PUBLIC SUMMARY DOCUMENT
Product: Doxorubicin hydrochloride, pegylated liposomal, suspension for I.V. infusion, 20 mg in 10 mL and 50 mg in 25 mL, Caelyx®
Sponsor: Schering-Plough Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought to extend the current PBS authority required listing for liposomal doxorubicin to include the treatment of refractory multiple myeloma, in combination with bortezomib.

2. Background

Liposomal doxorubicin had not previously been considered by the PBAC for this indication.

3. Registration Status

Liposomal doxorubicin was TGA registered on 25 February 2008 for the new indication, in combination with bortezomib, the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

Liposomal doxorubicin is also registered for:

- as monotherapy, for the treatment of metastatic breast cancer;
- advanced epithelial ovarian cancer in women who have failed a first-line platinum based chemotherapy regimen.
- Treatment of AIDS related Kaposi's sarcoma in patients with low CD4 counts (< 200 lymphocytes/mm3) and extensive mucocutaneous or visceral disease.

4. Listing Requested and PBAC's View

Authority required

The submission did not propose an actual restriction but stated that the restriction for liposomal doxorubicin was defined by the PBS listing for bortezomib, which provided therapy for multiple myeloma patients who have:

- progressive disease
- received at least one prior therapy other than thalidomide
- a World Health Organisation (WHO) performance status 0-2.
- already undergone or are ineligible for primary stem cell transplant
- experienced treatment failure after a trial of at least four weeks of thalidomide (≥ 100 mg/day), or experienced severe intolerance or toxicity to thalidomide.

See Recommendations and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Multiple myeloma (MM) is a haematological malignancy characterised by proliferation of plasma cells in the bone marrow. The MM cells produce aberrant immunoglobulin proteins termed M-protein which is found in the urine and serum of most patients with MM. Symptoms of the disease include anaemia, bleeding, bruising and recurrent or persistent bacterial infections. The disease spreads into the bone causing bone breakdown, fracture and hypercalcemia, which may affect kidney function. The median survival has been 3 years but

with high dose chemotherapy and stem cell transplant (SCT), median survival has increased to almost 5 years.

However, the vast majority of patients undergo relapse and need to receive further chemotherapy. Liposomal doxorubicin, in combination with bortezomib, will provide an additional therapy option for patients with refractory disease who have failed thalidomide and one other therapy, and have undergone or are unsuitable for stem cell transplant. The proposed treatment algorithm concurred with the management algorithm of bortezomib.

6. Comparator

The submission nominated bortezomib monotherapy as the main comparator. The PBAC considered this was appropriate.

7. Clinical Trials

The submission presented one randomised open-label trial (Trial 3001) comparing doxorubicin plus bortezomib with bortezomib monotherapy in patients with refractory multiple myeloma. Patients were excluded from the trial if they had received prior treatment with bortezomib.

A subgroup analysis of this trial with thalidomide- or lenalidomide-prior exposed patients published in February 2008, was also presented in the evaluation for completeness, although as this sub-group analysis was not pre-specified, the results needed to be interpreted with caution.

The details of the trials and associated reports which had been published at the time of submission are as follows:

Trial/First author	Publication citation
Trial 3001 Orlowski RZ, et al. 2007	Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. Journal of Clinical Oncology 25(25):3892-3901
Trial 3001 (subgroup analysis) Sonneveld P, et al;, 2008	Combined pegylated liposomal doxorubicin and bortezomib is highly effective in patients with recurrent or refractory multiple myeloma who received prior thalidomide/lenalidomide therapy. Cancer. 2008 112(7):1529-1537
EMEA 2008.	Scientific discussion of Caelyx. European Medicines Agency EMEA/H/C/00089/II/0045 London 15 November 2007 http://www.emea.europa.eu/humandocs/PDFs/EPAR/Caelyx/AR-H-089-II-45.pdf, accessed at 10 April 2008.

8. Results of Trials

The results of the primary outcome (time to progression) of Trial 3001 are presented in the table below.

Time to progression – adjusted for strata		**doxorubicin + bortezomib**	**bortezomib**	**HR (95% CI)**
Interim Analysis at 28 April 2006 (median time to follow-up 3.9 months)				
Censored	n/N (%)	225/324 (69.4)	172/322 (53.4)	1.82 (1.41, 2.53) p = 0.000004
Progressed or died	n/N (%)	99/324 (30.6)	150/322 (46.6)	
Days to progression	Median (95% CI)	282 (250, 338)	197 (170, 217)	
Efficacy Update at 28 November 2006 (median time to follow-up 10.9 months)				
Censored	n/N (%)	140/324 (43.2%)	99/322 (30.7%)	1.55 (1.27, 1.89) p = 0.000013
Progressed or died	n/N (%)	184/324 (56.8%)	223/322 (69.3%)	
Days to progression	Median (95% CI)	271 (246, 298)	209 (185; 222)	

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not achieved

The median time to progression at the efficacy update (median follow-up 10.9 months) was 8.9 months for doxorubicin and bortezomib compared to 6.9 months for bortezomib monotherapy (HR 1.55; 95% CI 1.27 to 1.89; p=0.000013).

The following table presents the overall survival in Trial 3001:

Overall survival in days – adjusted for strata		**Doxorubicin + bortezomib (n = 324)**	**Bortezomib (n = 322)**	**HR (95% CI)**
Interim Analysis at 28 April 2006 *(median time to follow-up 3.9 months)*				
Censored	n/N (%)	296/324 (91.4)	283/322 (87.9)	1.48 (0.91, 2.41) *p* = 0.113
Died	n/N (%)	28/324 (8.6)	39/322 (12.1)	
Survival in days	Median (95% CI)	(NA, NA)	(NA, NA)	
Whole trial population 28 November 2006 (median follow up 10.9 months)				
Censored	n/N (%)	266/324 (82.1)	241/322 (74.8)	1.41 (1.002, 1.97) p = 0.0476
Died	n/N (%)	58/324 (17.9)	81/322 (25.2)	
Survival in days	Median (95% CI)	NA	NA (551.0, NA)	
Whole trial population 10 August 2007 (median follow-up 18.0 months)				
Died	n/N (%)	96/324 (29.6)	110/324 (34.0)	1.16 (0.89, 1.54) p=0.265

CI, confidence interval; HR, hazard ratio; NA, not achieved; NR, not reported.

There was a statistically significant difference in overall survival, favouring doxorubicin plus bortezomib, compared to bortezomib alone at a median follow-up of 10.9 months (HR 1.41; 95% CI 1.002 to 1.97; p=0.0476) but there was no survival benefit at 18.0 months' follow-up (HR 1.16; 95% CI: 0.89 to 1.54; p=0.265).

Drug-related adverse events, drug-related serious adverse events and Grade 3 or 4 adverse events were more frequent in the doxorubicin and bortezomib group compared with bortezomib monotherapy. The most frequent Grade 3 and 4 adverse events were neutropenia

and thrombocytopenia. Grade 3 and 4 neutropenia was reported more frequently with doxorubicin plus bortezomib compared with bortezomib monotherapy (30% vs. 14%).

For PBAC's comments on these results, see Recommendations and Reasons.

9. Clinical Claim

The submission described doxorubicin plus bortezomib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over bortezomib monotherapy.

For PBAC's views, see Recommendations and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented.

The model was a single cohort model, with the age at entry of 62 years. The type of economic evaluation presented was a cost-effectiveness analysis using life years saved as the health outcome.

The first step was a trial based economic evaluation, the second step included the costs to treat adverse events and the third step included extrapolation beyond the trial period.

The submission used direct trial-based data for 650 days and then plotted the fourth line survival data from Kumar et al (2004), adjusted for Australian survival data, for an additional five years. Survival during the trial period up to day 650 was determined from the Kaplan-Meier curves of overall survival (Efficacy Update; median time to follow-up 10.9 months).

The model used three health states: i) alive, ii) dead within the trial duration and iii) dead following the trial duration.

The PBAC noted that the model was most sensitive to efficacy within the trial duration. Decreasing the difference in overall survival during the trial by 90% (as a surrogate of using 95% CI values), resulted in an ICER of greater than $200,000 per life year saved (LYS), whilst increasing the difference by 50% resulted in a reduction of the ICER (in the range of $15,000 - $45,000/LYS). The updated analysis (median follow-up 18.0 months) did not reveal a statistically significant difference in overall survival between the two treatment arms. This suggests that bortezomib monotherapy could be dominant within the 95% confidence interval for overall survival.

The model was also sensitive to the extrapolation data. Using the 6th line treatment from Kumar et al (2004), where all patients died 19.8 months into the extrapolation phase, resulted in an ICER in the range of $50,000 - $100,000/LYS.

The uncertainty about the magnitude of the clinical benefit means that there is unacceptably large uncertainty about the economic modelling, and hence the cost-effectiveness, with the ICER for LYG ranging over $50,000 - $100,000 in several sensitivity analyses. The PBAC noted that this uncertainty should be able to be addressed when mature survival data for the trial are available to the sponsor.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost per year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The Committee noted that this submission presented the results of one randomised open-label trial (Trial 3001) comparing doxorubicin plus bortezomib with bortezomib monotherapy in patients with refractory multiple myeloma. Patients were excluded from the trial if they had received prior treatment with bortezomib. A subgroup analysis of this trial with thalidomide- or lenalidomide-prior exposed patients published in February 2008, was also presented in the evaluation for completeness, although as this sub-group analysis was not pre-specified, the results need to be interpreted with caution.

The PBAC noted that in the key trial, overall survival for the doxorubicin plus bortezomib group compared with bortezomib monotherapy group just reached statistical significance (HR 1.41; 95% CI 1.002 to 1.97; p=0.0476) at a planned Efficacy Update (median follow-up 10.9 months), but that at a further unplanned update, the overall survival in the combined treatment group was not statistically significant different to the monotherapy group (HR 1.16; 95% CI: 0.89 to 1.54; p=0.265: median follow-up 18 months).

Although the evidence provided by the submission demonstrated a statistically significant improvement in time to progression, no statistically significant improvements in quality of life outcomes or in the number of partial and complete responders were observed. Furthermore, drug-related grade 3/4 adverse events occurred more frequently with doxorubicin and concomitant bortezomib therapy. The PBAC considered that the overall conclusion that the combination of liposomal doxorubicin and bortezomib is inferior with respect to safety, may also explain the absence of quality of life (QOL) benefit in comparison with bortezomib monotherapy.

The Committee further noted that a number of concerns with the stepped economic evaluation presented in the submission had been identified, including:

- the methodology overestimated the treatment effect and biases the model in favour of doxorubicin,
- the uncertainty of the clinical outcome observed in the clinical trials was not captured in the economic model,
- the difference in the toxicity of the two treatments was captured in the model in terms of costs but not in terms of treatment effect, and
- the outcomes were expressed as costs per extra life year saved, rather than as costs per incremental quality adjusted life year and as noted by PBAC the incremental cost per QALY may be expected to be greater than incremental cost per LY.

See Economic Analysis for PBAC's views on the economic model.

Thus, the PBAC considered that whilst the trial data allowed the conclusion that liposomal doxorubicin improves time to progressive disease when added to bortezomib in patients who have previously received thalidomide, there is increased toxicity, no identifiable improvement in QOL and significant uncertainty about the extent of survival benefit.

The PBAC therefore rejected the submission because of uncertain clinical benefit and high and uncertain cost-effectiveness.

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

The sponsor chose not to comment.