quality of life in patients with advanced soft tissue sarcoma (ASTS): Results from the TSAR randomized phase III trial of the French Sarcoma Group.	Conference: 43rd Congress of European Society for Medical Oncology, ESMO 2018, Germany. 29 (Supplement 8) (pp viii577).
	Le Cesne A, Blay J-Y, Cupissol D, Italiano A, Delcambre C, Penel N, Isambert N, Chevreau C, Bompas E, Bertucci F, Chaigneau L, Piperno-Neumann S, Salas S, Rios M, Guillemet C, Bay JO, Ray-Coquard IR, Haddag L, Mir O, and Foulon S. Results of a prospective randomized phase III T-SAR trial comparing trabectedin (T) vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS): A French Sarcoma Group (FSG) trial.	<i>Journal of Clinical Oncology</i> 2018; 36:15_suppl, 11508-11508.

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Trial ID	Protocol title/ Publication title	Publication citation
	<p>Results of a prospective randomized phase III T-SAR trial comparing trabectedin vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS).</p> <p>Maillard M, Chevreau C, Louedec F, Cassou M, Delmas C, Gourdain L, Blay J-Y, Cupissol D, Bompas E, Italiano A, Isambert N, Delcambre-Lair C, Penel N, Bertucci F, Guillemet C, Plenecassagnes J, Foulon S, Chatelut É, Le Cesne A, Thomas F. Pharmacogenetic Study of Trabectedin-Induced Severe Hepatotoxicity in Patients with Advanced Soft Tissue Sarcoma.</p>	<p>Conference: 41st European Society for Medical Oncology Congress, ESMO 2016. Denmark. 27 (Supplement 6) (no pagination).</p> <p><i>Cancers</i> 2020; 12. 3647. 10.3390/cancers12123647.</p>
<b>Pazopanib v Placebo</b>		
PALETTE	<p>EUCTR2008-001307-33-SE A randomized double blind phase III trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or following prior therapy. – PALETTE  <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-001307-33-SE">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-001307-33-SE</a>.</p>	2008
	<p>NCT00753688 Pazopanib Versus Placebo in Patients With Soft Tissue Sarcoma Whose Disease Has Progressed During or Following Prior Therapy  <a href="https://clinicaltrials.gov/show/NCT00753688">https://clinicaltrials.gov/show/NCT00753688</a>.</p>	2008
	<p>van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, Judson IR, Araki N, Ouali M, Marreaud S, Hodge R, Dewji MR, Coens C, Demetri GD, Fletcher CD, Dei Tos AP, Hohenberger P, EORTC Soft Tissue and Bone Sarcoma Group, PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial.</p>	<i>Lancet</i> 2012; 379(9829):1879-86.
	<p>Le Cesne A, Bauer S, Demetri GD, Han G, Dezzani L, Ahmad Q, Blay J-Y, Judson I, Schöffski P, Aglietta M, Hohenberger P, Gelderblom H. Safety and efficacy of Pazopanib in advanced soft tissue sarcoma: PALETTE (EORTC 62072) subgroup analyses.</p>	<i>BMC Cancer</i> 2019. 19 (1) (no pagination). Article Number: 794.
	<p>Van Der Graaf WTA, Blay J-Y, Chawla SP, Kim D-W, Nguyen BB, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, Judson IR, Araki N, Ouali M, Marreaud S, Hodge R, Dewji M, Dei Tos AP, Hohenberger P. PALETTE: Final overall survival (OS) data and predictive factors for OS of EORTC 62072/GSK VEG110727, a randomized double-blind phase III trial of pazopanib versus placebo in advanced soft tissue sarcoma (STS) patients.</p>	<p>Conference: 2012 Annual Meeting of the American Society of Clinical Oncology, ASCO. Conference Publication: (var. pagings). 30 (15 SUPPL. 1) (no pagination).</p>
<b>Indirect comparison</b>		
	<p>Jones RL, Blay J-Y, Lecesne A, Martin-Broto J, Pontes MJ, Fernandez Santos JM, Garcia San Andres B, Wang G, Wang S, Shin CR, Maki R, Patel S, Demetri GDS. A matching-adjusted indirect comparison of trabectedin and pazopanib for the treatment of advanced, metastatic, leiomyosarcomas.</p>	<p>Conference: 42nd ESMO Congress, ESMO 2017. Spain. 28 (Supplement 5) (pp v524-v525).</p>
<b>Systematic reviews</b>		

Trial ID	Protocol title/ Publication title	Publication citation
	Sharma S, Takyar S, Manson SC, Powell S, Penel N. Efficacy and safety of pharmacological interventions in second- or later-line treatment of patients with advanced soft tissue sarcoma: a systematic review.	<i>BMC Cancer</i> 2013; 13:385.
	Rafia R, Simpson E, Stevenson M, Papaioannou D. Trabectedin for the treatment of advanced metastatic soft tissue sarcoma: a NICE single technology appraisal.	<i>Pharmacoeconomics</i> 2013; 31(6):471-8.
	Gupta AA, Yao X, Verma S, Mackay H, Hopkins L, Sarcoma Disease Site Group and the Gynecology Cancer Disease Site Group. Systematic chemotherapy for inoperable, locally advanced, recurrent, or metastatic uterine leiomyosarcoma: a systematic review.	<i>Clinical Oncology (Royal College of Radiologists)</i> 2013; 25(6):346-55.
	Simpson EL, Rafia R, Stevenson MD, Papaioannou D. Trabectedin for the treatment of advanced metastatic soft tissue sarcoma.	<i>Health Technology Assessment</i> 2010; 14 Suppl 1:63-7.

Source: Table 12, pp 43-49 of the submission.

6.8 The key features of the included evidence are summarised in the table below.

**Table 3: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Trabectedin vs dacarbazine (Study 3007) or vs BSC (TSAR)</b>					
Study 3007	577	R, OL 21.2 mths*	Low	Patients with advanced L-type sarcoma who had previously received chemotherapy with at least an anthracycline and ifosfamide containing regimen or an anthracycline containing regimen and one additional cytotoxic agent.	OS, PFS
TSAR	101	R, OL 25.7 mths*	Unclear	Patients with histologically proven advanced STS who progressed after at least 1 anthracycline-containing regimen ( $\leq 3$ previous chemotherapy lines).	OS, PFS
<b>Pazopanib vs placebo</b>					
PALETTE	369	R, DB 14.6 mth*	Low	Patients with metastatic STS who had received at least one regimen containing anthracycline and a maximum of four previous lines of systemic therapy for metastatic disease	OS, PFS

Source: Sections 2.3 and 2.4, pp52-89 of the submission.

\*The median durations of follow-up for Study 3007 and TSAR are for OS, while that for PALETTE is for PFS. The median duration of follow-up for OS was not reported.

DB = double blind; L-type sarcoma = liposarcoma or leiomyosarcoma; mths = months; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised; BSC = best supportive care, STS = soft tissue sarcoma.

6.9 For the individual studies 3007 and PALETTE, the evaluation considered the risk of bias was low; the primary outcome of Study 3007 was OS, and a blinded panel validated the PFS assessment. The risk of bias for TSAR could not be determined based on the limited information available in the abstract.

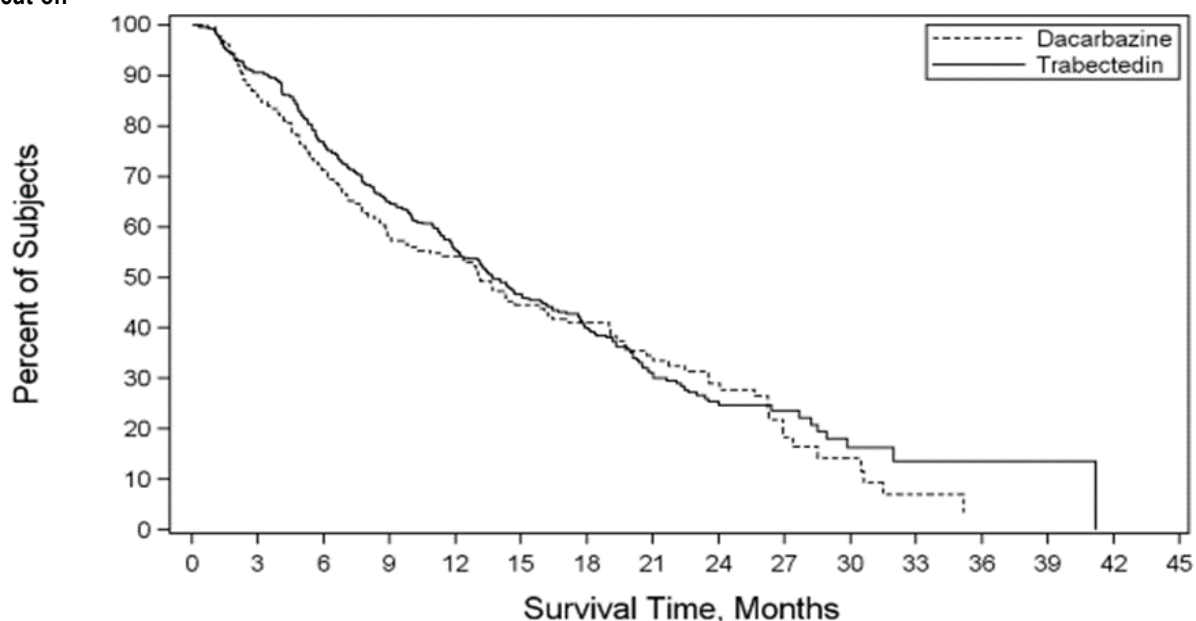
6.10 The submission did not present a formal indirect comparison of trabectedin and pazopanib. It was determined that the differences in comparator (dacarbazine versus placebo), use of subsequent therapies, duration of follow-up and patient demographics and histological subtypes precluded formal ITC. The risk of bias in a

standard Bucher method ITC would be high. The data from Study 3007 and PALETTE are presented together to provide an overview of the evidence.

### Comparative effectiveness

6.11 The Kaplan-Meier curves for OS from Study 3007 at final data cut-off are presented below. The unstratified HR was 0.927 (95% CI: 0.748, 1.150). The submission noted the survival curves intersect, meaning the proportional hazards assumption is likely violated and the reported hazard ratio must be interpreted cautiously. An analysis of OS stratified by ECOG performance status score, sarcoma type (LMS vs LPS), and number of prior lines of chemotherapy (the pre-specified stratification factors) was performed. When stratified by these factors, the results of the OS analysis (HR=0.939; 95% CI: 0.756, 1.167; p=0.5721) were consistent with the unstratified analysis of OS, and did not demonstrate a statistically significant improvement in OS with trabectedin treatment as compared to dacarbazine treatment.

Figure 2: Overall Survival - Stratified Analysis; All Randomised Subjects in the trabectedin trial (3007), final data cut-off



#### No. Subjects at Risk

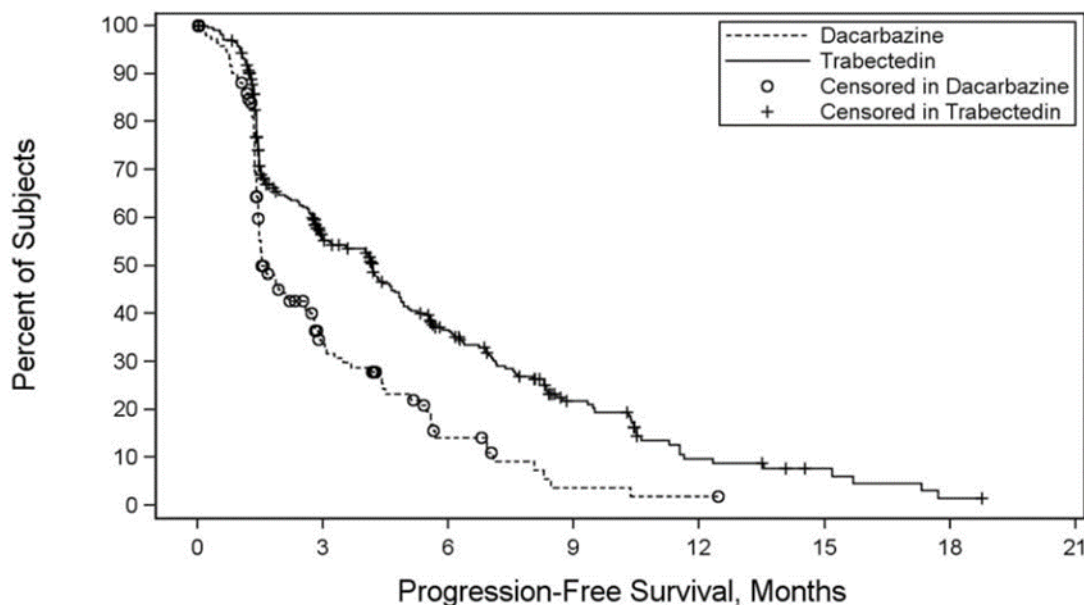
Dacarbazine	193	149	119	95	89	64	49	33	24	10	6	2	0		
Trabectedin	384	341	287	242	207	153	111	61	35	19	9	5	2	1	0

Source: Figure 16, p 91 of the submission.  
Final data cut-off: 05 January 2015.

6.12 The Kaplan-Meier curves for progression free survival (PFS) from Study 3007 are presented below. There was a statistically significant PFS benefit of approximately 2.7 months in the trabectedin arm compared to dacarbazine, with a median PFS of 4.21 months vs 1.54 months respectively. The HR was 0.550 (95% CI: 0.436, 0.696; p < 0.0001). An independent radiologist review carried out on 60% of the patients found a similar PFS benefit (HR= 0.549, 95% CI: 0.399, 0.754; p=0.0001). This analysis was

performed at the interim clinical cut-off of 16 September 2013, after 329 PFS events (approximately 64% of participants) had occurred. This was the only planned PFS analysis, with no further PFS analyses conducted at final data cut-off.

Figure 3: Progression-Free Survival; All Randomised Subjects in the trabectedin trial (3007), interim data cut-off



**No. Subjects at Risk**

Dacarbazine	173	35	10	2	1	0		
Trabectedin	345	133	71	29	10	5	1	0

Source: Figure 24, p 104 of the submission.  
Interim data cut-off: 16 September 2013

6.13 There was no statistically significant difference in OS between trabectedin and BSC in TSAR, with a median OS of 13.6 vs 10.8 months respectively (HR not reported). 92% of patients in the BSC arm switched to trabectedin on or after disease progression. A statistically significant PFS benefit of 1.6 months favouring trabectedin over BSC was observed in this study, with a median PFS of 3.1 vs 1.5 months (HR 0.39,  $p < 0.0001$ ). The PFS benefit was more pronounced in the LPS/LMS subgroup, where median PFS for trabectedin was 5.1 months, compared to 1.4 months for BSC (HR 0.29,  $p < 0.0001$ ).

Subgroup analyses

6.14 The table below provides the results from Study 3007 in the ITT and LMS/LPS subgroups.

**Table 4: Overall Survival and Progression-free survival - Subgroup Analysis by histological type in Study 3007**

	Trabectedin	Dacarbazine	Hazard ratio (95% CI)
<b>Overall Survival</b>			
<b>ITT</b>			
Number of events	258/384 (67.2)	123/193 (63.7)	
Median – months (95% CI)	13.73 (12.16, 16.00)	13.14 (9.10, 16.23)	0.927 (0.748, 1.150)
<b>Leiomyosarcoma</b>			
Number of events	187/282 (63.8)	91/141 (64.5)	
Median – months (95% CI)	14.1	13.6	0.892 (0.694, 1.147)
<b>Liposarcoma</b>			
Number of events	71/102 (69.6%)	35/52 (67.3%)	
Median – months (95% CI)	13.1	12.6	1.048 (0.687, 1.600)
<b>Progression-free Survival</b>			
<b>ITT</b>			
Number of events	217/345 (62.9%)	112/173 (64.7%)	
Median – months (95% CI)	4.21 (2.99, 4.83)	1.54 (1.48, 2.60)	0.550 (0.436, 0.696)
<b>Leiomyosarcoma</b>			
Number of events	154/252 (61.1%)	85/126 (67.5%)	
Median – months (95% CI)	4.3	1.6	0.555 (0.423, 0.727)
<b>Liposarcoma</b>			
Number of events	63/93 (67.7%)	27/47(57.4%)	
Median – months (95% CI)	3	1.5	0.546 (0.341, 0.873)

Source: Table 60, pp 139-140 and Table 63, p 141 of the submission.

CI = confidence interval; ITT = Intention-to-treat population; *n* = number of participants with event; *N* = total participants in group

6.15 In Study 3007, 252/384 (73%) patients in the trabectedin arm had LMS, compared to 109/246 (44%) patients in the pazopanib arm of PALETTE. The PFS and OS results for the LMS patients in Study 3007 and PALETTE are summarised below.

**Table 5: Summary of results of the indirect comparison for overall survival and progression free survival in LMS**

Comparison [Trial ID]	Interventional Median – months (95% CI)	Comparator Median – months (95% CI)	Hazard ratio (95% CI)
<b>Overall Survival</b>			
Trabectedin vs dacarbazine [3007]	14.1	13.6	0.892 (0.694, 1.147)
Pazopanib vs placebo [PALETTE]	16.7 (12.6, 19.0)	14.1 (11.8, 18.5)	0.84 (0.56, 1.26)
<b>Progression-free Survival</b>			
Trabectedin vs dacarbazine [3007]	4.3	1.6	0.555 (0.423, 0.727)
Pazopanib vs placebo [PALETTE] <sup>a</sup>	4.6 (3.1, 5.3)	1.9 (1.8, 2.1)	0.37 (0.23, 0.60)

Source: Table 72, p 149 and Table 73, p 150 of the submission.

<sup>a</sup> Results reported in weeks and manually converted to months

LMS = Leiomyosarcoma; CI = confidence interval.

- 6.16 As noted above, the submission acknowledged considerable transitivity issues between Study 3007 and PALETTE and did not perform any statistical analysis between the two studies.
- 6.17 The submission further presented a published matching-adjusted indirect comparison performed by Jones et al. (2017)\*, which looked at the LMS subgroups of Study 3007 and PALETTE, and reported no significant difference in terms of PFS (HR 0.82, 95%CI 0.63, 1.06) or OS (HR 0.86, 95%CI 0.64, 1.18) between trabectedin and pazopanib. This publication was a half-page abstract, which lacked details on how the ITC was performed. Therefore, the validity of the results from this matching-adjusted indirect comparison could not be assessed. The submission did not nominate a non-inferiority margin. Further, the non-significant difference may be due to inadequate statistical power, given this is a subgroup analysis. The conduct of this ITC based on Study 3007 and PALETTE was in conflict with the submission's claim that, there were significant issues affecting the transitivity assumption of an indirect comparison between Study 3007 and PALETTE, which precluded statistical analysis. The ESC considered that as only a conference abstract was available for the indirect comparison; there was insufficient information to consider it reliable for decision-making.
- 6.18 The submission claimed that the more sequential treatments available for advanced/metastatic LMS, the greater the OS. However, the submission did not present any specific data for the effectiveness of sequential trabectedin/pazopanib or pazopanib/trabectedin.

### **Comparative harms**

- 6.19 The key safety data from Study 3007 and the PALETTE trial are presented below.

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\* Jones, R.L. et al. A matching-adjusted indirect comparison of trabectedin and pazopanib for the treatment of advanced, metastatic, leiomyosarcomas. *Annals of Oncology* 2017, Volume 28, v524 - v525.

**Table 6: Comparison of the Grade 3-4 adverse events reported for trabectedin in Study 3007 (in at least 5% of patients) and pazopanib in the PALETTE trial (common adverse events), at final analysis**

System organ class Preferred term	Trabectedin N = 378 n (%)			Pazopanib N = 239 n <sup>a</sup> (%)		
	Grade 3/4	Grade 3	Grade 4	Grade 3/4	Grade 3	Grade 4
Total number of subjects with grade 3–4 treatment-emergent adverse events	307 (81.2)	196 (51.9)	111 (29.4)	59%	49%	10%
Investigations	204 (54.0)	145 (38.4)	59 (15.6)	-	-	-
Alanine aminotransferase increased	111 (29.4)	106 (28.0)	5 (1.3)	10%	8%	2%
White blood cell count decreased	75 (19.8)	58 (15.3)	17 (4.5)	-	-	-
Neutrophil count decreased	77 (20.4)	45 (11.9)	32 (8.5)	-	-	-
Aspartate aminotransferase increased	57 (15.1)	53 (14.0)	4 (1.1)	8%	5%	3%
Platelet count decreased	39 (10.3)	22 (5.8)	17 (4.5)	-	-	-
Blood creatinine phosphokinase increased	22 (5.8)	10 (2.6)	12 (3.2)	-	-	-
Blood and lymphatic system disorders	140 (37.0)	85 (22.5)	55 (14.6)	-	-	-
Neutropenia	91 (24.1)	49 (13.0)	42 (11.1)	4%	4%	0
Anaemia	67 (17.7)	66 (17.5)	1 (0.3)	-	-	-
Leukopenia	37 (9.8)	26 (6.9)	11 (2.9)	1%	1%	0
Thrombocytopenia	40 (10.6)	15 (4.0)	25 (6.6)	4%	3%	<1%
Gastrointestinal disorders	69 (18.3)	68 (18.0)	1 (0.3)	-	-	-
Nausea	26 (6.9)	26 (6.9)	0	8 (3.3)	8 (3)	0
Vomiting	-	-	-	8 (3.3)	8 (3)	0
Abdominal pain	16 (4.2)	16 (4.2)	0	-	-	-
Diarrhoea	-	-	-	11 (4.6)	11 (5)	0
Anorexia	-	-	-	14 (5.9)	14 (6)	0
General disorders and administration site conditions	59 (15.6)	58 (15.3)	1 (0.3)	-	-	-
Fatigue	32 (8.5)	32 (8.5)	0	31 (13.0)	30 (13)	1 (<1)
Hypertension	-	-	-	16 (6.7)	16 (7)	0
Rash or desquamation	-	-	-	1 (0.4)	1 (<1)	0
Mucositis	-	-	-	3 (1.3)	3 (1)	0

Source: Table compiled during the evaluation, based on Table 20, p 41 of the Study 3007 Final CSR and Table 3, p 1884 of Van der Graaf (2012)<sup>†</sup> and Table 22, pp 30 – 33 of the pazopanib EPAR Assessment (2012).

<sup>a</sup> Some adverse events only had percentages provided. - = not common enough to be reported.

<sup>†</sup> van der Graaf WT et. al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*, 2012 May 19;379(9829):1879-86.

- 6.20 A higher incidence of Grade 4 AEs was recorded for trabectedin than pazopanib (29.4% vs 10%). The Grade 4 AEs most commonly associated with trabectedin were neutropenia and thrombocytopenia, compared to pazopanib that was associated with increased levels of alanine and aspartate aminotransferases. Trabectedin was also associated with higher rates of Grade 3 nausea compared to pazopanib (6.9% vs 3%). The submission considered the trials were too heterogeneous for a formal ITC. The PSCR argued that the majority of high-grade adverse events associated with trabectedin were laboratory abnormalities. The ESC noted that 11.1% of patients in Study 3007 treated with trabectedin experienced Grade 4 neutropenia. The ESC noted the findings of a phase II study of two different trabectedin treatment regimens<sup>‡</sup> in relation to AEs reported (Demetri 2009). The study found the incidence of Grade 4 neutropenia to be 21% for the 24 hour infusion regimen with a granulocyte colony-stimulating factor (G-CSF) administered in 28% of these patients. The ESC noted that febrile neutropenia was 0.8% in each study arm, with no medically important sequelae (Demetri 2009).

### **Clinical claim**

- 6.21 The submission described trabectedin as non-inferior in terms of effectiveness and safety compared to pazopanib in the treatment of LMS. The presented evidence did not adequately support the therapeutic conclusion presented in the submission. The two relevant trials Study 3007 and PALETTE were determined to be too heterogeneous to perform an ITC, and the matching-adjusted ITC that was provided had insufficient detail to determine whether this heterogeneity had been satisfactorily addressed. Therefore, the evaluation considered no conclusion regarding the comparative effectiveness and safety of trabectedin and pazopanib can be drawn.
- 6.22 Further, the fact that the ITC failed to demonstrate a statistically significant difference does not necessarily mean that the two treatments are equivalent, particularly when it cannot be determined if the analysis was powered to detect a difference.
- 6.23 The ESC advised that future comparative data with pazopanib are unlikely to become available. The ESC considered the claim of non-inferior effectiveness was uncertain, but possibly reasonable in the context of advanced LMS being a rare cancer with a poor prognosis.
- 6.24 The submission did not consider any comparison between Study 3007 and the PALETTE trial in terms of AEs to support its claim of non-inferior safety.
- 6.25 The ESC noted that laboratory anomalies were a major driver of the Grade 4 AEs observed with trabectedin treatment. The ESC considered that based on a naïve comparison of the AEs reported in Study 3007 and PALETTE trabectedin appeared to

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<sup>‡</sup> Two regimens used: 24 hour infusion once every 3 weeks (n=136); and a 3 hour infusion every week for 3 weeks of a 4 week cycle (n=134).

have an inferior safety profile compared to pazopanib. However, the ESC considered that a proportion of the laboratory anomalies may be manageable in clinical practice possibly improving the safety comparison.

- 6.26 While there were uncertainties with the clinical comparison due to the lack of a common comparator and heterogeneity issues between the trabectedin and pazopanib trials, the PBAC considered the claim of non-inferior comparative effectiveness to pazopanib for this rare cancer was reasonable.
- 6.27 The PBAC considered that the data was unlikely to support a claim of non-inferior safety to pazopanib and a claim of inferior safety was more appropriate. However, the PBAC agreed with the ESC that many of the laboratory anomalies driving the differences in Grade 4 AEs observed may be manageable in clinical practice.

### **Economic analysis**

- 6.28 The submission presented a cost-minimisation analysis of trabectedin compared with pazopanib. The key components and assumptions of the cost-minimisation analysis are summarised below.

**Table 7: Key components and assumptions of the cost-minimisation analysis**

<b>Component</b>	<b>Claim or assumption</b>
Therapeutic claim: effectiveness	Based on evidence presented, efficacy is assumed to be non-inferior to pazopanib.
Therapeutic claim: safety	Based on evidence presented, safety is assumed to be non-inferior to pazopanib.
Evidence base	Indirect comparison of randomised trials
Equi-effective doses based on Study 3007 and PALETTE	<ul style="list-style-type: none"> <li>• Trabectedin 2.93 mg* via a central venous catheter as a 24-hour infusion on Day 1 of each 21-day treatment cycle for 12 weeks.</li> <li>• Pazopanib 700.35** mg once daily orally for 19.36 weeks</li> </ul>
Direct medicine costs	The drug cost per course for trabectedin is lower than that for pazopanib (\$ [REDACTED] vs. \$17,000.10).
Other costs or cost offsets	Yes. Premedication cost, cost for management of adverse effect, and administration cost.

Source: Table 83 of the submission.

\*recommended dose of 1.5 mg/m<sup>2</sup>, with an average body surface area of 2.14 m<sup>2</sup>, and dose intensity of 0.91, as observed from Study 3007

\*\*Mean dose of pazopanib in PALETTE.

- 6.29 The submission used trial-based median treatment durations of 12 weeks for trabectedin and 19.36 weeks for pazopanib. This was not appropriate. Mean treatment duration should have been used in estimating the cost of treatment per course. At the final data cut-off, the mean treatment duration of trabectedin in Study 3007 was reported as 21.80 weeks. The mean treatment duration of pazopanib in PALETTE was 19.6 weeks. The PSCR argued the treatment durations applied in the cost-minimisation analysis were reflective of the durations of therapy included in the two trials. The ESC agreed with the evaluation that the mean rather than the median treatment duration should be used and noted this was longer in Study 3007 and PALETTE (21.8 and 19.6 weeks respectively).
- 6.30 The clinical claim underpinning the cost-minimisation analysis was that trabectedin was non-inferior to pazopanib in terms of effectiveness (e.g. PFS) and safety, and as

both treatments continue until disease progression or unacceptable toxicity, the ESC considered the duration of these two medicines should be approximately similar. The ESC noted a sensitivity analysis was performed during the evaluation by assuming an identical treatment duration of 21.80 weeks for both trabectedin and pazopanib. The ESC noted an alternative approach would be to use the reported mean treatment durations of 21.80 weeks for trabectedin and 19.6 weeks for pazopanib.

- 6.31 Trabectedin is administered via a central venous catheter as a 24-hour infusion. In Study 3007, of the 378 patients who were treated with trabectedin, 100 (27%) and 277 (73%) first received trabectedin in the inpatient and outpatient setting, respectively. The submission assumed 100% of patients would be treated as outpatients in clinical practice, based on consultations with pharmacists and nursing unit managers. The cost per patient per course of trabectedin included an administration cost of \$111.40 (MBS Item 13950) per infusion. The ESC disagreed with the PSCRs assertion that patients in this line of therapy usually have a central line already in place. The ESC noted that a cost for insertion of a central venous device had not been accounted for in the cost-minimisation analysis. The Pre-PBAC Response argued that it was reasonable to assume most patients would have a central venous device prior to commencing treatment with trabectedin on the basis that most patients in Study 3007 had received prior therapy with doxorubicin or another chemotherapy agent that required a central line.
- 6.32 The submission considered the cost of treating Grade 3-4 adverse events (AEs) that occurred in at least 10% of subjects in the Study 3007 and PALETTE. The rationale for selecting the 10% occurrence was not well justified, as data on the incidence of AEs using a lower threshold of 5% was available for Study 3007 and PALETTE. Using a lower threshold of 5% AE incidence captures a more comprehensive toxicity profile of trabectedin and pazopanib. The ESC considered a sensitivity analysis for the CMA using a 5% threshold for selection of AEs would be informative. The Pre-PBAC Response presented a sensitivity analysis based on a 5% AE incidence threshold (see paragraph 6.40).
- 6.33 The submission used the difference in the incidence of Grade 3-4 AEs between the two treatment arms in each trial (Study 3007 and PALETTE) in estimating the cost of AEs associated with trabectedin and pazopanib. This was not appropriate. Only considering the incremental incidence of AEs from trabectedin compared with dacarbazine observed in Study 3007 underestimated and distorted the AE profile associated with trabectedin. As dacarbazine is not PBS-listed for LMS, nor included in the eviQ guideline<sup>§</sup>, its AE profile has limited relevance to the requested listing. In addition, pazopanib was compared to placebo, which caused fewer AEs than dacarbazine; this means that using the incremental difference in AEs recorded in the

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<sup>§</sup> <https://www.eviq.org.au/medical-oncology/sarcoma/soft-tissue-sarcoma>

two treatment arms of each trial likely favoured trabectedin. The ESC considered a sensitivity analysis for the cost-minimisation analysis using the incidence of AEs reported for trabectedin, rather than the additional AEs reported for trabectedin over those reported for dacarbazine, would be more informative than the current analysis. The Pre-PBAC Response presented a sensitivity analysis for the cost-minimisation analysis using the incidence of adverse events reported for trabectedin (see paragraph 6.40).

- 6.34 Furthermore, the submission combined Grade 3 and Grade 4 AEs when estimating the costs of AE treatments, which is likely to have favoured trabectedin. Whilst the incidence of Grade 3 AEs were similar between trabectedin and pazopanib in Study 3007 and PALETTE (51.9% and 49% respectively), trabectedin treatment was associated with approximately three times as many Grade 4 AEs as pazopanib (29.4% vs 10% respectively). The submission assumed all AEs would be managed in the outpatient setting. Given the higher incidence of Grade 4 AEs in patients treated with trabectedin, compared with pazopanib treatment, the exclusion of hospitalisation costs associated with management of AEs favoured trabectedin. The ESC noted the cost of treating a Grade 3 versus a Grade 4 AE may be substantially different, and may include hospitalisation, not just outpatient, costs. The ESC therefore considered Grade 3 and grade 4 AEs should be costed separately in the cost-minimisation analysis.
- 6.35 The ESC also noted that in the Demetri 2009 study, 28% of patients in the 24-hour infusion group received G-CSF as secondary prophylaxis, and in Study 3007 3.17% (n=12/378) of patients had febrile neutropenia.
- 6.36 The submission also included the cost of methylprednisolone as a premedication in the administration of trabectedin.
- 6.37 The results of the cost-minimisation analysis, based on the published price of pazopanib, are presented below.

**Table 8: Results of the cost-minimisation analysis: trabectedin versus pazopanib**

	<b>Trabectedin</b>	<b>Pazopanib</b>	<b>Data source / explanation</b>
A. Unit cost	\$ [REDACTED] per 1 mg vial	\$71.68 per 400 mg tablet <sup>a</sup>	Ex-manufacturer price
B. Dose	2.93 mg <sup>b</sup>	700.35 mg	Trial based mean dose
C. Units required per dose	3 (1 mg vials)	1.75 (400 mg tablets)	As above
D. Cost per dose	\$ [REDACTED]	\$125.44	= A x C
E. Dose per week	0.33	7	Dose frequency: trabectedin Q3W vs. pazopanib QD
F. Treatment duration in weeks	12	19.36	Median treatment duration from the clinical trials
G. Total drug costs	\$ [REDACTED]	\$17,000.10	= D x E x F
H. Methylprednisolone	\$120.92	–	= \$30.23 (ex-manufacturer price) x E x F
I. Parenteral administration of antineoplastic agents	\$445.60	–	= \$111.40 (MBS item 13950) x E x F
J. Management of AEs	\$49.90	\$3.29	Trial-based incidence of AEs, relevant MBS items
<b>K. Total cost of Therapy</b>	<b>\$ [REDACTED]</b>	<b>\$17,003.39</b>	<b>=G + H + I + J</b>

Source: Table 86 of the submission; 'Cost-Min' spreadsheet, "Yondelis\_utilisation-and-cost-minimisation\_March2021" Excel workbook

AEs = adverse events; Q3W = every 3 weeks; QD = once daily

<sup>a</sup> Ex-manufacturer price for pazopanib is \$4,300.92 for 400 mg x 60 tablets pack. This equals to \$71.68 per 400 mg tablet

<sup>b</sup> The dose of trabectedin was calculated as dose regimen (1.5 mg/m<sup>2</sup>), multiplied by average body surface area (2.14 m<sup>2</sup>), multiplied by dose intensity in Study 3007 (0.91)

6.38 The cost-minimisation analysis overestimated the requested drug price for trabectedin because:

- It assumed a shorter treatment duration of trabectedin than that of pazopanib (12 weeks vs. 19.36 weeks). If the treatment duration for both treatments was standardised to 21.80 weeks (the mean treatment duration in the final analysis of Study 3007), then the requested ex-manufacturer price for trabectedin would decrease to \$ [REDACTED] per 1 mg vial, compared with \$ [REDACTED] proposed in the submission (see Table 9 below). The ESC noted if the reported mean treatment durations of 21.80 weeks for trabectedin and 19.6 weeks for pazopanib were used the price of trabectedin will reduce further.
- The incidence of adverse events associated with trabectedin was underestimated, as the incremental differences in incidence between trabectedin and dacarbazine (comparator) arms of Study 3007 were used to estimate the incidence of AEs from trabectedin, which was inappropriate. Further, the Grade 3 and 4 AEs were combined, which obscured the number of immediately life-threatening AEs experienced in the trabectedin arm of Study 3007 and the consequent resource use. The ESC considered this should be corrected for in the cost-minimisation analysis and the costs associated with managing AEs reviewed to ensure all appropriate costs are included (see paragraph 6.35).

- The cost of adverse events was limited to outpatient management. Hospitalisations due to treatment-related AEs are likely to occur more frequently in patients taking trabectedin than pazopanib. The ESC considered hospitalisations should be accounted for in the cost-minimisation analysis.

6.39 The results of sensitivity analyses assuming the same treatment duration for trabectedin and pazopanib are presented below.

**Table 9: Results of the cost-minimisation analysis – sensitivity analysis, assuming similar treatment duration for trabectedin and pazopanib**

	Trabectedin	Pazopanib	Data source / explanation
A. Unit cost	\$██████ per 1 mg vial	\$71.68 per 400 mg tablet <sup>a</sup>	Ex-manufacturer price
B. Dose	2.93 mg <sup>b</sup>	700.35 mg	Trial based mean dose
C. Units required per dose	3 (1 mg vials)	1.75 (400 mg tablets)	As above
D. Cost per dose	\$██████	\$125.44	= A x C
E. Dose per week	0.33	7	Dose frequency: trabectedin Q3W vs. pazopanib QD
F. Treatment duration in weeks	21.80	21.80	Same treatment duration of the two therapies
G. Total drug costs	\$██████	\$19,142.68	= D x E x F
H. Methylprednisolone	\$219.67	–	= \$30.23 (ex-manufacturer price) x E x F
I. Parenteral administration of antineoplastic agents	\$809.51	–	= \$111.40 (MBS item 13950) x E x F
J. Management of AEs	\$49.90	\$3.29	Trial-based incidence of AEs, relevant MBS items
<b>K. Total cost of Therapy</b>	<b>\$██████</b>	<b>\$19,145.96</b>	<b>=G + H + I + J</b>

Source: Sensitivity analysis performed during the evaluation

AEs = adverse events; Q3W = every 3 weeks; QD = once daily

<sup>a</sup> Ex-manufacturer price for pazopanib is \$4,300.92 for 400 mg x 60 tablets pack. This equals to \$71.68 per 400 mg tablet

<sup>b</sup> The dose of trabectedin was calculated as dose regimen (1.5 mg/m<sup>2</sup>), multiplied by average body surface area (2.14 m<sup>2</sup>), multiplied by dose intensity in Study 3007 (0.91).

Note: Due to rounding, calculation of total cost of therapy varies slightly when only two decimal places are used.

6.40 The pre-PBAC Response presented a sensitivity analysis for the cost-minimisation analysis based on the 5% AE incidence threshold (see paragraph 6.32) and using the incidence of adverse events reported for trabectedin rather than the incremental difference (see paragraph 6.33). The resulting vial cost for trabectedin increased from \$██████ per 1 mg vial in the base case to \$██████ per 1 mg vial in the pre-PBAC response sensitivity analysis.

6.41 The PBAC noted the cost-minimisation analysis presented in the pre-PBAC response was not independently evaluated. However, the PBAC noted the 5% AE incidence threshold data for trabectedin used in the revised CMA was based on an interim analysis rather than the final Clinical Study Report. In addition, the PBAC noted the cost-minimisation analysis provided in the pre-PBAC response appeared to incorrectly attribute blood transfusion as a treatment for neutropenia events and used the incorrect hospital code for febrile neutropenia. The PBAC also noted the treatment duration in the pre-PBAC response sensitivity analysis remained 12 weeks for

trabectedin and 19.36 weeks for pazopanib. As such, the PBAC considered the pre-PBAC response cost-minimisation analysis was not informative.

### **Drug cost/patient/course**

- 6.42 The cost of trabectedin was \$ [REDACTED] for a 12-week treatment course (as in the base case CMA presented in the submission), using an average dose of 2.93 mg per administration and the effective dispensed price for trabectedin (public hospital vs. private hospital: 34.02% vs. 65.98%). The cost of comparator pazopanib was \$17,637, based on a treatment duration of 19.36 weeks (as in the base case CMA), an average dose of 700.35 mg per day and the published dispensed price for pazopanib.
- 6.43 If the treatment duration of both trabectedin and pazopanib were assumed to be 21.80 weeks (as in the CMA sensitivity analysis performed during the evaluation), the cost of trabectedin would be \$ [REDACTED] based on the trabectedin dispensed price calculated from an AEMP of \$ [REDACTED] per 1mg vial (Table 9). The cost of pazopanib would be \$19,860.

### **Estimated PBS usage & financial implications**

- 6.44 DUSC did not consider this submission. The submission employed a market share approach to estimating the expected patient population for trabectedin in the treatment of LMS. Summarised below are the key inputs for the financial estimates.

**Table 10: Key inputs for financial estimates**

<b>Data</b>	<b>Value and source</b>	<b>Comment</b>
<b>Market share</b>		
Number of pazopanib scripts	1,335 in Year 1, to 1,759 in Year 6 PBS item statistics 2017-2020, assuming a linear projection	Appropriate
Proportion of pazopanib scripts for treatment of leiomyosarcoma	25.37%, Bessen et al 2016	This estimate was reasonable only if the uptake of pazopanib was the same amongst all soft tissue sarcoma types.
Uptake rate, initial treatment	40% in Year 1, to 70% in Years 4-6 Assumption	Considering the choice between a 24-hour central venous infusion every 21 days or a single oral tablet once per day, patients would likely prefer the convenience of the tablet. As such, the uptake rate is likely to be overestimated.
Proportion of patients receiving trabectedin who would subsequently be treated with pazopanib	56.1%, Study 3007	This was an error. In Study 3007, 47.0%, not 56.1%, of patients in the trabectedin arm received subsequent anti-cancer therapy upon disease progression.
Proportion of patients receiving pazopanib who would subsequently be treated with trabectedin	49.0%, PALETTE	Appropriate
Scripts equivalence for trabectedin vs. pazopanib	1 : 21/30 Treatment frequency (Q3W vs. QD) and pack size (1 dose vs. 30 days of treatment) of trabectedin and pazopanib	Appropriate

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Data	Value and source	Comment
Number of trabectedin vials per script	3 x 1mg vials + 1 x 0.25 mg vial Dose regimen of 1.5mg/m <sup>2</sup> and an average BSA of 2.14m <sup>2</sup>	The PBAC noted dose of 3.25 mg was based on a high BSA (2.14m <sup>2</sup> )
Dose intensity of trabectedin	0.91, Study 3007	Appropriate
Scripts equivalence for methylprednisolone vs. pazopanib	1 : 1 Submission's assumption. Effectively assuming one methylprednisolone injection every 30 days	The frequency of premedication should equal the frequency of trabectedin administration (Q3W) instead, meaning there should be more methylprednisolone scripts per 30 days compared to pazopanib.
<b>Grandfathering</b>		
Number of grandfathered patients	20 in Year 1, Assumption	The PBAC noted that including LMS patients in the listing may increase the number of eligible grandfathered patients.
Number of trabectedin treatment cycles subsidised via PBS in grandfathered patients	1 dose, Assumption	The assumption of one dose of PBS-subsidised trabectedin therapy (i.e. 3 weeks therapy) in grandfathered patients could be an underestimate, depending on which line of therapy they are up to, and how many doses they have received prior to grandfathering.
<b>Costs</b>		
Trabectedin	\$█ per infusion (3.25 mg) Requested effective price	Appropriate
Pazopanib	\$4,462 for 60 x 400mg pack 3,387 for 90 x 200mg pack PBS price	Appropriate
Methylprednisolone	\$44.52 per administration PBS price	Appropriate
Patient co-payment	\$21.02 for PBS; \$4.77 for RPBS Medicare data from January to December 2020 on pazopanib items	Reasonable
IV administration	\$111.40, MBS item 13950	Appropriate

Source: Table compiled during the evaluation, based on information provided in Sections 4.1-4.5, 172-177 of the submission.  
BSA = body surface area; IV = intravenous; Q3W = once every 3 weeks; QD = once every day;

- 6.45 The submission assumed that trabectedin would displace pazopanib for some patients and be used as an additional line of therapy after pazopanib for others. The market share approach was adapted to reflect this.
- 6.46 As the pazopanib scripts were for 30 days of treatment, but trabectedin treatment cycles are 21 days, the equivalent script amounts were adjusted. The approach in the financial analysis effectively assumed a similar treatment duration for trabectedin and pazopanib. The PBAC noted the financial estimates assumed a 12-week treatment duration for trabectedin.
- 6.47 The financial analysis considered grandfathered patients. The submission estimated that, in the first year of trabectedin listing, the Access Program would treat 40 patients with trabectedin; and half of these patients would meet the proposed restriction. It was, therefore, expected that approximately 20 patients would require grandfathered

access to trabectedin following listing. Each of these grandfathered patients was assumed to receive one dose of PBS subsidised trabectedin therapy (1 x 0.25 mg vial + 3 x 1 mg vials). This could be an under-estimate, depending on their line of therapy and the number of trabectedin doses they received under the Access Program before the availability of PBS-subsidised therapy. The PBAC considered that grandfathered patients would likely receive more than 1 dose of PBS subsidised therapy. In addition, the PBAC noted that including LPS patients in the listing may increase the number of eligible grandfathered patients.

6.48 Summarised below are the estimated use of trabectedin and its financial implications.

**Table 11: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
<b>Estimated financial implications of trabectedin</b>						
Cost to PBS/RPBS less copayments	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>
<b>Estimated financial implications for other medicines</b>						
Cost of pazopanib to PBS/RPBS less copayments	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>
Cost of methylprednisolone to PBS/RPBS less copayments	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>
Total net cost of other medicines to PBS/RPBS	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>	-\$■ <sup>2</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>
Net cost to MBS	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>
Net cost to PBS/RPBS/MBS	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>	\$■ <sup>2</sup>

Source: Tables 90-95 of the submission

<sup>a</sup> The dose regimen of trabectedin is 1.5mg/m<sup>2</sup> every three weeks. Assuming an average body surface area of 2.14 m<sup>2</sup>, the trabectedin dosage per infusion would be 3.21 mg. Therefore, it was assumed that each trabectedin script would include 3x 1mg vials and 1x 0.25mg vials.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> \$0 to < \$10 million

6.49 The net costs to the PBS/RPBS was a result of the availability of an additional line of therapy following the listing of pazopanib (pazopanib after trabectedin or vice versa, compared with pazopanib only in current clinical practice). This was based on the proposed published price for trabectedin and the published PBS listed price for pazopanib.

6.50 The only MBS cost considered in the financial analysis was the administration cost associated with trabectedin therapy. The financial implications for the health budget may have been underestimated in the submission, as the costs associated with management of AEs were not taken into account in the financial analysis. This would

be offset to an unknown extent by the likely over-estimated uptake of trabectedin, given its safety profile and the oral formulation of pazopanib. The PSCR argued that treatment-emergent AEs in Study 3007 were primarily due to additional investigations and blood/lymphatic system disorders in the trabectedin arm of the clinical trial and stated the financial impact of treating these was likely to be minimal.

- 6.51 The estimated financial impact is moderately sensitive to the proportion of pazopanib scripts assumed to be used for LMS. If this figure is increased from 25.37% to 35.37%, the net cost to the health budget is increased by approximately 36% in the first year and 39% in the sixth year. As discussed above, the justification for the 25.37% may be inaccurate, and depends on uniform prescribing practices amongst a wide range of STS types.
- 6.52 The PBAC estimated, based on PBS prescription data provided by the DUSC Secretariat for eribulin for advanced LPS from 2017 to 2021, that approximately < 500 patients per year would receive trabectedin for LPS. This was based on trabectedin being used in 80% of eribulin patient population. The PBAC considered the trabectedin dose and treatment duration for patients with LPS would be similar to that for patients with LMS.

### **Quality Use of Medicines**

- 6.53 The submission included a copy of the European Risk Management Plan (RMP) for trabectedin and the Australian Specific Annex in its attachments.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing of trabectedin for the treatment of leiomyosarcoma (LMS). Noting the evidence presented for trabectedin included a population with liposarcoma (LPS) and that the treatment effect was similar across both sarcomas, together with the high clinical need for additional treatment options for LPS that is a rare and aggressive cancer, the PBAC also recommended the Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing of trabectedin for LPS.
- 7.2 The PBAC's recommendation for listing in LMS was based on, among other matters, its assessment, that the cost-effectiveness of trabectedin would be acceptable if it were cost-minimised against pazopanib. The PBAC's recommendation for listing in LPS was based on, among other matters, its assessment, that the cost-effectiveness of trabectedin would be acceptable if it were priced the same as for the LMS population.
- 7.3 The PBAC welcomed input from healthcare professionals and organisations and acknowledged there was a high clinical need for effective treatments for LMS and LPS that are rare and difficult to treat cancers with limited treatment options for patients whose condition has progressed following first-line chemotherapy. The PBAC advised

there was a clinical place for trabectedin as an alternative and additional treatment option for second (or subsequent) line treatment of LMS and LPS and that patients should be able to use trabectedin and other later line agents sequentially within their listed indications, as deemed clinically appropriate.

- 7.4 The PBAC accepted the nominated comparator for LMS of pazopanib although considered placebo is also a relevant comparator where trabectedin is used sequentially with pazopanib and noted that this was estimated to occur in approximately 50% of patients.
- 7.5 The PBAC noted that no overall survival benefit (OS) versus dacarbazine was observed in the pivotal trabectedin study (Study 3007). However, a statistically significant progression free survival (PFS) benefit of approximately 2.7 months was seen in the trabectedin arm compared to dacarbazine (Hazard Ratio (HR) 0.550, 95% CI: 0.436, 0.696) for the intention to treat (ITT) population. The PBAC advised it was reasonable to consider a benefit in PFS without a demonstrated OS benefit in patients with LMS and LPS. The PBAC recalled that pazopanib had been considered superior to best supportive care with respect to extending PFS alone at its July 2013 meeting where the Committee considered that this reflected an advantage to patients with LMS (section 8, pazopanib Public Summary Document (PSD), July 2013 PBAC Meeting).
- 7.6 The PBAC noted that, consistent with the ITT population, no OS benefit was observed in the LMS subgroup. The observed PFS benefit of approximately 2.7 months for patients treated with trabectedin in this subgroup (HR 0.555, 95% CI 0.423, 0.727) was similar to that for the ITT population. The LMS subgroup of the key pazopanib trial (PALETTE) also reported a PFS benefit of approximately 2.7 months for patients treated with this drug compared to placebo (HR 0.37, 95% CI 0.23, 0.60). The PBAC noted that a formal indirect comparison with pazopanib for LMS was not undertaken due to the lack of a common comparator and differences in trial populations. However, the PBAC noted the naïve results were numerically similar and advised that, given further comparative evidence is unlikely to become available and the high clinical need for additional treatments, the Committee was satisfied that trabectedin was likely of similar comparative effectiveness to pazopanib for LMS.
- 7.7 The PBAC noted that, consistent with the ITT and LMS populations, no OS benefit was observed in the LPS subgroup. A PFS benefit of approximately 1.5 months was observed in patients treated with trabectedin in the LPS subgroup (HR 0.546, 95% CI 0.341, 0.873). The PBAC noted the consistency in the HRs reported for the ITT population and the LMS and LPS subgroups. The PBAC also noted the results of the TSAR study in which the PFS benefit in the LPS/LMS subgroup was 5.1 months compared to 1.4 months for best supportive care (BSC) (HR 0.29,  $p < 0.0001$ ). The PBAC considered the level of clinical benefit with trabectedin was likely to be similar across all L-type sarcoma based on the evidence presented.
- 7.8 The PBAC noted that only a side-by-side comparison of adverse events of trabectedin and pazopanib was presented. The PBAC also noted that trabectedin appeared to have

a higher incidence of Grade 4 adverse events, of which a major driver was laboratory abnormalities. Given these apparent differences, the PBAC considered that trabectedin is likely of inferior safety to pazopanib. However, the PBAC agreed with the ESC that many of the laboratory anomalies may be manageable with supportive care measures.

- 7.9 The PBAC considered that a cost-minimisation analysis of trabectedin compared with pazopanib was appropriate to establish the cost-effectiveness of listing trabectedin for LMS. The PBAC agreed with the ESC that a shorter treatment duration with trabectedin versus that with pazopanib was not supported. The PBAC considered the equi-effective doses should be based on the mean (rather than median) estimate of the treatment duration and that the same duration (21.8 weeks) should be assumed for both trabectedin and pazopanib. The PBAC noted ESC's comment that if the reported mean treatment durations of 21.80 weeks for trabectedin and 19.6 weeks for pazopanib were used, the cost minimised price of trabectedin would be lower. However, noting the financial risk associated with assuming the same treatment duration for both drugs is small, and the need for alternative treatment options, the PBAC considered in this instance it would be reasonable to assume a treatment duration of 21.8 weeks for both drugs. The PBAC advised the equi-effective doses are:
- Trabectedin 2.93 mg as a 24-hour infusion Day 1 of each 21-day treatment cycle for 21.80 weeks; and
  - Pazopanib 700.35 mg orally once daily for 21.80 weeks.
- 7.10 The PBAC noted, as for LMS, trabectedin would provide an additional line of therapy for patients with LPS. The PBAC further noted the efficacy of trabectedin in LPS was similar to that observed in LMS. The PBAC therefore considered trabectedin would be cost-effective in LPS at the same price as determined cost-effective for LMS (as outlined in paragraph 7.9).
- 7.11 The PBAC noted the financial estimates for LPS were based on the median treatment duration of 12 weeks and considered that it would have been more appropriate to use the mean duration (21.80 weeks). Countering this, the PBAC noted that the trabectedin dosing used in the analysis was based on a body surface area of 2.14m<sup>2</sup>, the maximum amount used for the proposed listing, rather than the likely average BSA.
- 7.12 The PBAC advised that a listing for LPS would increase the patient population eligible for treatment with trabectedin by approximately 50 patients per year (see paragraph 6.52). The PBAC also noted that listing for LPS may increase the number of patients eligible for grandfathering (see paragraph 6.47).
- 7.13 The PBAC considered that trabectedin would incur an incremental cost to the PBS, as trabectedin would provide an additional line of therapy for many patients with LMS and LPS. However, given that these are rare, aggressive cancers, the PBAC considered the overall number of patients and financial cost of trabectedin to the PBS would be

contained and relatively low. The PBAC noted the financial estimates presented in Table 11 would need to be recalculated to take into account the addition of patients with LPS and the outcome of the cost-minimisation considerations outlined in paragraph 7.9.

- 7.14 The PBAC considered the proposed PBS restriction should be extended to include patients with LPS. Consistent with the Study 3007 population, the PBAC considered patients must have the differentiated, myxoid, round-cell or pleomorphic LPS subtype. Consistent with the TGA indication, the PBS restriction should include the criteria: 'Patient must have received prior chemotherapy treatment including an anthracycline'. As per paragraph 3.6, the PBAC advised that an age restriction was not required in the trabectedin listing.
- 7.15 The PBAC recommended that trabectedin should not be treated as interchangeable with any drugs.
- 7.16 The PBAC advised that is not suitable for prescribing by nurse practitioners.
- 7.17 The PBAC recommended that the Early Supply Rule should not apply.
- 7.18 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because trabectedin is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over pazopanib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.19 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
TRABECTEDIN Powder for I.V. infusion, 0.25mg Powder for I.V. infusion, 1 mg	NEW (Public) NEW (Private)	3.25mg	3
<b>Available brands</b>			
Yondelis®			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]			
<b>Administrative Advice:</b> This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Severity:</b> Advanced (unresectable and/or metastatic)			
<b>Condition:</b> Leiomyosarcoma or liposarcoma			
<b>Indication:</b> Advanced (unresectable and/or metastatic) leiomyosarcoma or liposarcoma			
<b>Treatment Phase:</b> Initial treatment			
<b>Clinical criteria:</b> Patient must have an ECOG performance status of 2 or less			
<b>AND</b>			
<b>Clinical criteria:</b> Patient must have received prior chemotherapy treatment including an anthracycline			
<b>AND</b>			
<b>Clinical criteria:</b> The treatment must be the sole PBS-subsidised therapy for this condition.			
<b>AND</b>			
<b>Clinical Criteria:</b> The condition must be one of the following subtypes for patients with liposarcoma: (i) dedifferentiated; (ii) myxoid; (iii) round-cell; or (iv) pleomorphic			

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
TRABECTEDIN Powder for I.V. infusion, 0.25mg Powder for I.V. infusion, 1 mg	NEW (Public) NEW (Private)	3.25mg	7
<b>Available brands</b>			
Yondelis®			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]			
<b>Administrative Advice:</b>			

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This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Episodicity:</b>
<b>Severity:</b> Advanced (unresectable and/or metastatic)
<b>Condition:</b> Leiomyosarcoma or liposarcoma
<b>Indication:</b> Advanced (unresectable and/or metastatic) leiomyosarcoma or liposarcoma
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised therapy with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not develop progressive disease while being treated with this drug for this condition,
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must be the sole PBS-subsidised therapy for this condition.

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
TRABECTEDIN Powder for I.V. infusion, 0.25mg Powder for I.V. infusion, 1 mg	NEW (Public) NEW (Private)	3.25mg	7
<b>Available brands</b>			
Yondelis®			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Restriction type:</b>			
<input checked="" type="checkbox"/> Authority Required – Streamlined [new code]			
<b>Administrative Advice:</b>			
This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Episodicity:</b>			
<b>Severity:</b> Advanced (unresectable and/or metastatic)			
<b>Condition:</b> Leiomyosarcoma or liposarcoma			
<b>Indication:</b> Advanced (unresectable and/or metastatic) leiomyosarcoma or liposarcoma			
<b>Treatment Phase:</b> Grandfather treatment (transition from non-PBS-subsidised to PBS-subsidised treatment)			
<b>Clinical criteria:</b>			
Patient must have been receiving treatment with this drug for this condition prior to <PBS listing date>			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must have an ECOG performance status of 2 or less prior to initiating non-PBS subsidised treatment			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must have received chemotherapy treatment including an anthracycline prior to initiating non-PBS subsidised treatment			
<b>AND</b>			
<b>Clinical criteria:</b>			
Patient must not develop progressive disease while being treated with this drug for this condition,			
<b>AND</b>			
<b>Clinical criteria:</b>			
The treatment must be the sole PBS-subsidised therapy for this condition.			

	AND
	<b>Clinical Criteria:</b>
	The condition must be one of the following subtypes for patients with liposarcoma: (i) dedifferentiated; (ii) myxoid; (iii) round-cell; or (iv) pleomorphic.

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## **9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **10 Sponsor's Comment**

Despite the welcome positive PBAC recommendation, albeit at a lower price than was sought, Specialised Therapeutics cannot proceed with the listing due to the impact of international reference pricing, and unviable commercial feasibility. We wish to thank the medical oncologists and rare cancer patient groups for their support with this application.