

**7.11 VORINOSTAT**  
**Capsule 100 mg,**  
**Zolinza<sup>®</sup>,**  
**Merck Sharp & Dohme (Australia) Pty Ltd.**

**Application submitted by Rare Cancers Australia**

Rare Cancers Australia lodged a submission to the November 2016 PBAC meeting for histone deacetylase (HDAC) inhibitor therapies for the treatment of relapsed/refractory T-cell lymphoma. This submission requested PBS listing of two drugs: romidepsin (item 5.13 refers) and vorinostat. During the evaluation process, two commentaries were prepared to enable thorough consideration of the effectiveness, safety and cost-effectiveness of each drug. The current document provides the PBAC consideration of the evidence submitted for vorinostat.


**1 Purpose of Application**

1.1 Section 85, Authority Required listing for vorinostat for treatment of relapsed or chemotherapy refractory cutaneous T-cell lymphoma.

**2 Requested listing**

2.1 The resubmission requests a Section 85 Authority Required listing for vorinostat for the treatment of relapsed or chemotherapy refractory CTCL in patients who: have received and failed prior systemic therapy; are not currently candidates for a stem cell transplant; and will not receive concomitant treatment with other systemic therapies.

2.2 An abridged version of the proposed listing is presented below, which omits the Administrative Advice, including the notes that no increase to the maximum quantity or repeats will be authorised. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty. (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
VORINOSTAT <i>vorinostat 100 mg capsule, 120</i>	120	Initial therapy: <del>0-2</del> Continuing therapy: 1		Zolinza® Merck Sharp & Dohme (Australia) Pty Ltd

<b>Category / Program</b>	Section 85 – General Schedule
<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>Severity:</b>	<del>Relapsed or refractory</del>
<b>Condition:</b>	Cutaneous T-cell lymphoma
<b>PBS Indication:</b>	<del>Relapsed or chemotherapy refractory</del> cutaneous T-cell lymphoma

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<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Clinical criteria:</b>	<p><i>The treatment must be for curative intent, AND Patient must have undergone appropriate prior front-line curative intent chemotherapy, AND Patient must demonstrate relapsed or chemotherapy-refractory disease,</i></p> <p><del>Patient must have received and failed prior systemic therapies, AND Patient must not be a candidate for a stem cell transplant, Patient must be ineligible for a stem cell transplantation, AND The treatment must not be used in combination with other systemic therapies</del> <i>The treatment must be the sole PBS-subsidised therapy for this condition.</i></p>
<b>Prescriber Instructions</b>	<p>Applications for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed CTCL vorinostat PBS Authority Application - Supporting Information Form [to be determined] which includes the following: (i) <del>The date of initial diagnosis of CTCL</del> <i>a histological diagnosis of relapsed or chemotherapy-refractory peripheral T-cell lymphoma;</i> (ii) <del>Dates of commencement and completion of prior systemic therapy or therapies;</del> (iii) <del>Details of prior treatment including name(s) of drug(s) and date of most recent treatment cycle; and</del> (iv) <i>a declaration of the patients ineligibility for stem cell transplant.</i> (iii) <del>a declaration of whether the patient's disease is relapsed or refractory, and the date and means by which the patient's disease was assessed as being relapsed or refractory.</del></p>

<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic
<b>Clinical criteria:</b>	<p><del>Patient must have previously qualified for PBS-subsidised vorinostat and, in the opinion of the prescribing physician, is receiving clinical benefit from the treatment</del>  <del>And</del>  <del>The treatment must not be used in combination with other systemic therapies</del>  <i>Patient must have previously received PBS-subsidised treatment with this drug for this condition,</i>          AND  <i>Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition,</i>          AND  <i>The treatment must be a sole PBS-subsidised treatment with this drug for this condition.</i></p>

2.3 Given that the median time to response was 1.8 months in Study P001, one month of treatment for initiation would be insufficient to allow patients the opportunity to respond. It may be more appropriate to allow for two repeats for initial therapy, to allow for three months of treatment before evaluation of benefit as the basis to access continuing treatment on the PBS. The ESC agreed that the number of repeats for initial treatment should allow for three months of treatment.

- 2.4 The requested clinical criteria for continuing treatment with vorinostat specify that a patient must, in the opinion of the prescribing physician, be receiving clinical benefit from treatment. “Clinical benefit” has not been defined. In the previous submissions for vorinostat, continuing treatment for patients who had taken vorinostat for up to three months was dependent on improvement of disease, defined as a 25%/50% (different definitions used) reduction in the modified Severity-Weighted Assessment Tool (mSWAT).
- 2.5 The resubmission requested grandfathering of patients currently receiving vorinostat via an Expanded Access Program (EAP). Currently, less than 10,000 CTCL patients receive vorinostat through the EAP. Given the non-specific selection criteria and the absence of a stopping rule, patients on the EAP may not fulfil the proposed PBS restriction.
- 2.6 The Pre-PBAC response (p3) noted that the intent of treatment with vorinostat was not curative, but to prolong remission without adversely compromising a patient’s quality of life. It also noted that therapies other than chemotherapy may be used as front-line therapy for CTCL and that patients receiving vorinostat should be also allowed to access PBS-subsidised topical therapies.
- 2.7 The PBAC noted the proposed restriction and:
- agreed with the ESC that the number of repeats for initial treatment should provide access to vorinostat for three months to allow patients the opportunity to respond to treatment;
  - agreed with the Pre-PBAC response’s (p3) claim that the aim of vorinostat treatment in the proposed PBS population was not curative, but to safely induce prolonged remission without adversely affecting a patient’s quality of life. As such, the PBAC advised that the criterion “The treatment must be for curative intent” be removed from the initial treatment criteria;
  - considered that continuing treatment should be restricted to patients who demonstrate an objective response to initial treatment with vorinostat, given that the data presented in the resubmission indicated that benefit from vorinostat treatment was confined to responders.
  - agreed with the Pre-PBAC Response (p3) that therapies other than chemotherapy may be used as first-line treatment, and recommended that the Secretariat proposed criterion should be changed to “Patient must have undergone appropriate prior front-line ~~curative intent chemotherapy systemic therapies~~”.
  - considered that vorinostat may be used as a bridging therapy to transplantation (see “Clinical place of the proposed therapy”), and that the criterion “Patient must be ineligible for a stem cell transplantation” might not be appropriate.
- 2.8 Based on evidence presented in Section B of the resubmission, the requested basis for listing is cost-effectiveness compared with “no active treatment”.

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

### **3 Background**

- 3.1 **TGA status at the time of PBAC consideration:** vorinostat was TGA registered on 17 December 2009 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease subsequent to prior systemic therapies. The registration of vorinostat was approved by the TGA without referral to the Australian Drug Evaluation Committee. The FDA evaluation reports were available to the TGA and the same clinical data were submitted to support registration in both jurisdictions.
- 3.2 This was the second submission to the PBAC for the consideration of vorinostat for the treatment of relapsed or refractory T cell lymphoma. The previous submission was made by Merck Sharp & Dohme (Australia) Pty Ltd and was considered at the March 2011 PBAC meeting. Further to this, a submission was considered by the ESC at its October 2009 meeting, as part of the Early and Extended Evaluation Pilot Project. The key differences between the submissions were outlined in the commentary. The key clinical evidence remained the same as presented in the previous submission.
- 3.3 Vorinostat is an inhibitor of class I and II histone deacetylase enzymes (HDACs). HDACs regulate a variety of cell functions involved in cell survival, cell cycle progression, angiogenesis, and immunity.

### **4 Clinical place for the proposed therapy**

- 4.1 Cutaneous T-cell lymphoma (CTCL) is a rare subtype of non-Hodgkin's lymphoma that initially predominantly presents in the skin.
- 4.2 The resubmission proposed listing for vorinostat for CTCL patients who have previously received and failed prior systemic therapies and who are not a candidate for a stem cell transplant. In the November 2011 submission, the proposed listing for vorinostat was for CTCL patients who have failed four systemic therapies, at least one of which had to be a chemotherapy regimen. The ESC noted vorinostat may provide some patients with sufficient disease control to enable a stem cell transplant. The ESC also noted that vorinostat may reduce the size of the lesions and enable local treatments (eg radiotherapy) to be used. The PBAC agreed with ESC that vorinostat could be used as bridging therapy to transplantation, and that this may be an important use of this drug in Australian practice.

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

### **5 Comparator**

- 5.1 The resubmission nominated "no active therapy" as the main comparator. The previous submissions nominated palliative care as the comparator. In March 2011, the PBAC considered that a comparison with best available care, as represented by chemotherapy, was more appropriate. The ESC agreed, and noted there are no clear guidelines for best available or standard of care, but there are a range of alternative systemic therapies for patients with relapsed/refractory CTCL, including retinoids,

interferons, extracorporeal photophoresis, methotrexate, gemcitabine, liposomal doxorubicin, cyclophosphamide, chlorambucil, etoposide, temozolomide, and bortezomib. The ESC considered that other active therapies would be either replaced by vorinostat or displaced to become third or subsequent lines of treatment. If a patient was not fit for further active therapy, they would likely not be fit for vorinostat. The PBAC agreed with the ESC and noted that vorinostat may be used earlier in the treatment algorithm for some patients on the basis of its toxicity profile or as a bridging therapy to transplantation.

- 5.2 The ESC noted the comments in the Pre-Sub-Committee Response about alternative treatments and clinical need, and considered that the availability of active treatments does not mean that there cannot also be high clinical need in a disease area. In the case of relapsed or refractory T-cell lymphoma, the ESC considered there was a clinical need for new treatments as although currently available active treatments are likely to have some benefits they do not result in cure or long term remission.
- 5.3 While the resubmission argued for “no active therapy” as the comparator, survival in the comparator arm of the economic evaluation was based on Australian registry data from patients who did not respond to HDAC inhibitors. These patients had received a variety of other systemic treatments before and after the HDAC inhibitor. Therefore, the economic evaluation essentially compared patients who received an HDAC inhibitor following other active treatments with patients who received (but did not respond to) an HDAC inhibitor and other active treatments.
- 5.4 The Pre-PBAC response (p1) claimed that given the limitations of the available clinical evidence, an inactive comparator was the best way forward to provide PBAC with a rationale for considering a new treatment for this rare cancer. The PBAC noted ESC’s concerns regarding “no active therapy” being the nominated comparator but considered that if recommended for PBS listing, vorinostat would be used to displace, rather than replace currently available treatments, which vary widely in nature and applicability to individual cases. As such, the PBAC viewed that “no active therapy” could reasonably be considered a comparator. Regardless, the PBAC noted that no comparative analysis against either comparator was presented.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The applicant, Rare Cancers Australia, requested a hearing for this item. At the hearing, representatives from the organisation acknowledged the limitations of the available data and urged the PBAC to consider the resubmission in the light of CTCL being a rare form of cancer, and the unmet need for a PBS-subsidised HDAC inhibitor to treat this malignancy. The PBAC noted Rare Cancers Australia’s willingness to facilitate further discussion with the drug sponsor, and seek clarification around any uncertainties. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease, and shed further light on an unconventional resubmission.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (2) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments noted support for availability of this drug and a hope for improved quality of life under treatment. The PBAC noted the advice from Rare Cancers Australia, which included feedback from patients how vorinostat treatment was effective, well-tolerated, and resulted in considerable improvements in quality of life, prior to progression. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.3 Representatives of the PBAC also met with Rare Cancers Australia prior to the PBAC meeting. The meeting covered the PBAC consideration of romidepsin for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) (Romidepsin PSD, November 2016 refers) and vorinostat for the treatment of patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). The November 2016 meeting was the PBAC's first consideration of romidepsin and second consideration of vorinostat for these conditions. The following points provide a summary of the perspectives presented by Rare Cancers Australia to PBAC representatives:
- There are currently limited treatment options for patients with relapsed or refractory PTCL and CTCL, and available treatment options have high toxicity.
  - The physical manifestations of the condition have a profound effect on patients' quality of life. In particular the impact of ulcerated lesions associated with CTCL on patients, including lesion pain, frequent need for painful local treatment, and the cost of associated consumables (for instance bandages and dressings) were described.
  - Romidepsin and vorinostat are offered to some patients currently, but (unless the patient is able to access treatment through a clinical trial) this is at a very high cost to the patient. Patients consider that this is inequitable.
  - Patients consider romidepsin to be mostly well tolerated, noting that side effects had been transient, manageable, or able to be resolved with reduction of dose.

### **Clinical trials**

- 6.4 The resubmission was based on two key, single-arm phase II studies (n=74 and n=33) of vorinostat in CTCL and four supplementary, single-arm studies (two of romidepsin in CTCL and two of romidepsin in Peripheral T-cell Cutaneous Lymphoma (PTCL)). The key clinical studies for vorinostat were the same as in the previous submissions. The supplementary evidence presented in the resubmission differed from that presented in the previous submissions. The PBAC previously noted that the quality of the data was extremely limited and the studies presented were small, non-comparative and heterogeneous.
- 6.5 The efficacy and safety data were difficult to assess in the absence of a comparative analysis. The ESC noted that in the absence of comparative data, the effectiveness and safety of the comparator arm would usually be informed by other types of data, for instance: historical controls, registry data, or other single arm studies.
- 6.6 Details of the key trials presented in the resubmission are provided in the table

below.

**Table 1: Studies and associated reports presented in the resubmission**

Study	Description	Reports
<b>Vorinostat in CTCL</b>		
<i>Nonrandomised studies (key)</i>		
Study P001	Prospective, multicentre, single arm, phase IIB study	Phase IIB multicenter Clinical Study of Oral Suberoylanilide Hydroxamic Acid (SAHA) in Advanced Cutaneous T-Cell Lymphoma. 27 February 2006.  Duvic M, Olsen EA, Breneman D, Pacheco TR, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. <i>Clinical Lymphoma &amp; Myeloma</i> 2009; 9(6):412-416.  Olsen EA, Kim YH, Kuzel TM, Pacheco TR, et al. Phase IIB multicenter study of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. <i>J Clin Oncology</i> 2007; 25(21):3109-15.
Study P005	Prospective, single centre, single arm, phase II study	Phase II Clinical Study of Oral Suberoylanilide Hydroxamic Acid (SAHA) in patients with Cutaneous T-Cell Lymphoma and peripheral T cell lymphoma unresponsive to conventional treatment. 11 January 2006.  Duvic M, Talpur R, Ni X, Zhang C, et al. Phase 2 study of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). <i>Blood</i> 2007; 109(1):31-39.

Source: Table 16, pp 66-68 of the resubmission.

6.7 The key features of the key clinical studies are summarised in the table below.

**Table 2: Key features of the included evidence**

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Vorinostat in CTCL</b>						
Study P001	74	N-R, MC, OL 14.7 months	High	Relapsed/refractory	Response rate, TTR, TTP, DOR, pruritus relief	Yes (response rate)
Study P005	33	N-R, OL 40 months	High	Relapsed/refractory	Response rate, TTR, DOR, TTP, pruritus relief	No

Source: compiled during the evaluation

Abbreviations: DOR, duration of response; MC, multi-centre; N-R, non-randomised; OL, open label; TTP, time to disease progression; TTR, time to response.

6.8 Based on the per-protocol dosage regimen, the intervention in Study P001 and for one cohort (n=13) in Study P005 matched the proposed use of vorinostat on the PBS.

6.9 There was a high probability of selection bias (no allocation concealment), performance bias (no blinding of participants or personnel) and detection bias (no blinding of outcome assessment), the magnitude and direction of which cannot be determined. Due to the high risk of bias, effectiveness estimates are subject to considerable uncertainty.

6.10 Patients in Study P001 had at least two prior, systemic therapies including bexarotene which is not available in Australia, while patients in Study P005 were “refractory to or intolerant of conventional therapy”. This was different from the

expected PBS population, where patients would not receive bexarotene. In addition, patients in Study P005 did not necessarily receive multiple prior therapies and these were not necessarily systemic (as reported in CSR Study P005). Pre-treatment in the clinical studies may therefore be different from expected pre-treatment in clinical practice. The effect of that difference on treatment outcomes is unknown.

- 6.11 Required patient performance status for eligibility in both key clinical trials was ECOG  $\leq 2$ , the minimum life expectancy was 12 weeks, and patients in Study P001 required adequate bone marrow and organ function. It is unknown what proportion of patients in Australian clinical practice would fulfil the study entry criteria. The proposed PBS population was not limited by ECOG status, and may include patients with a worse performance status, life expectancy and/or bone marrow/organ function compared with those in the clinical studies, as these criteria are not specified in the proposed listing. It is unknown if the efficacy and/or safety of vorinostat would be different for patients with worse baseline characteristics than those in the clinical studies.

### Comparative effectiveness

- 6.12 No comparative effectiveness data were presented. Effectiveness measures for vorinostat, obtained from the key clinical studies, are provided in Table 3 below. These have changed compared to previous submissions due to longer duration of follow-up (previously, median duration of response and median time to progression were not reached).

Table 3: Effectiveness of vorinostat in the key clinical studies

Trial ID	Objective response rate n with event/N (%)	Time to response Median (range) in months	Duration of response Median (range) in months	Time to progression (TTP) / progression free survival (PFS) Median in months	Overall survival
Study P001	22/74 (30)	1.8 (0.9-5.7)	>5.5 (>1.1->14.7)	All: 4.9 CR+PR: >8.5	NR
Study P005	8/33 (24)	2.8 (0.8-5.1)	3.5 (2.2-4.5)	All: 2.8 CR+PR: 7.1 SD: 2.8 PD: 1.2	NR

Source: Table 27, pp 104-105 of the submission.

Abbreviations: CR, complete response; CRu, complete response unconfirmed; NR, not reported; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease; TTP, time to progression.

- 6.13 Given that the studies had only one treatment arm, information about the comparator and absolute or relative differences was not available.
- 6.14 For the economic evaluation, response was translated into survival outcomes using a surrogate relationship inferred from Australian registry data.

### Comparative harms

- 6.15 No comparative safety data were presented. All safety data originated from non-randomised, single arm, open-label studies. In Study P001, the most frequent

grade  $\geq 3$  adverse events were fatigue (5%), diarrhoea (5%), thrombocytopenia (5%) and pulmonary embolism (5%). The ESC considered that the range and severity of most adverse events were similar to those seen with alternative therapies, with the exception of pulmonary embolism. The ESC noted that this would have significant implications in patients that are likely to go onto treatments with agents that induce thrombocytopenia.

- 6.16 The ESC noted that harms were measured in the context of clinical trials which required patients to have a performance status of ECOG  $\leq 2$  at baseline. This was inconsistent with the proposed PBS patient population, which could include patients with a worse performance status, and therefore at greater risk of severe toxicity.

### Benefits/harms

- 6.17 A summary of the benefits and harms for vorinostat is presented in the table below. Comparative information on benefits or harms was not available given the lack of comparative studies presented in the resubmission.

**Table 4: Summary of benefits and harms for vorinostat and comparator**

Trial	Vorinostat	No active treatment	RR (95% CI)	Event rate/100 patients <sup>a</sup>		RD (95% CI)
				Vorinostat	No active treatment	
<b>Benefits (objective response)</b>						
Study P001	22/74	NE	NE	30	NE	NE
Study P005	8/33	NE	NE	24	NE	NE
<b>Harms</b>						
	Vorinostat	No active treatment	RR (95% CI)	Event rate/100 patients <sup>a</sup>		RD (95% CI)
				Vorinostat	No active treatment	
<b>Grade <math>\geq 3</math> fatigue</b>						
Study P001	4/74	NE	NE	5	NE	NE
Study P005	1/33	NE	NE	3	NE	NE
<b>Grade <math>\geq 3</math> diarrhoea</b>						
Study P001	4/74	NE	NE	5	NE	NE
Study P005	1/33	NE	NE	3	NE	NE
<b>Grade <math>\geq 3</math> thrombocytopenia</b>						
Study P001	4/74	NE	NE	5	NE	NE
Study P005	7/33	NE	NE	19	NE	NE
<b>Grade <math>\geq 3</math> pulmonary embolism</b>						
Study P001	4/74	NE	NE	5	NE	NE
Study P005	2/33	NE	NE	5	NE	NE

Source: Compiled during the evaluation

Abbreviations: CI, confidence interval; NE, not evaluable; NR, not reported; RD, risk difference; RR, risk ratio

<sup>a</sup> Maximum duration of follow-up: Study P001 = 14.7 months at cut-off; Study P005 = ~40 months at cut-off.

### Clinical claim

- 6.18 The resubmission described vorinostat as superior in terms of comparative effectiveness and marginally inferior in terms of comparative safety over no active therapy. The evaluation considered this claim was not adequately supported. The key studies presented in the resubmission were non-randomised, single arm, open-label studies. As such, the studies were subject to considerable bias and the effectiveness estimates were subject to considerable uncertainty. The ESC

considered that the clinical claim could not be reliably assessed in the absence of data for the comparator arm, but noted that in March 2011, the PBAC agreed that vorinostat was an active drug that had superior efficacy to palliative care. The March 2011 comparison was made on the basis of response, rather than survival.

- 6.19 From the evidence presented in the resubmission, the PBAC considered that vorinostat was effective in a minority of patients with advanced CTCL; however the magnitude of any benefit was uninterpretable due to the limited and non-comparative nature of the data.
- 6.20 The PBAC was concerned that the combination of thrombocytopenia and pulmonary embolism, two of the most frequent grade  $\geq 3$  adverse events reported with vorinostat, could have significant implications in patients who receive subsequent treatment with agents that induce thrombocytopenia, and patients may require life-long treatment with anticoagulation agents, as well as monitoring with more frequent clinical reviews and investigations. The PBAC also noted that the adverse events reported were from patients with ECOG performance status  $\leq 2$ . Patients in the proposed PBS population could have a worse performance status, and therefore be at greater risk of harm. The PBAC therefore considered that vorinostat was inferior in safety compared with ‘no active therapy’.

### **Economic analysis**

- 6.21 The resubmission provided a modelled cost-utility analysis, compared to trial-based cost per responder analysis in the previous submission. This approach was appropriate in the context of the condition, but is not substantiated by the clinical evidence presented in the resubmission.

**Table 5: Summary of model structure and rationale**

Time horizon	The maximum time horizon was based on the observed median survival of 88.2 months in responders in the Australian registry data. In that registry, survival was assessed using Kaplan-Meier analyses with a maximum of 10.8 years follow-up.
Outcomes	QALYs, costs
Methods used to generate results	Translation from response to survival, with the application of utility values from HL and sALCL on the basis of patients' responder status. A decision tree analysis was performed.
Clinical inputs	Probability of response was 0 for the comparator and 0.30 for vorinostat, as obtained from Study P001. Discounted PFS was 0.21 years for the comparator and 0.46 years for vorinostat, based on Australian registry data. Discounted OS was 3.38 years for the comparator and 4.17 years for vorinostat, based on Australian registry data.
Discount rate	5% for outcomes, costs were not discounted
Software package	Microsoft Excel (version not reported)

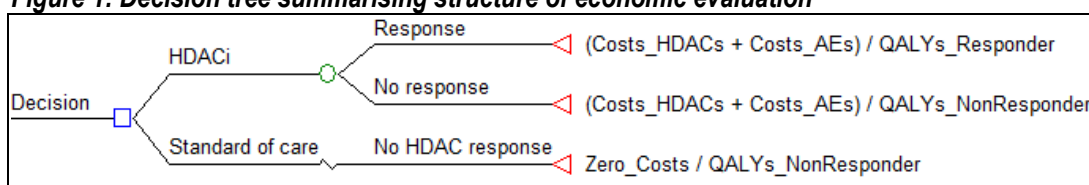
Source: constructed during the evaluation.

Abbreviations: HL, Hodgkin's lymphoma; OS, overall survival; PFS, progression free survival; QALYs, quality-adjusted life years; sALCL systemic anaplastic large cell lymphoma.

- 6.22 The use of the Australian registry data, and particularly the use of data from patients who did not respond to HDAC therapies (and who had received a variety of other therapies before and after the HDAC therapy), essentially compares patients who received an HDAC inhibitor following other active treatments with patients who received but did not respond to an HDAC therapy (and other active treatments). The

ESC considered that this was a fundamental problem with the structure of the model.

**Figure 1: Decision tree summarising structure of economic evaluation**



Source: Figure 28, p 150 of the submission.

Abbreviations: AEs, adverse events; HDACi, histone deacetylase inhibitor; HDACs, histone deacetylase inhibitors; QALYs, quality-adjusted life years.

6.23 The ESC noted that the approach to modelling survival effectively biases the estimated survival of the ‘no active treatment’ arm, by selecting patients who progressed or died within 6 months of receiving a HDAC inhibitor (thereby ensuring progression free survival in this arm of less than 6 months). By contrast, responders are selected on the basis of a time to next treatment of greater than 6 months. This meant that the model assumed:

- all responders have a minimum survival of 6 months.
- there were no responders in the ‘no active treatment’ arm. The ESC noted the argument in the PSCR (p4) that ‘spontaneous’ response reported in Prince et al (2010) was likely to reflect waxing and waning of skin lesions, rather than true response.

Both of these assumptions bias the survival rates in favour of vorinostat, and were not well justified in the resubmission and PSCR. The PBAC recognised the intent of the approach as explained in the resubmission, PSCR and pre-PBAC response to model outcomes in the absence of vorinostat, but like the ESC, considered that the model was flawed and was not informative to the assessment of cost effectiveness.

6.24 Response rates for vorinostat treated patients were obtained from Study P001. The resubmission did not compare baseline characteristics of the study population to the expected PBS population. Patients in the vorinostat studies were likely to have a better prognosis than the expected PBS population, given that the study entry criteria were based on adequate performance status, life expectancy and organ function, while the proposed PBS eligibility criteria are not. Furthermore, patients in Study P001 must have received bexarotene, which is not registered in Australia.

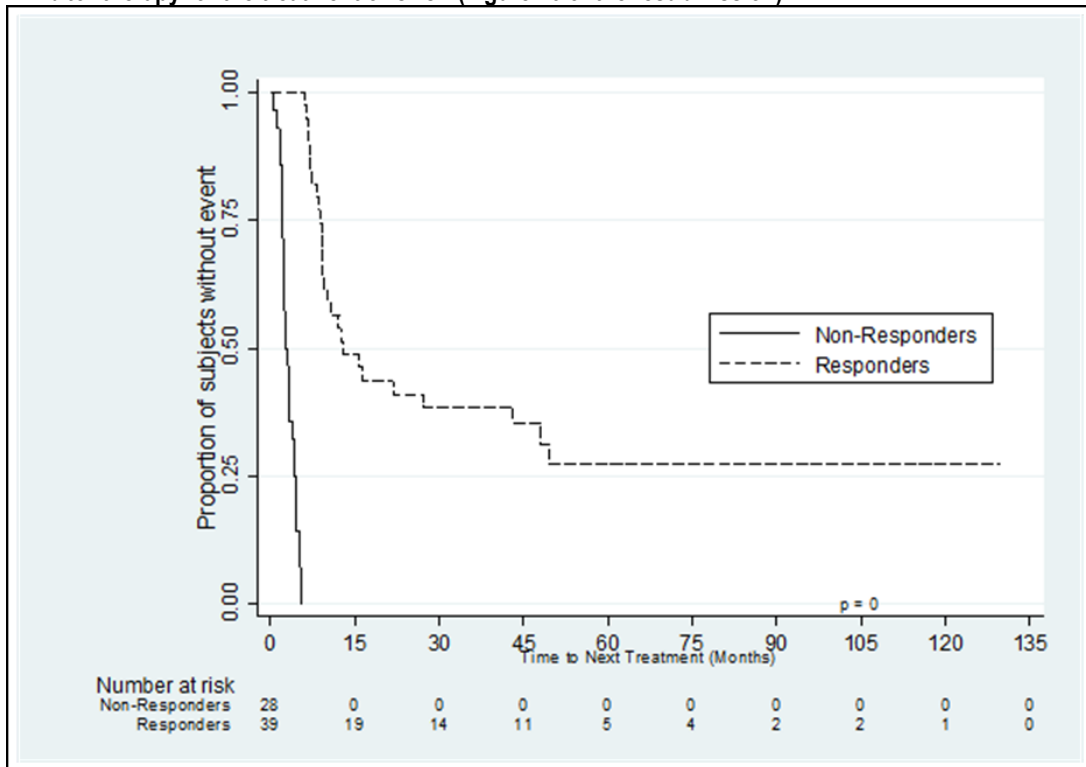
6.25 Australian registry data were used to determine survival outcomes on the basis of response. These analyses did not discriminate between the different types of HDAC inhibitors used by patients in that registry. The results are therefore not specific to vorinostat in CTCL (n=29), but also include patients treated with romidepsin (n=17) and panobinostat (n=21) in CTCL. No information is provided to assess whether survival observed following other HDAC inhibitor can be used as a proxy for vorinostat.

6.26 For the economic evaluation, a surrogate relationship was assumed to apply between response in CTCL and the median durations of PFS and OS from the registry. This link between the surrogate outcome (response) and the final outcome (survival) was not justified in the resubmission. The application of this link from response to survival may not be appropriate in CTCL since, unlike in other NHL subtypes, response criteria for Mycosis Fungoides / Sézary Syndrome(MF/SS) have

not been demonstrated to correlate with prognosis for survival.<sup>1</sup> The ESC noted from the PSCR (p3) that “Coiffier et al (2014) established a link between response to romidepsin and overall survival in patients with PTCL. The Australian registry data were then used to investigate whether this relationship between response to HDAC inhibitors and overall survival would hold in Australian patients with either CTCL or PTCL.”

- 6.27 Patients with a time to next treatment (TTNT)  $\geq$  6 months were considered to have received a meaningful treatment benefit and were classified as “responders”. The ESC noted that clinically, this would be considered a response in this disease. However, this definition of response ensures that all responders in the model have a minimum survival of six months, while non-responders could die within six months. This, along with the assumption of a 0% response rate in the comparator arm, biases survival in favour of the vorinostat arm, see Figure 2. The ESC considered that neither of these assumptions were well justified in the resubmission and PSCR. Furthermore, using TTNT as a proxy for PFS is problematic because it does not account for switching for other reasons (besides non-response), or patients who progress but do not switch treatments.

Figure 2: Kaplan Meier plot for time to next treatment for responders versus non-responders to HDAC inhibitor therapy for the treatment of CTCL (Figure 26 of the resubmission).



Source: Figure 26 of the resubmission, p142.

- 6.28 The economic evaluation applied the survival of non-responders to all patients in the comparator arm. This was not appropriate since not all patients receiving “no active treatment” would be expected to progress within six months. Patients may have stable disease or spontaneous remissions. In a trial in 44 patients with previously

<sup>1</sup> NCCN guidelines, Non-Hodgkin’s Lymphomas Version 3.2016. MFSS-5 (slide 109).

treated CD25-positive recurrent/persistent MF/SS, the overall response for placebo recipients was 15.9% (CR: 2.3%, PR: 13.6%).<sup>2</sup> The PSCR (p4) argued that the primary trial publication (Prince et al, 2010) noted the “spontaneous” response in the placebo arm likely reflected the waxing and waning of skin lesions, and analysis of the placebo responses indicated shorter PFS and other lesser benefits as measured by secondary outcomes.

- 6.29 The types and order of treatments may have influenced the benefit accruing to patients in the registry. There were insufficient data to evaluate the effect on response and survival of differences in the timing of HDAC inhibitors, the number of prior therapies, or indeed the HDAC inhibitors with which patients were treated.
- 6.30 The Pre-PBAC response (p2-3) acknowledged the confounding and bias involved in using the registry data in the economic model, but argued that this was a reasonable approach for assessing the potential value of response, as responders and non-responders were well-matched at baseline in terms of key clinical and demographic characteristics.
- 6.31 Utility values in the economic evaluation were obtained from Swinburn et al. 2015, a study in relapsed/refractory Hodgkin’s lymphoma (HL) and systemic anaplastic large-cell lymphoma (sALCL), which is a subtype of PTCL. The selected utility values may not represent the patient experience for CTCL. The ESC considered that these utilities might be appropriate for PTCL patients, but would not capture all relevant symptoms of CTCL, particularly skin symptoms (which would be expected to have a significant impact on quality of life). In addition, the utility value of Progressed Disease (PD) was assumed to be 0.67 (utility of Stable Disease in Swinburn et al. 2015) instead of 0.32 (utility of PD in Swinburn et al. 2015). This utility was selected on the basis that patients with PD can receive another treatment and would therefore not have a utility value of 0.32 as this represents patients effectively under BSC where the objective is management of pain and relief of symptoms at the end of life. The ESC considered that this further highlighted the issue with nominating “no active treatment” as the comparator.
- 6.32 The calculation of drug cost did not take into account wastage. Assuming an average of 5 packs per patient was used (instead of 4.27 packs), the drug cost per patient increased from \$██████ to \$██████. This increased the ICER from \$15,000 - \$45,000 to \$45,000 - \$75,000 per QALY gained.
- 6.33 The economic evaluation included the costs of vorinostat and treating adverse events. Disease management costs were not considered. The resubmission excluded these costs for simplicity and because they were assumed to be relevant regardless of being on active treatment or not. This was not appropriate. Costs of supportive therapies (e.g. anti-emetics), disease monitoring and follow-up are likely to be higher in the vorinostat arm so excluding them favours vorinostat. Treatment with vorinostat requires clinical monitoring in order to diagnose and treat potential adverse events, make timely dose adjustments and evaluate treatment response. Furthermore, after treatment, patients who received vorinostat were assumed to live

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<sup>2</sup> Prince HM, Duvic M, Martin A, Sterry W et al. 2012 Incidence of spontaneous remission in patients with CD25-positive mycosis fungoides/Sézary syndrome receiving placebo, *Journal of the American Academy of Dermatology*.

substantially longer than patients in the comparator arm. During these additional life years, patients are likely to accrue additional health care costs. The failure to include any costs of concomitant therapies or disease monitoring (for vorinostat) or the costs of active therapies/best supportive care (for the comparator) introduced considerable uncertainty to the model. Excluding these costs resulted in biases in both directions, so the overall effect is unclear. The PBAC considered that this was a fundamental source of uncertainty in the economic analysis.

- 6.34 A summary of the key drivers of the model is provided in Table 6.

**Table 6: Key drivers of the model**

Description	Method/Value	Impact
Response in the comparator arm	Assumed 0%	High, favours vorinostat
Utility for progressive disease	Obtained from Swinburn et al. 2015; 0.32	High, favours vorinostat
Treatment duration	Obtained from Study P001; 4.3 months	High, favours vorinostat
Response to vorinostat	Obtained from Study P001; 29.9%	High, high response rate favours vorinostat

Source: compiled during the evaluation

- 6.35 In the proposed PBS listing patients may continue treatment as long as they are receiving clinical benefit from it in the opinion of the prescribing clinician. This is similar to treatment in the EAP and may result in longer treatment duration than in Study P001, which had defined, albeit subjective, stopping criteria (including disease progression).
- 6.36 The results of the economic evaluation are provided in Table 7. The redacted table below shows an ICER in the range of \$15,000 - \$45,000 per QALY.

**Table 7: Results of the economic evaluation**

Component	Vorinostat	No active treatment	Increment
Costs	\$ [REDACTED]	\$0 <sup>a</sup>	\$ [REDACTED]
LYs	4.1743	3.3846	0.7897
QALYs	2.8696	2.3013	0.5683
<b>Incremental cost per LY gained</b>			<b>\$ [REDACTED]</b>
<b>Incremental cost per QALY gained</b>			<b>\$ [REDACTED]</b>

Source: Table 3, p 4 of attachment 2 of the resubmission ("Pricing, cost-effectiveness and budget impact of vorinostat for CTCL").

Abbreviations: LY, life years; QALYs, quality-adjusted life years.

<sup>a</sup>Table 3 in the attachment to the resubmission shows these costs to be \$ [REDACTED], equal to the costs in the vorinostat arm. This is an error since costs in the comparator arm were assumed to be \$0.

- 6.37 The results of sensitivity analyses performed by the resubmission and during evaluation showed that the model was sensitive to response in the comparator arm, treatment duration and utility value applied to the PD health state. Additional sensitivity analyses were provided in section D.6 of the Commentary. The redacted table below shows results of the sensitivity analysis in the range of \$45,000 - \$75,000 to \$75,000 - \$105,000.

**Table 8: Results of univariate sensitivity analyses**

Univariate analyses	ICER
Base case	\$ [REDACTED]
Response in comparator arm 15.9% (instead of 0%) <sup>b</sup>	\$ [REDACTED]
Treatment duration 6.2 months instead of 4.3 months, including wastage <sup>a, b</sup>	\$ [REDACTED]
Utility for progressive disease 0.32 instead of 0.67	\$ [REDACTED]

Source: Table 4, pp 5 of attachment 2 of the resubmission (“Pricing, cost-effectiveness and budget impact of vorinostat for CTCL”) and compiled during the evaluation

<sup>a</sup> Based on treatment duration in the Australian registry (excluding all patients with a missing stop date), as discussed in section C(i)1.2 of the Commentary.

<sup>b</sup> Calculated during the evaluation.

- 6.38 The Pre-PBAC Response (p2-3) acknowledged the limitations of the economic model, and stated that Rare Cancers Australia was willing to work with the PBAC to resolve issues with the economic analysis. The Pre-PBAC response further stated that if the PBAC, like ESC, considered that a cost per responder analysis was a better approach, the model presented in the current submission was sufficiently robust to assist in quantifying vorinostat’s cost-effectiveness in terms of cost per responder. The PBAC considered the cost per responder analysis as presented in the March 2011 submission was more informative than the model presented in the current submission given the flaws as noted in paragraphs 6.17-6.29. Moreover, the PBAC considered that a cost per responder analysis was informative in the context of CTCL, as “response” in this condition may include a variety of benefits such as substantial improvements in quality of life, enabling local treatment for lesions (e.g. radiotherapy), the potential of being eligible for a stem cell transplant and cost offsets for reduced use of alternative treatments. Such benefits were acknowledged as difficult to model, particularly within a small population with a rare malignancy. Critically, the PBAC further noted that the cost per responder was substantially reduced when calculated using the new drug price offered in the resubmission. Whilst the PBAC recalled its previous concerns with the 2011 economic model (see vorinostat Public Summary Document, March 2011), it considered that those uncertainties were more acceptable given the sizeable reduction in price offered in the resubmission.

**Drug cost/patient/course: \$ [REDACTED] (\$ [REDACTED] including wastage).**

- 6.39 The drug cost per patient is \$ [REDACTED] per pack. On average, patients received 4.27 packs in Study P001.

**Estimated PBS usage & financial implications**

- 6.40 The resubmission adopted an epidemiological approach based on a published CTCL incidence rate (Rodd et al. 2012), an assumed 0.294 proportion of CTCL patients who progress to stage IIB or higher (based on stage distribution at diagnosis, Agar et al. 2010), and the assumption that [REDACTED]% of patients with relapsed/refractory CTCL will use vorinostat on the PBS. The resulting financial estimates are provided in Table 9.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated	█	█	█	█	█
Market share	█%	█%	█%	█%	█%
Packs	█	█	█	█	█
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█
Net cost to MBS	\$0	\$0	\$0	\$0	\$0
<b>Estimated total net cost</b>					
Net cost to PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS/MBS including wastage determined during the evaluation	\$█	\$█	\$█	\$█	\$█

Source: Table 58, Table 59 and Table 61, pp 159-160 of the submission.

- 6.41 There is potential for the net cost/year for the PBS to be lower than the estimate in the resubmission given that:
- Uptake in eligible patients is likely to be lower than █%. Assuming lower and staggered uptake (from █% in year 1 to █% in year 5) decreases the 5-year cost from less than \$10 million to less than \$10 million.
  - The resubmission did not consider the treatments given to patients that would be substituted if vorinostat was listed on the PBS.
- 6.42 There is also potential for the net cost/year for the PBS to be higher than the estimate in the resubmission given that:
- CTCL incidence may be higher. Using incidence data from 9 registries of the Surveillance, Epidemiology, and End Results (**SEER**) Program of the National Cancer Institute increases the 5-year cost from less than \$10 million to less than \$10 million.
  - The proportion of CTCL patients who progress to stage IIB+ may be higher. This may increase the 5-year cost from less than \$10 million to less than \$10 million.
  - Wastage has not been taken into account in the base case (see Table 9).
  - The mean treatment duration may be longer than 4.3 months. With a treatment duration of 6.2 months (based on Australian registry data) the 5-year cost increased to less than \$10 million.
  - Costs of prophylactic and supportive treatments have not been included in the financial forecasts.
- 6.43 Overall, the net cost/year to the PBS is likely to be higher than what was estimated.
- 6.44 Based on the information provided in the evaluation the drug costs are unlikely to exceed \$10 million/year. At year 5, the estimated number of patients was less than 10,000, and the net cost to the PBS would be less than \$10 million per year.
- 6.45 The PBAC considered that the patient numbers and financial impact should be updated to include those patients currently receiving vorinostat under the EAP, who would have met the PBS initiation criteria at the time of commencement with therapy (that is, the patients suitable for ‘grandfathering’).

### **Financial Management – Risk Sharing Arrangements**

- 6.46 In a letter of support attached to the resubmission, the manufacturer of vorinostat (MSD) stated: “[...] we confirm the proposed pricing of Zolinza (vorinostat) in the submission (\$████ DPMQ) and if successful, we are prepared to undertake any required negotiations with the Department of Health and confirm our ability to supply the drug”.
- 6.47 The PBAC considered that on the basis of uncertain financial estimates while introducing an additional line of therapy to the PBS, a Risk Sharing Arrangement would need to be agreed between the sponsor and the Department. The PBAC considered that it would potentially be appropriate to have a 100% rebate over a cap based on the sponsor-confirmed price, and based on patient numbers including the patients from the EAP who would have met the PBS initiation criteria.

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

## **7 PBAC Outcome**

- 7.1 The PBAC deferred its decision on whether to recommend the Section 85 Authority Required listing of vorinostat for the treatment of cutaneous T-cell lymphoma. The PBAC considered that the uncertainty of the cost-effectiveness analysis presented in the previous submission was diminished in the context of a substantial price reduction offered in the resubmission. The PBAC then considered that given the high and unmet clinical need in a small group of patients, the reasonable evidence of some clinical benefit, and the modest overall financial impact, it would be appropriate to seek further clarification from the sponsor regarding the financial impact of listing on the PBS, specifically, the patient numbers and an agreement to a Risk Sharing Arrangement.
- 7.2 The PBAC viewed that there was a high and unmet clinical need for an additional or alternative effective therapy for the small group of patients (<100/year) with advanced CTCL after the failure of prior systemic therapies and noted that if recommended for listing, vorinostat would be the first HDAC inhibitor available on the PBS. The PBAC also agreed with the ESC that vorinostat could be used as bridging therapy to transplantation, and that this may be an important use of this drug in Australian practice. The PBAC considered that the consumer comments received in relation to the resubmission, both from people living with the condition and on behalf of patients, were informative in providing a clinical perspective on this rare malignancy.
- 7.3 The PBAC noted the ESC’s concerns regarding “no active therapy” being the nominated comparator but considered that if recommended for PBS listing, vorinostat would be used to displace, rather than replace currently available treatments, which vary widely in nature and applicability to individual cases. As such, the PBAC viewed that “no active therapy” could reasonably be considered a comparator. Regardless, the PBAC noted that no comparative analysis against either comparator was presented.

- 7.4 The PBAC considered that the assessment of efficacy against “no active therapy” as a comparator would ideally be evidenced by randomised data versus placebo. However, the PBAC acknowledged the difficulty of such a trial in this rare form of cancer where the standard of care was highly varied. The PBAC then agreed with the ESC’s advice that in the absence of comparative data, the effectiveness and safety of the comparator arm would usually be informed by other types of data, for instance: historical controls, registry data, or other single arm studies.
- 7.5 The PBAC noted that the key clinical evidence presented in the resubmission constituted two single-arm phase II studies (n=74 and n=33) of vorinostat in CTCL, that these were the same key trials presented in the previous submission. The PBAC recalled its previous view that due to the small, non-comparative and heterogeneous nature of the evidence, effectiveness estimates would be subject to considerable uncertainty.
- 7.6 The PBAC noted that in its previous consideration of vorinostat for CTCL, it had agreed that vorinostat was an active drug that had superior efficacy to palliative care, compared on the basis of response, rather than survival (vorinostat Public Summary Document, March 2011). From the evidence presented in the resubmission, the PBAC considered that the vorinostat induced a durable response and this is likely to be associated with a marked improvement in quality of life in a minority of patients with advanced CTCL; however the magnitude of any benefit was uninterpretable due to the limited and biased nature of the data.
- 7.7 In terms of drug harms, the PBAC was concerned that the combination of thrombocytopenia and pulmonary embolism, two of the most frequent grade  $\geq 3$  adverse events reported with vorinostat, could have significant implications in patients that are likely to subsequently receive treatment with agents that induce thrombocytopenia. The PBAC also noted that the adverse events reported were from patients with ECOG performance status  $\leq 2$ . Patients in the proposed PBS population could have a worse performance status, and therefore be at greater risk of toxicity. The PBAC therefore considered that vorinostat was inferior in safety than “no active therapy”.
- 7.8 The PBAC noted that the resubmission provided a modelled cost-utility analysis, compared with trial-based cost per responder analysis in the previous submission (vorinostat Public Summary Document, March 2011). In terms of the economic model, the PBAC further noted that:
- Australian registry data, from patients who progressed or died within 6 months of receiving a HDAC inhibitor (thereby ensuring progression free survival in this arm of less than 6 months), was used to model the comparator arm. By contrast, responders were selected on the basis of a time to next treatment (TTNT) of greater than 6 months. The PBAC considered that these assumptions biased the survival rates in favour of vorinostat, and were not well justified. The PBAC recognised that the intent of the approach, as explained in the resubmission, PSCR and pre-PBAC response, was to model outcome in the absence of vorinostat, but like the ESC, considered that the model was severely flawed.
  - Costs of concomitant therapies or disease monitoring (for vorinostat) or the costs of active therapies/best supportive care (for the comparator) were not included in the model; excluding these costs resulted in biases in both directions, so the

overall effect was unclear. The PBAC considered that this was a fundamental source of uncertainty in the economic analysis.

- The Australian registry data did not differentiate between the types of HDAC inhibitors contributing to survival. The results were therefore not specific to vorinostat in CTCL (n=29), but also included patients treated with romidepsin (n=17) and panobinostat (n=21) in CTCL. The PBAC considered that there was a high degree of uncertainty on whether survival observed following other HDAC inhibitors can be used as a proxy for vorinostat.

7.9 The PBAC agreed with ESC's assessment of the limited quality of data and the flawed assumptions in the economic model, but, like ESC, acknowledged that "response" in CTCL may include a variety of benefits such as substantial improvements in quality of life, enabling local treatment for lesions (e.g. radiotherapy), potential of being eligible for a stem cell transplant and cost offsets for reduced use of alternative treatments, and that these benefits were difficult to model, particularly in the context of a small population with a rare malignancy. The PBAC recalled that a cost per responder analysis was undertaken in the previous submission for vorinostat (vorinostat Public Summary Document, March 2011), and agreed with ESC that a similar analysis would be a more robust approach to assess the cost-effectiveness of vorinostat in the proposed PBS population. The PBAC noted that the cost per responder was substantially reduced (compared to the previous submission) when calculated using the new drug price offered in the resubmission. Whilst the PBAC recalled its previous concerns with the 2011 economic model (see vorinostat Public Summary Document, March 2011), it considered that those uncertainties were more acceptable given the sizeable reduction in price offered in the resubmission.

7.10 The PBAC noted the proposed restriction and:

- agreed with the ESC that the number of repeats for initial treatment should provide access to vorinostat for three months to allow patients the opportunity to respond to treatment;
- agreed with the Pre-PBAC response's (p3) claim that the aim of vorinostat treatment in the proposed PBS population was not curative, but to safely induce prolonged remission without adversely affecting a patient's quality of life. As such, the PBAC advised that the criterion "The treatment must be for curative intent" be removed from the initial treatment criteria;
- considered that continuing treatment should be restricted to patients who demonstrate an objective response to initial treatment with vorinostat, given that the data presented in the resubmission indicated that benefit from vorinostat treatment was confined to responders.
- agreed with the Pre-PBAC Response (p3) that therapies other than chemotherapy may be used as first-line treatment, and recommended that the Secretariat proposed criterion should be changed to "Patient must have undergone appropriate prior front-line curative intent ~~chemotherapy~~ *systemic therapies*".
- considered that as vorinostat may be used as a bridging therapy to transplantation, the criterion "Patient must be ineligible for a stem cell transplantation" might not be appropriate.

- 7.11 The PBAC noted the resubmission's request for a grandfathering arrangement for less than 10,000 patients receiving vorinostat through the sponsor's Expanded Access Program (EAP). The PBAC noted that the EAP had a non-specific selection criteria and the absence of a stopping rule, and considered that in order to be eligible for treatment under a grandfathering arrangement, patients on the EAP would need to have met the initial criteria at the time of commencing vorinostat.
- 7.12 The PBAC advised that the patient numbers in the financial estimates should be updated to account for the patients from the sponsor's EAP who would qualify for PBS-subsidised treatment under proposed grandfathering arrangement.
- 7.13 The PBAC also considered that on the basis of uncertain financial estimates while introducing an additional line of therapy to the PBS, a Risk Sharing Arrangement would need to be agreed between the sponsor and the Department. The PBAC considered that it would potentially be appropriate to have a 100% rebate over a cap based on the sponsor-confirmed price, and based on updated patient numbers as per the EAP who would have met the PBS initiation criteria.
- 7.14 The PBAC noted the drug sponsor's willingness to undertake further negotiations, and the willingness of Rare Cancer Australia to facilitate further development of the submission. The PBAC considered the following should be confirmed with the drug sponsor (MSD):
- patient numbers (paragraph 7.12);
  - changes to restriction criteria proposed by the PBAC (paragraph 7.10);
  - a Risk Share Arrangement.

**Outcome:**

Deferred

**8 Context for Decision**

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

**9 Sponsor's Comment**

The sponsor had no comment.