PUBLIC SUMMARY DOCUMENT
Product: Vinflunine, solution concentration for I.V. infusion, 50 mg in 2 mL and 250 mg in 10 mL (as ditartrate), Javlor®
Sponsor: Pierre Fabre Medicament Australia Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

The submission sought an Authority Required (STREAMLINED) listing for the treatment of an adult patient with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Vinflunine was registered by TGA on 11 February 2011 for the indication:

- Treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Treatment of an adult patient with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Cancer of the urothelium, known as transitional cell carcinoma of the urothelial tract or TCCU, represents greater than 90% of diagnosed bladder cancers. Urothelial tract tumours also include tumours of the renal pelvis, ureters and urethra. In invasive or metastatic TCCU, cancer that begins in the urothelial cells may spread through the lining of the bladder and invade the muscle wall of the bladder or spread to nearby organs such as the prostate, uterus, vagina, pelvic or abdominal wall and lymph nodes.

Clinical management of advanced or metastatic TCCU typically involves surgery, chemotherapy and radiotherapy. While bladder cancers are sensitive to systemic chemotherapy such as platinum-based treatment e.g. cisplatin in combination with gemcitabine, patients with metastatic disease experiencing recurrence or progression after an initial platinum-based treatment regimen can have a poor response to subsequent therapies.

The submission proposed that the place in therapy of vinflunine is as a further treatment option for patients with advanced or metastatic TCCU who have failed treatment with chemotherapy regimens containing a platinum compound.

6. Comparator

The submission nominated best supportive care (BSC) as the main comparator, on the basis that there were no approved and/or reimbursed medicines available currently on the PBS for these patients.

The PBAC agreed that whilst best supportive care (BSC) is an appropriate comparator in determining the efficacy of vinflunine, it is not relevant in Australian clinical practice as vinflunine will likely replace or defer other drugs.

7. Clinical Trials

The submission presented Study 302, a randomised unblinded trial comparing BSC and vinflunine (280 mg/m^2 or 320 mg/m^2 every three weeks) depending on performance status and prior pelvic irradiation or special haematological or biochemical status with BSC alone in patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen. The PBAC considered that BSC, as it was defined in the study, was not consistent with current practice in Australia.

The following trials had been published at the time of submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Study 302		
Bellmunt,J.et al	Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract.	Journal of Clinical Oncology (2009) 27(27): 4454-4461.
Bellmunt, J.et al	Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens.	Journal of Clinical Oncology (2010) 28(11): 1850-1855.
Von Der Maase, H et al	Multicentre phase III trial comparing vinflunine (V) plus best supportive care (BSC) vs BSC alone as 2nd line therapy after a platinum-containing regimen, in advanced transitional cell carcinoma of the urothelium (TCCU).	Annals of Oncology (2008) 19(S8): viii202.
Culine, S et al	Updated survival results of the phase III trial comparing vinflunine (V) to Best Supportive Care (BSC) in advanced Transitional Cell Carcinoma of the Urothelium (TCCU) after failure of a prior platinum-containing regimen. Presentation at the 25th Annual EAU Congress.	Presentation at the 25th Annual EAU Congress. (2010)

8. Results of Trials

The submission used the eligible intent-to-treat (ITT) result as the base case, which is a sub-group of the ITT group, with 13 patients removed because it was identified post-randomisation that they did not meet the inclusion criteria (9 in the BSC arm and 4 in the vinflunine arm).

The PBAC noted that the exclusion of the 13 patients occurred post-hoc, and given that these patients received treatment in a clinical trial setting, it is likely that they would also receive treatment in practice.

A summary of the results for overall survival in the ITT and eligible ITT populations are shown in the table below:

Summary of results on overall survival in ITT and eligible ITT

	Median overall survival *(months)*		HR (95 % CI) p value	
	VFL+BSC	BSC	Stratified log-rank test	Extended multivariate analysis
ITT	6.9	4.6	0.88 (0.69, 1.12) p = 0.2868	0.74 (0.57, 0.96) p = 0.0221
Eligible ITT	6.9	4.3	0.78 (0.61, 0.99) p = 0.0403	0.68 (0.52, 0.88) p = 0.0035

The PBAC noted that the increment in overall survival (OS) is uncertain and, at best, is between 2.3 (ITT) and 2.6 months (eligible ITT). Therefore, the PBAC considered the choice of population is important as the choice of analysis group determines if the hazard ratio is statistically significantly different from 1. Therefore, the selection of the eligible ITT population was considered highly uncertain.

The PBAC agreed that the ITT population should be used in considering the effectiveness of vinflunine as the eligibility criteria in the trial were tighter than the PBS restriction criteria and the ITT population more closely approximates the likely PBS population.

The results of overall survival analysis (OS) across the three populations ITT, Per Protocol and Eligible ITT at three different time cut-off points are shown below:

Main Results from Study 302

	ITT		Per Protocol		Eligible ITT	
	VFL + BSC N=253	BSC N=117	VFL + BSC N=244	BSC N=107	VFL + BSC N=249	BSC N=108
OS analysis (Cut-off 30 Nov 2006)						
No. of events	204	103	198	98	202	98
No. censored (%)	49 (19.4)	14 (12.0)	46 (18.9)	9 (8.4)	47 (18.9)	10 (9.3)
Median (95% CI) (month)	6.9 (5.7, 8.0)	4.6 (4.1, 7.0)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)
HR (95% CI)	0.88 (0.69, 1.12)		**0.75 (0.59, 0.96)**		**0.78 (0.61, 0.99)**	
p value[a]	0.2868		0.0197		0.0403	
OS analysis (Cut-off 31 May 2007)						
No. of events	223	108	216	102	220	102
No. censored (%)	30 (11.9)	9 (7.7)	28 (11.5)	5 (4.7)	29 (11.7)	6 (5.6)
Median (95% CI) (month)	6.9 (5.7, 8.0)	4.6 (4.1, 6.6)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)
HR (95% CI)	0.88 (0.69, 1.10)		**0.74 (0.59, 0.94)**		**0.77 (0.61, 0.98)**	
p value[a]	0.2546		0.0130		0.0320	
OS analysis (Cut-off 30 Nov 2008)						
No. of events	237	115	not performed		234	108
No. censored (%)	16[b] (6.3)	2[c] (1.7)			15 (6.0)	0
Median (95% CI) (month)	6.9 (5.7, 8.0)	4.6 (4.1, 6.6)			6.9 (5.7, 8.0)	4.3 (3.8, 5.4)
HR (95% CI)	0.88 (0.70, 1.10)				**0.78 (0.61, 0.96)**	
p value[a]	0.2613				0.0227	

Abbreviations:VFL, vinflunine; BSC, best supportive care; HR, hazard ratio; CI, confidence interval.
a: Stratified log-rank test;
b: Including 1 non eligible patient (#550543 lost to follow-up with an OS=15.7 months);
c: Two non eligible patients alive at the cut-off (#600401 with an OS=34.2 months & #110504 with an OS=45.4 months)
Statistically significant HR values noted in **bold**.

The PBAC noted that if the results for OS are evaluated from the ITT population analysis, the hazard ratios at all three time cut-off points were not statistically significantly different from the null. Therefore, the evidence of a real increase in OS was considered uncertain. The PBAC also noted that the results of a Cox multivariate analysis presented in the sponsor's Pre-Sub-Committee Response demonstrated that potential differences in the prognostic factors from excluding the 13 ineligible patients did not alter overall survival in the eligible ITT.

The adverse events that were both common (reported by at least 10% of the patient population of Study 302) and statistically significantly more frequent in those receiving vinflunine were abdominal pain, constipation, diarrhoea, nausea, stomatitis, vomiting, fatigue, injection site reactions, weight decrease, anorexia, myalgia, headaches, peripheral sensory neuropathy and alopecia. The Grade III/IV adverse events experienced more frequently in the vinflunine arm of Study 302 were abdominal pain, constipation, nausea, vomiting, fatigue, infestations and infections, anorexia, myalgia and headache.

One death due to pancytopenia was reported as directly related to vinflunine, although sixteen patients (6%) in the vinflunine and BSC group, and 1 patient (1%) in the BSC group died within 30 days of either the final vinflunine dose (for the intervention arm) or the final visit (for the BSC arm) for reasons other than progressive disease.

The PBAC noted that the rates of adverse events (AE) were higher in the vinflunine +BSC group than in the BSC group and that the pattern of AE and serious adverse events (SAE) suggested very high levels of toxicity that would need to be traded off for a relatively small increase in overall survival.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials. The PBAC noted that neither of these identified different patterns of adverse events from those noted in Study 302.

9. Clinical Claim

The submission described vinflunine as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care.

The PBAC accepted that vinflunine may be superior in terms of comparative efficacy over BSC although the magnitude of the overall survival gain is uncertain (less than 3 months) and is at the expense of significant toxicity. The PBAC agreed that vinflunine is inferior in terms of comparative safety over best supportive care.

10. Economic Analysis

The submission presented a cost-utility analysis (CUA) based on the eligible ITT population in Study 302.

The economic model was a decision analysis comparing IV vinflunine plus BSC with BSC alone for treatment of patients with advanced or metastatic TCCU who have progressed after prior platinum-containing treatment.

The model excluded costs of BSC that were not expected to differ between treatment arms, and underestimated the cost of adverse events (AEs) by assuming that all AEs were captured

by the risk difference for hospitalisations, based on the number of patients hospitalised in each arm of Study 302.

The results of the stepped economic evaluation produced a base case ICER between $45,000 and $75,000.

The results of the sensitivity analyses presented in the submission indicated that the model was most sensitive to the number of episodes of palliative radiotherapy (PRT).

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 M in Year 5, this was considered to be very uncertain. The sources of uncertainty were the estimated number of patients and number of treatment cycles per patient, the number of palliative radiotherapy episodes and net costs of BSC and AEs, which were considered to be underestimated.

12. Recommendation and Reasons

The submission presented one randomised, unblinded trial (Study 302) comparing vinflunine (280 mg/m^2 or 320 mg/m^2 every three weeks) and BSC with BSC alone in patients with advanced or metastatic TCCU after failure of a prior platinum-containing regimen as the key clinical trial. However, the PBAC considered that BSC as it was defined in the study is not consistent with current practice in Australia.

The PBAC agreed that whilst BSC is an appropriate comparator in determining the efficacy of vinflunine, it is not relevant in Australian clinical practice as vinflunine will likely replace or defer other drugs. The PBAC considered that current standard of care is preferable for the determination of relative effectiveness and therefore the translatability of the trial data to the proposed use in Australia is an area of significant uncertainty.

The PBAC noted that both the proposed clinical management algorithm and the requested restriction allow use in patients who are intolerant to first-line therapy with a platinum compound. However, the trial data did not provide information on this group of patients. The PBAC also noted that patients who had received neoadjuvant or adjuvant treatment were excluded from the trial, but would meet the requested restriction if they failed adjuvant treatment with a platinum compound (second-line therapy). The sponsor acknowledged the patient's exclusion in its Pre-Sub-Committee Response.

The PBAC noted that the submission used the eligible ITT result as the base case, which is a sub-group of the ITT group, with 13 patients removed because it was identified post-randomisation that they did not meet the inclusion criteria (9 in the BSC arm and 4 in the vinflunine arm). The PBAC noted that the exclusion of the 13 patients occurred post-hoc, and given that these patients received treatment in a clinical trial setting, it is likely that they would also receive treatment in practice. The PBAC agreed that whilst the eligible ITT population may be reasonable to assess the efficacy of vinflunine, the ITT population should be used in considering the effectiveness of vinflunine as the eligibility criteria in the trial are tighter than the PBS restriction criteria and the ITT population more closely approximates the likely PBS population.

The PBAC accepted that vinflunine is superior in terms of comparative efficacy over BSC but noted that the increment in overall survival is uncertain and, at best, is between 2.3 (ITT) and 2.6 months (eligible ITT) and was at a cost of significant treatment-related toxicity. The PBAC agreed that vinflunine is inferior in terms of comparative safety over best supportive care. The PBAC considered that realising the possible beneficial effects of vinflunine in clinical practice may be challenging because of a patient's age (likely to be older in clinical practice), the effect of previous radiotherapy and performance status on dose and hence the ability to adhere to the dose escalation protocols. In this regard, vinflunine also appears to have a narrow therapeutic window. The PBAC acknowledged that although vinflunine may have efficacy in some patients with high clinical need, the magnitude of survival gain is uncertain (less than 3 months) and this benefit is at the expense of significant toxicity. Therefore, the PBAC considered that there is uncertainty regarding the clinical place of vinflunine.

The PBAC agreed that the selection of pre-modelling issues in the submission is appropriate. However, the degree to which Study 302 represents the Australian setting was uncertain for three reasons: (1) treatment for those with a poorer performance status is not excluded under the proposed listing and is not considered in Study 302; (2) BSC does not adequately represent the set of replaced interventions in an Australian setting where other therapies are often used in the second-line; (3) the age of the patient population in Study 302 is likely to be lower than the age of patients in an Australian population.

The economic evaluation was a cost-utility analysis (CUA) based on the eligible ITT population in Study 302. The PBAC noted that the results from this analysis are uncertain as they are based on the eligible ITT population rather than the ITT population. The overall survival gain in the ITT population was less than observed in the eligible ITT and was not statistically significant. The PBAC considered that the results are highly uncertain as they are based on the eligible ITT population rather than the ITT population. The PBAC agreed that the results of the CUA, which compare vinflunine to BSC, do not reflect the cost effectiveness of vinflunine relative to the range of second line treatments currently used in 50-60% of patients. Therefore, it is likely that the ICER of between $45,000 and $75,000 per QALYG is an underestimate in the submission.

The PBAC considered that an Authority Required (STREAMLINED) listing is appropriate.

The PBAC rejected the submission on the basis of uncertainty about the clinical benefit and a high and highly uncertain incremental cost-effectiveness ratio.

The PBAC noted that the submission meets the criteria for an independent review.

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

Pierre Fabre Medicament wishes to emphasise that vinflunine is the only registered drug in Australia for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum containing regimen. All other drugs which are currently used to treat second line metastatic bladder cancers in Australia are used “off label”.

Pierre Fabre Medicament Australia is disappointed with the recommendation and is committed to working with the PBAC to provide an approved treatment for patients with metastatic TCCU after failure of a prior-platinum containing regimen.