PUBLIC SUMMARY DOCUMENT
Product: Vorinostat, capsule, 100 mg, Zolinza®
Sponsor: Merck Sharp & Dohme Australia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an Authority Required listing for the treatment of advanced (stage IIB-IV) cutaneous T-cell lymphoma (CTCL) where treatment has failed with four systemic therapies.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Vorinostat was TGA registered on 15 December 2009 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease subsequent to prior systemic therapies.

4. Listing Requested and PBAC's View

Authority Required
Initial PBS-subsidised treatment, as monotherapy, in advanced stage (stage IIB - IV) Cutaneous T-cell Lymphoma, where treatment failure has occurred with four systemic therapies, unless contraindicated. At least one of these therapies should be a chemotherapy regimen.

Treatment failure is defined as:
(a) disease progression following treatment, or
(b) intolerance or toxicity to a particular treatment.

Patients will be eligible for a maximum of 3 scripts as initial therapy to enable their response to treatment to be assessed. If no response is achieved after 3 months, the patient is no longer eligible for PBS-subsidised treatment with vorinostat.

Authority Required
Continuing PBS-subsidised treatment, as monotherapy, in patients with advanced stage (stage IIB - IV) Cutaneous T-cell Lymphoma who have taken vorinostat for up to 3 months and whose disease has improved. Improvement is defined as a 50% reduction in the mSWAT score.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Cutaneous T-cell lymphoma (CTCL) is collective term for a group of non-Hodgkin lymphomas (NHL) that initially present in the skin and may ultimately involve lymph nodes, blood and internal organs. CTCL is a rare disease and accounts for about 3.9% of all NHLs.

The disease initially presents as red or pink scaly patches, which evolve into skin tumours as the disease progresses. The tumours may ulcerate and result in secondary infection. The disease may also present as erythroderma, a mass of red lesions covering greater than 80% of

the body area which may or may not include clinically significant blood involvement. In addition to disfiguring, painful skin lesions, CTCL patients are often troubled with intense pruritus (itching).

Early stage disease is usually managed with topical steroids, topical nitrogen mustard, topical retinoids, phototherapy, localised radiotherapy or total skin electron beam (TSEB). Advanced stage disease is usually managed with systemic treatments such as interferon alfa (with or without phototherapy or acitretin), extracorporeal photopheresis, and single agent or combination chemotherapy.

The submission proposed that vorinostat would provide a further treatment option for patients with advanced stage CTCL when other alternative treatments have failed, prior to palliative care.

6. Comparator

The submission nominated palliative care, comprising of radiation; topical steroids; occlusive dressings, wet wraps, wound dressings and bandages; and related hospital admissions.

Although the submission presented multiple case series of various chemotherapy treatments used to manage advanced stage cutaneous T-cell lymphoma (CTCL), no formal comparison between vorinostat and these chemotherapies was conducted.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented one 'key' case series study (P001) of vorinostat and 13 supplementary open-label studies (one vorinostat dose finding study (P005), 8 case series chemotherapy studies, three non-randomised studies comparing different chemotherapies and one case series study of bortezomib (Zinzani (2007). The patient populations, study treatments, endpoints and follow-up varied considerably among these studies.

The trials and associated reports published at the time of the submission are in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Single arm studies or single arms of studies presented in the submission		
"Key" Single arm study: Vorinostat		
P001 Olsen et al.	Phase II multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma.	J Clin. Oncology 2007; 25(21): 3109-15
Duvic M et al	The systemic effects of vorinostat in patients with cutaneous T-cell lymphoma (CTCL): Post-hoc analyses in patients with high blood tumor burden.	Blood 2009; ASH Annual Meeting Abstracts(114):1709.
Duvic M et al	Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma.	Clinical Lymphoma & Myeloma 2009; 9(6):412-416.
Supplementary single arm studies		
Vorinostat		

P005 Duvic et al	Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid, (SAHA)) for refractory cutaneous T-cell lymphoma.	Blood 2007; 109: 31-39
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and it variations: COP/ CVP (cyclophosphamide, vincristine, prednisone) or HOP (doxorubicin, vincristine, prednisone)		
Fierro et al	Systemic polychemotherapy in the treatment of primary cutaneous lymphomas: a clinical follow-up study of 81 patients treated with COP or CHOP.	Leukaemia and Lymphoma 1998;34:583-588
Molin et al	Combination chemotherapy in tumour stage of mycosis fungoides with cyclophosphamide, vincristine, VP-16, Adriamycin and prednisolone (COP, CHOP, CAVOP) A report from the Scandinavian Mycosis Fungoides Group.	Acta Derm Verneol 1980;60:542-4
Fludarabine + cyclophosphamide or cladribine		
Mazur et al	Treatment of cutaneous T-cell lymphomas with purine analogues (fludarabine and 2-chlorodeoxyadenosine).	Journal of BUON 2003;8:247-251
Scarrisbrick et al	A trial of fludarabine & cyclophosphamide combination chemotherapy in the treatment of advanced refractory primary cutaneous T-cell lymphoma.	British J Derm 2001;144:1010-1015
Kong LR et al	2-chlorodeoxyadenosine in cutaneous T-cell lymphoproliferative disorders.	Leukemia & Lymphoma 1997;26(1-2):89-97
Gemicitabine		
Duvic et al	Phase II evaluation of gemcitabine monotherapy for cutaneous T Cell lymphoma.	Clinical Lymphoma & Myeloma 2006;7(1):51-58
Zinzani et al.	Gemcitabine treatment in pre-treated CTCL. Experience in 44 patients.	Clin Oncology 2000;18(13):2603-2606
Zinzani PL et al	Therapy with gemcitabine in pre-treated peripheral T-cell lymphoma patients.	Annals of Oncology 1998;9(12):1351-1353.
Zinzani PL et al	Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome.	Annals of Oncology 2010;21(4):860-863
Bortezomib		
Zinzani PL et al	Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma.	Journal of Clinical Oncology 2007;25(27):4293-4297.
Liposomal doxorubicin		
Quereux G et al	Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary Syndrome.	Arch Dermatol 2008; 144(6): 727-733.
Pulini S et al	Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas.	Haematologica 2007; 92: 686-689.

8. Results of Trials

Study P001:

The results for the primary outcome, objective response and time to progressive disease, from the single vorinostat arm are summarised below:

Response rates:

The objective response rate (as measured by the modified Severity Weighted Assessment Tool (mSWAT) (a ≥ 50% reduction in skin disease from baseline using mSWAT) in advanced stage CTCL disease (Stage IIB or higher) was 29.5% (95% CI: 18.5, 42.6) and this exceeded the pre-specified criteria for vorinostat to be considered as an "active drug" defined

as a response rate of at least 20% with the lower limit of the confidence interval higher than and excluding 5%. Only one response (in patients with Stage IIB or higher) from the total number of objective responses (1/18) was a complete response (the rest were partial responses).

The median time to objective response was around 2 months for patients with Stage IIB disease or higher. The duration of objective response ranged from 34 - 322 days in all patients treated with vorinostat and from 34-280 days for patients with Stage IIB or greater disease.

Pruritus relief:
The PBAC noted of 59 patients, 18 (30.5%) with Stage IIB or higher disease had pruritus relief and 8 (13.6%) had complete resolution of their pruritus symptoms. Relief in pruritus was maintained for at least 4 weeks without any increase in pruritus medication.

Supplementary studies:
The PBAC noted there was substantial heterogeneity in the definitions of response and numerical estimates of objective response, partial response and complete response rates, among the supplementary studies included in the submission. The proportion of patients experiencing 1) an overall response varied from 24% in Kong (1997) to 84% in Pulini (2007), 2) a partial response varied from 8% in Scarrisbrick to 60% in Zinzanni (2000) and 3) a complete response varied from 0% (P005, Molin and Mazur) to 42% in Pulini.

Comparison of vorinostat with chemotherapy:
The PBAC noted that the submission presented one comparison analysis conducted by Prince et al (2010) to examine the effectiveness and safety of vorinostat compared to different chemotherapy regimens using different sources of clinical data (Combined Skin Lymphoma Clinic data).

For PBAC's view, see Recommendation and Reasons.

Overall, about 27% of patients had a serious adverse event and approximately 16% of patients discontinued vorinostat therapy due to an adverse event. Thrombocytopenia and anaemia were the most common haematologic toxicities. Other laboratory abnormalities reported included increased serum glucose in 69% of CTCL patients (59 of 86), transient increases in serum creatinine in 46.5% of patients (40 of 86), and proteinuria in 51.4% of patients (38 of 74). Serious adverse events included pulmonary embolism (4.7%); squamous cell carcinoma (3.5%); and anaemia (2.3%).

9. Clinical Claim

The submission described vorinostat as superior in terms of comparative effectiveness and inferior in terms of comparative safety over the main comparator of palliative care.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a partially modelled (primarily trial-based) evaluation. This is a cost-effectiveness model where in one arm (incremental) costs and effects are estimated from the single arm study P001, and other arm is assumed to have zero (incremental) costs/effects.

The time horizon of the evaluation is one year. The outcomes in the model are: the *incremental* cost per additional patient with response (≥50% and ≥25% decrease in mSWAT); and the incremental cost per additional year with response (≥50% and ≥25% decrease in mSWAT).

For the surrogate outcome number of patients with response (≥25% decrease in SWAT) in patients with stage IIB or greater disease, the submission estimated the incremental cost/additional responder to be in the range $75,000 to $105,000.

For the surrogate outcome years with response (≥50% decrease in SWAT) in patients with stage IIB or greater disease, the submission estimated the incremental cost/additional year of response to be greater than $200,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost per year to the PBS was estimated by the submission to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that the submission proposed palliative care as the comparator. However, the PBAC considered that a comparison with best available care, as represented by chemotherapy, is more appropriate than end-of life palliative care as the drug may not be used as last-line treatment. The PBAC noted that consumer comments and expert comments indicated that vorinostat would be used earlier in the treatment algorithm than proposed in the requested restriction (after failure of at least four systemic therapies) and that more toxic treatments would be reserved for patients with refractory disease.

The submission presented one 'key' case series study (P001) of vorinostat, several supplementary open-label and case series chemotherapy studies, three non-randomised studies comparing different chemotherapies and one case study of bortezomib. The objective response rate (a ≥ 50% reduction in skin disease from baseline using mSWAT) of Study P001 was 29.5%, (95% CI 18.5, 42.6) and only one response (in patients with Stage IIB or higher) from the total number of objective responses (1/18) was a complete response (the rest were partial responses). Of 59 patients, 18 (30.5%) with Stage IIB or higher disease had pruritis relief and 8 (13.6%) had complete resolution of their symptoms. The median duration of response was not reached but was estimated to be greater than 4 months with a range of 1 month to 9 months or more. The application would have been stronger if additional data about durability of benefit was presented. The PBAC noted that no survival data are available/ presented from Study P001 or from the non-comparative chemotherapy studies.

The PBAC noted that the quality of the data is extremely limited and the studies presented in the submission are small, non comparative and heterogeneous. The PBAC acknowledged that a meaningful comparison of the effectiveness of vorinostat relative to chemotherapy is difficult. A comparison analysis was conducted by Prince et al (2010) to examine the effectiveness and safety of vorinostat compared to different chemotherapy regimens using different sources of clinical data (Combined Skin Lymphoma Clinic data) but was methodologically flawed. The PBAC noted that better evidence about therapeutic advances

may be forthcoming as there are numerous clinical trials being undertaken which are recruiting patients with cutaneous T-cell lymphoma (Clinical trials.gov).

The submission claimed that vorinostat is superior in terms of comparative effectiveness and inferior in terms of comparative safety over the main comparator of palliative care. The PBAC agreed that vorinostat is an active drug that has superior efficacy to palliative care. However, no conclusion can be reached with respect to comparisons with other available therapies. The PBAC agreed that vorinostat has significant toxicities, and is inferior in safety to palliative care. However, expert testimony suggests it is less toxic than cytotoxic chemotherapies.

A partially modelled (primarily trial-based) evaluation is presented. This is a cost-effectiveness model where in one arm (incremental) costs and effects are estimated from the single arm study P001, and other arm is assumed to have zero (incremental) costs/effects. The PBAC noted that no studies identifying utility weights in CTCL health states were identified and that consequently, a cost-utility analysis could not be performed. The costs of vorinostat are modelled on the basis that patients without a 50% improvement in mSWAT will stop vorinostat treatment after 12 weeks (consistent with the requested restriction). The trial-based outcome (proportion of patients with response) is incorporated into the ICER. The ICER is calculable only for surrogate outcome measures of response and response duration and was therefore considered to be highly uncertain. The ICER was estimated by the submission to be in the range $75,000 to $105,000 per additional responder (surrogate outcome number of patients with response (≥25% decrease in SWAT) in patients with stage IIB or greater disease) to greater than $200,000 per additional year of response (years with response (≥50% decrease in SWAT) in patients with stage IIB or greater disease).

The PBAC noted that the total cost to the PBS was relatively low, however, the clinical place of the drug was uncertain and there was potential for use beyond the requested restriction. Therefore, the financial estimates were considered to be uncertain.

The PBAC acknowledged that that there was a high clinical need for vorinostat and a treatment benefit of around 30% in patients with cutaneous T-cell lymphoma. However, the incremental costs for measurable health gains far exceeded those accepted for other chronic, intractable diseases and other cancers. Cost offsets and toxicities of chemotherapies in the comparator arm may help improve the ICER, although some reduction in the treatment benefit would also need to be assumed.

The PBAC therefore rejected the submission on the basis of unacceptably high and uncertain cost-effectiveness ratios.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:
Reject

13. Context for Decision

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

medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Vorinostat fulfils an unmet medical need by providing a treatment option for patients who have exhausted other effective systemic treatments. The negative impact of the disease on patient's quality of life and survival is significant and patients who respond to treatment with vorinostat experience significant relief from their symptoms.

The sponsor acknowledges that the data provided was limited. This is because the rareness of the disease and the individualised approach to treatment makes it difficult to conduct randomised controlled trials (RCT's) in this population.