

7.06 VINFLUNINE

solution concentration for IV infusion, 50 mg in 2 mL and 250mg in 10 mL (as ditartrate)

Javlor®, Pierre Fabre Medicament Australia.

1 Purpose of Application

- 1.1 The re-submission requested listing under the Efficient Funding of Chemotherapy program for vinflunine for treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen. The first submission was reviewed in November 2011.

2 Requested listing

- 2.1 The requested listing was:

Name, Restriction, Manner of administration and form	Max. Amt.	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
VINFLUNINE DITARTRATE 50mg/2 mL 250mg/10 mL	700	4-2 or 3		Javlor Pierre Fabre

Category / Program	Chemotherapy (Public/Private)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	
Severity:	Locally advanced or metastatic
Condition:	Transitional cell carcinoma of the urothelial tract
PBS Indication:	Locally advanced or metastatic transitional cell carcinoma of the urothelial tract
Treatment phase:	
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

Public Summary Document – November 2015 PBAC Meeting

Clinical criteria:	<p>Patient must have disease progression following treatment with a platinum-containing regimen for advanced or metastatic disease</p> <p>Patient must have failed a platinum-containing regimen for this condition AND Patient must not have received neoadjuvant or adjuvant chemotherapy AND Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or less. AND Treatment must be discontinued in patients who experience disease progression while on treatment.</p>
Population criteria:	adults
Prescriber Instructions	
Administrative Advice	<p>Note No increase in the maximum number of repeats may be authorised.</p> <p>Note No increase in the maximum quantity or number of units may be authorised.</p> <p>Note Special Pricing Arrangements apply.</p>

- 2.2 The clinical criteria of a WHO/ECOG performance status (PS) of ≤ 1 was not included in the November 2011 submission but was agreed to by the Sponsor in its Pre-Sub-Committee Response. The clinical trial (Study 302) restricted inclusion to patients with an ECOG/WHO performance status of ≤ 1 .
- 2.3 The clinical criterion that patients must not have received neoadjuvant or adjuvant chemotherapy is in response to the PBAC's previous concern that Study 302 excluded these patients. Neoadjuvant/adjuvant chemotherapy is recommended for the treatment of localised muscle-invasive tumours. This criterion is likely to exclude a substantial proportion of otherwise eligible patients, and the exclusion would apply even if the patient has received a line of therapy for their recurrent metastatic disease. Despite criteria excluding these patients from participating in Study 302, 10 patients who had received prior neoadjuvant/adjuvant therapy were enrolled. Similarly there is the potential for use in these patients through the PBS despite the proposed PBS criterion precluding them. The PSCR (p4) notes that the sponsor is willing to discuss the wording of the proposed listing.
- 2.4 Listing was sought on the basis that vinflunine is cost-effective compared with best supportive care (BSC).

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

3 Background

- 3.1 **TGA status:** Vinflunine was registered by the TGA on 22 February 2011 for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen.
- 3.2 Vinflunine was previously considered by PBAC in November 2011.
- 3.3 A summary of the key differences between the re-submission and November 2011 submission is presented in Table 1.

Table 1: Summary of the previous submission and current re-submission

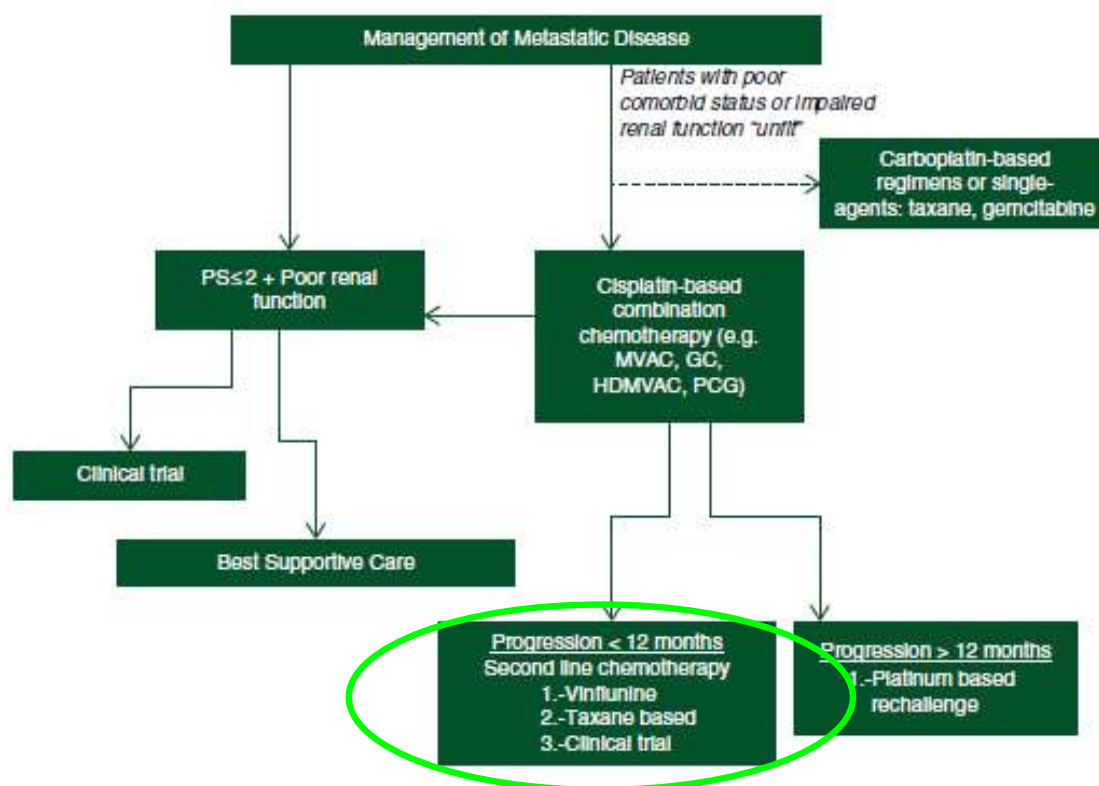
	Vinflunine, November 2011	Current re-submission
Requested PBS listing	Treatment of an adult patient with advanced or metastatic TCCU after failure of a prior platinum-containing regimen. PBAC Comment: Patients who had received neoadjuvant/ adjuvant treatment were excluded from the trial, but would meet the restriction (section 12, p5, November 2011, PBAC PSD).	Proposed listing includes criteria that patients must not have received neoadjuvant or adjuvant chemotherapy, and restricts to ECOG PS ≤ 1.
Requested price	Effective ex-man prices: \$████ per 50 mg vial; \$████ per 250 mg vial; RSA proposed with a funding cap of 3 cycles per patient. A █████% price reduction was offered in the Pre-PBAC Response.	Effective ex-man prices: \$████ per 50 mg vial; \$████ per x 250 mg vial. No RSA.
Main comparator	BSC PBAC Comment: BSC is not relevant in Australian clinical practice as vinflunine will likely replace or defer other drugs (section 6, p2, November 2011, PBAC PSD, item 5.3).	<ul style="list-style-type: none"> • BSC • Active chemotherapy (estimated to be used in 75-80% of patients)
Clinical evidence	Study 302: RCT comparing vinflunine + BSC and BSC (N=370). PBAC Comment: None	<ul style="list-style-type: none"> • Study 302 • 20 non-comparative studies assessing active chemotherapy in the proposed patient population • 3 vinflunine observational studies
Clinical claim	Vinflunine is superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC. PBAC Comment: Vinflunine may be superior in terms of comparative efficacy although the magnitude of the OS gain is uncertain (< 3 months) and is at the expense of significant toxicity. Vinflunine is inferior in terms of comparative safety (section 12, p6, November 2011, PBAC PSD, item 5.3).	BSC: Same as for 2011 submission. Active chemotherapy: Vinflunine is superior in terms of comparative effectiveness and similar in terms of comparative safety over active chemotherapy.
Economic evaluation	Cost/QALY: \$████ PBAC Comment: The results are highly uncertain as they are based on the mITT rather than the ITT population. The ICER does not reflect the cost effectiveness of vinflunine relative to second line treatments. It is likely that the ICER is an underestimate (section 12, p6, November 2011, PBAC PSD, item 5.3).	Cost/QALY: \$████ vs BSC (mITT population). Sensitivity analysis for ITT population: cost/QALY \$████ Sensitivity analysis for vinflunine vs active chemotherapy: cost/QALY \$████. The ESC noted this sensitivity analysis. While it is correct to compare Vinflunine relative to active chemotherapy, the ESC considered that there was inadequate amount of data to give an informative assessment of the cost-effectiveness compared to active chemotherapy.
PBAC decision	Reject on the basis of uncertainty about the clinical benefit and a high and highly uncertain incremental cost-effectiveness ratio (section 12, p6, November 2011, PBAC PSD, item 5.3).	-

Source: Compiled during the evaluation. The patient population was referred to as the 'eligible' population in the November 2011 submission.

4 Clinical place for the proposed therapy

- 4.1 Cancer of the urothelium, known as transitional cell carcinoma of the urothelial tract or TCCU, represents greater than 90% of diagnosed bladder cancers, with the next most common being squamous cell carcinoma (5%) and adenocarcinoma and small cell carcinoma. Urothelial tract tumours also include tumours of the renal pelvis, ureters and urethra. In metastatic TCCU, cancer may spread to nearby organs, lymph nodes, bone, lung and liver among other organs. Untreated, metastatic TCCU is associated with a short median survival, rarely exceeding 3 to 6 months. Clinical management of advanced or metastatic TCCU typically involves surgery, chemotherapy, radiotherapy and best supportive care. First-line chemotherapy usually involves a platinum-based compound in combination with gemcitabine or as part of the MVAC regimen.
- 4.2 The re-submission proposed vinflunine as a treatment option for patients with advanced or metastatic TCCU who have failed treatment with chemotherapy regimens containing a platinum compound, as outlined in the figure below.

Figure 1: Recommended treatment options for progression/failure with first-line platinum-containing chemotherapy regimens for the treatment of advanced or metastatic bladder cancer



Source: Figure 3 of the re-submission, p34. Abbreviations: PS, performance status; MVAC, methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin; GC, gemcitabine and cisplatin; HD, high-dose; PCG, paclitaxel, cisplatin and gemcitabine.

Source: Adapted from Figure 3 of Bellmunt et al 2014 for the European Society for Medical Oncology

Note: While not included in the figure above (likely reflecting its use in the first-line setting), gemcitabine appears to be widely used and indicated as a potential treatment option in Australia (as also confirmed by the local expert survey; see Attachment A of the submission). Its use is also recommended by other treatment guidelines reviewed in the submission (in Section A.5 of the Commentary).

5 Comparator

5.1 The re-submission presented two comparators:

- BSC; it was previously considered by PBAC to be an appropriate comparator to determine efficacy of vinflunine, but not relevant in Australian clinical practice.
- 'Active chemotherapy' defined as 'the set of replaced interventions in an Australian clinical setting'.
- The re-submission acknowledged that active chemotherapy is the treatment most likely to be replaced in clinical practice should vinflunine be included on the PBS, and therefore should be the main comparator (re-submission p2). For the financial forecasts it was assumed that vinflunine would replace chemotherapy in 80% of patients and BSC in 20% of patients. The re-submission considered, because the cost effectiveness of these active chemotherapy agents in the treatment of TCCU is

unknown, and because it is not possible with the available evidence to assess their cost-effectiveness, that the cost-effectiveness of vinflunine can only be established based on a comparison with BSC. The Pre-Sub-Committee-Response (PSCR, p1) argues that in the absence of evidence for the efficacy of chemotherapy agents, the comparison of vinflunine versus BSC is the most relevant for PBAC decision making. The ESC considered that comparisons against both active chemotherapy and BSC were relevant.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The key clinical evidence (Study 302) presented in the re-submission was a head-to-head trial comparing vinflunine + BSC with BSC (n=370). This trial was presented in the previous submission.

6.4 Additional clinical evidence presented in the resubmission:

- 20 single arm studies assessing active chemotherapy in patients with TCCU who have failed prior platinum-based chemotherapy in an advanced/metastatic setting. These studies assessed gemcitabine monotherapy (3 studies), gemcitabine combination (6 studies), taxane-based regimens (7 studies) and MVAC (methotrexate / vinblastine / adriamycin / cisplatin) or modified MVAC (4 studies).
- 3 vinflunine observational single arm studies.

6.5 Details of the key trial presented in the re-submission are provided in the table below.

Table 2: Trials and associated reports presented in the re-submission

Trial	Reports	Publication citation
Included study		
Study 302	<p><u>Study reports</u> Prospective, Randomised phase III Trial of IV Vinflunine plus Best Supportive Care as Second-Line Therapy versus Best Supportive Care after a Platinum-containing Regimen, in Patients with Advanced Transitional Cell Carcinoma of Urothelial Tract: Final Report.</p> <p><u>Publications</u> Bellmunt, J., Theodore, C., 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." (November 2006 analysis)</p> <p>Bellmunt, J., et al. "Long-term survival results of a randomised phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy." (November 2008 analysis)</p> <p>Bellmunt Molins, J., et al. "Randomised phase III trial of vinflunine (V) plus best supportive care (B) vs B alone as 2nd line therapy after a platinum-containing regimen in advanced transitional cell carcinoma of the urothelium (TCCU)."</p> <p>Bellmunt, J., Choueiri, T. K., et al. "Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens."</p> <p>Von Der Maase, H., James, N., 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)."</p> <p>Harshman, L. C., et al. "The impact of prior platinum therapy on survival in patients with metastatic urothelial cancer receiving vinflunine."</p>	<p>December 2007 (November 2006 analysis) CSR</p> <p>Journal of Clinical Oncology (2009) 27(27): 4454-4461</p> <p>Annals of oncology (2013) 24.6 (2013): 1466-1472 ^a</p> <p>ASCO Annual Meeting Proceedings (2008) Vol. 26. No. 15_suppl</p> <p>Journal of Clinical Oncology (2010) 28(11): 1850-1855</p> <p>Annals of Oncology (2008) 19(S8): viii202</p> <p>British journal of cancer (2013) 109.10: 2548-2553^a</p>

Source: Table 19, p63 of the re-submission. Note: ^a new publications since the November 2011 submission.

6.6 The key features of the direct randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Vinflunine + BSC vs BSC						
Study 302	370	R, OL, MC, Median follow-up: vinflunine + BSC = 42 months; BSC = 45 months	Low	Failed platinum based chemotherapy (first-line); PS 0 or 1; not received adjuvant/neoadjuvant chemotherapy treatment.	OS, PFS, EORTC QLQ-C30	Used

DB, double blind; MC, multi-centre; OL, open label; OS, overall survival; PFS, progression-free survival; R, randomised; QoL, quality of life. Source: compiled during the evaluation

Comparative effectiveness

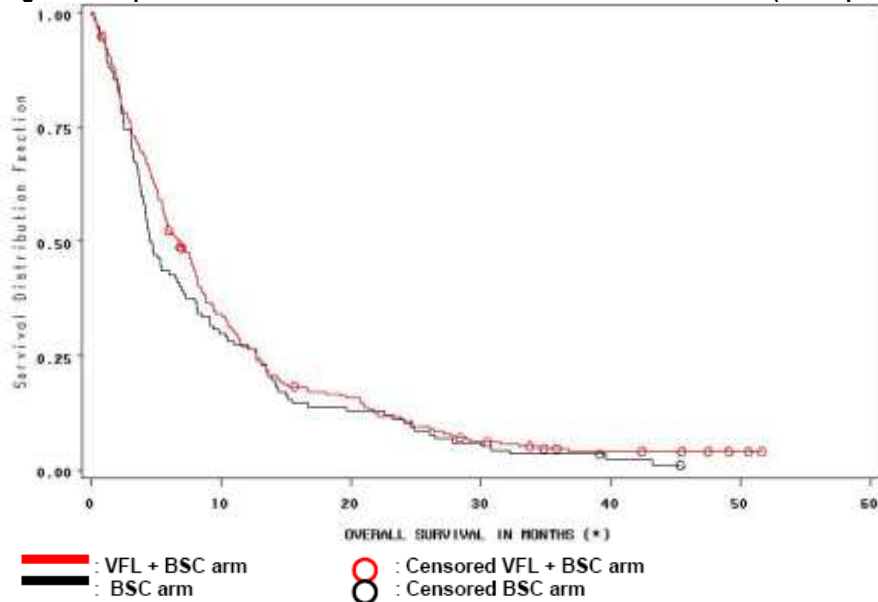
6.7 OS results from Study 302 are summarised in Table 4 and the accompanying figures for the ITT and mITT populations.

Table 4: Results of OS in the direct randomised trial

	ITT		Modified ITT	
	VFL + BSC N=253	BSC N=117	VFL + BSC N=249	BSC N=108
OS analysis (Cut-off 30 Nov 2008)				
No. of events	237	115	234	108
No. censored (%)	16 (6.3)	2 (1.7)	15 (6.0)	0
Median (95% CI) (months)	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	0.2613		0.0227	

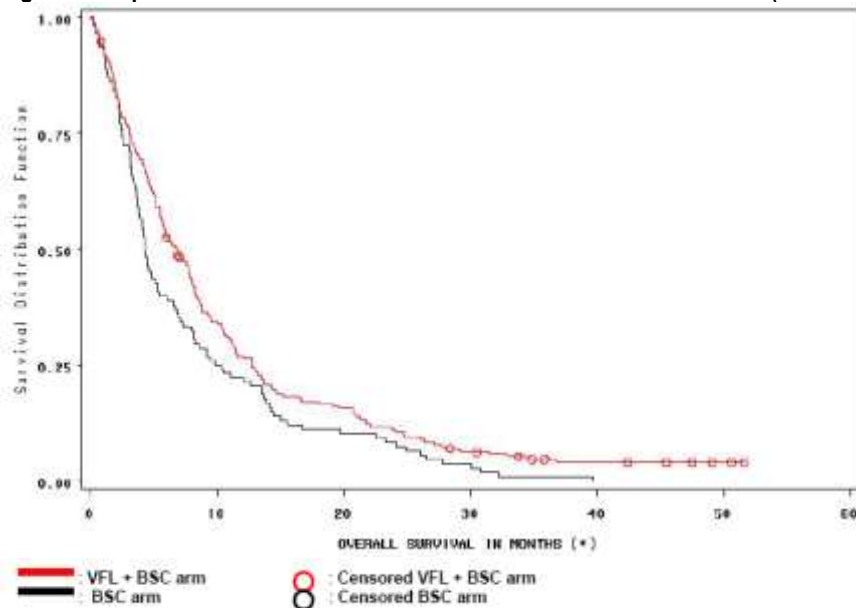
Abbreviations: VFL, vinflunine; BSC, best supportive care; HR, hazard ratio; CI, confidence interval.
Source: Table 37, p97 of the re-submission. Statistically significant HR values noted in **bold**.

Figure 2 Kaplan Meier curve of overall survival at November 2008 cut-off (ITT Population)



Source: Figure B6.1 of the Commentary. Figure 8 of the re-submission, p97, of the re-submission

Figure 3 Kaplan Meier curve of overall survival at November 2008 cut-off (modified ITT Population)



Source: Figure B.6.2 of the Commentary. Figure 7 of the re-submission, p98 of the re-submission

- 6.8 The mITT population excluded 13 patients (4 [1.6%] from the vinflunine + BSC arm and 9 [7.7%] from the BSC arm) post-randomisation who did not meet the key trial inclusion and exclusion criteria. The re-submission considered the mITT population is the most relevant population (and hence is used in the economic evaluation) because the 13 excluded patients would not be eligible under the proposed PBS listing. Excluding the 13 patients reduced the OS for the BSC arm relative to that for the vinflunine + BSC arm because the average OS for the excluded patients was longer for patients in the BSC arm (23.4 vs 8.4 months).
- 6.9 The potential for bias for the mITT analysis is high as the patients were excluded post-hoc. The PBAC's previous concern regarding the 13 patients receiving treatment in a clinical trial setting (despite the trial inclusion and exclusion criteria) and therefore being likely to also receive treatment in practice (despite the PBS listing criteria) remains valid.
- 6.10 A multivariate analysis for OS was included in the PSCR for the November 2011 submission and a similar analysis was included in the re-submission. For this analysis the difference in OS for the two treatment groups was statistically significant using the ITT population (HR 0.72, 95% CI 0.57, 0.91, $p=0.0052$) and the mITT population (HR 0.63, 95% CI 0.50, 0.80, $p=0.0002$). The reduction in the HR for the multivariate analysis appears to be due to adjusting for the imbalance in PS across the treatment arms at baseline. The PBAC previously noted that the results of the multivariate analysis 'demonstrated that potential differences in the prognostic factors from excluding the 13 ineligible patients did not alter overall survival in the eligible ITT' (section 8, p4, November 2011, PBAC PSD, Item 5.3).

- 6.11 The single arm studies differed with respect to chemotherapy regimens and criteria regarding prior treatment. The median OS for the active chemotherapy agents ranged from 3.1 to 12.6 months (gemcitabine monotherapy: 5 to 12.6 months; gemcitabine combination regimens: 7.7 to 12.4 months; taxane-based regimens: 4 to 12.5 months; MVAC/accelerated MVAC: 3.12 to 11.3 months) (see Attachment B of the commentary). The median OS for vinflunine in the observational studies was 7.7 to 10 months. In Study 302 the median OS for the vinflunine group was 6.9 months.

Comparative harms

- 6.12 A summary of the adverse events reported in Study 302 is presented in Table 5.

Table 5: Results of AEs in the direct randomised trial

	VFL+ BSC (N=248)	BSC (N=117)	VFL+BSC vs. BSC			Initial VFL dose 280 mg/m ² (N=182)	Initial VFL dose 320 mg/m ² (N=66)
			RR (95% CI)	RD (95% CI)	NNH (95% CI)		
AEs	248 (100.0)	117 (100.0)	1	0	n.c.	182 (100.0)	66 (100.0)
SAEs	153 (61.7)	55 (47.0)	1.31 (1.06, 1.63)	0.15 (0.04, 0.26)	6.81 (26.32, 3.91)	113 (62.1)	40 (60.6)
Deaths within 30 days ^a	28 (11.3)	27 (23.1)	0.49 (0.30, 0.79)	-0.12 (-0.20, -0.03)	-8.48 (-4.90, -31.25)	25 (13.7)	3 (4.5)
AEs leading to discontinuation	56 (22.6)	8 (6.8)	3.30 (1.63, 6.70)	0.16 (0.09, 0.23)	6.35 (11.36, 4.41)	40 (22.0)	16 (24.2)

Abbreviations: AE, adverse event; RR, relative risk; RD, risk difference; NNH, number needed to harm; VFL, vinflunine; BSC, best supportive care; SAE, serious adverse event; CI, Confidence Interval; n.c., not calculable.

Notes: a Within 30 days of the last dose (VFL+BSC group) or within 30 days of the last visit (BSC group).

Source: Table B.6.3, of the commentary

- 6.13 The adverse events that were experienced by at least 10% of the patient population, and at a statistically significantly higher rate 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 at higher rates in the vinflunine arm were abdominal pain, constipation, nausea, vomiting, fatigue, infections and infestations, anorexia, myalgia and headache.
- 6.14 One death due to pancytopenia was reported as directly related to vinflunine. Sixteen patients (6%) in the vinflunine 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.
- 6.15 The re-submission stated in comparison to gemcitabine monotherapy, gemcitabine combination regimens, taxane regimens and MVAC, 'the safety profile of vinflunine is

relatively mild' (re-submission, Attachment A, p25). A systematic comparison of the specific AEs and their incidence was not presented in the re-submission.

- 6.16 The PSCR (Table 1) provided a comparison of grade 3/4 AEs in Study 302 and studies of active chemotherapy. The ESC noted that rates of grade 3/4 neutropenia (50%), thrombocytopenia (5.7%) and anaemia (19%) (though not provided in the table but extrapolated from the study report) and non-haematologic AEs for vinflunine were within the range of grade 3/4 AEs reported for studies of active chemotherapy. The PSCR (Table 2) also provided a comparison of grade 3/4 AEs between Study 302 and observational studies of vinflunine, which did not find worse AEs in a non-trial setting. The ESC however disagreed with the assertion that 'the safety profile of vinflunine is relatively mild'.

Benefits/harms

- 6.17 A summary of comparative benefits and harms for vinflunine + BSC versus BSC is presented in the Table 6.

Table 6: Summary of comparative benefits and harms for vinflunine + BSC and BSC

Benefits						
OS: Study 302, November 2008 cut-off, ITT						
	VFL + BSC	BSC	Absolute Difference	HR (95% CI)		
Survival*	237/253	115/117	-	0.88 (0.70, 1.10)		
Median (mths)	6.9 (5.7, 8.0)	4.6 (4.1, 7.0)	2.3	-		
OS: Study 302, November 2008 cut-off, mITT						
	VFL + BSC	BSC	Absolute Difference	HR (95% CI)		
Survival*	234/253	108/117	-	0.78 (0.61, 0.96)		
Median (mths)	6.9 (5.7, 8.0)	4.3 (3.8, 5.4)	2.6	-		
Harms						
	VFL + BSC	BSC	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				VFL + BSC	BSC	
Study 302 (all patients evaluable for safety), Grade 3 or 4 events only						
Febrile neutropenia	15/248	0	14.69 (0.89, 243.43)	6.0	0	0.06 (0.03, 0.09)
Infections with severe neutropenia ^a	16/248	0	9.95 (0.59, 168.40)	6.5	0	0.04 (0.01, 0.07)
Myocardial infarction/ischaemia	10/248	0	9.95 (0.59, 168.40)	4.0	0	0.04 (0.01, 0.07)

*Median duration of follow-up: Study 302 = 42 months (vinflunine + BSC arm) and 45-months (BSC arm).

Abbreviations: PBO, placebo; RD, risk difference; RR, risk ratio. Note: a, clinically relevant infections (potential bacterial origin)

Source: Compiled during the evaluation, Table B.6.3, of the commentary. Table 47, p115, of the re-submission.

- 6.18 On the basis of the head to head trial, the comparison of vinflunine + BSC and BSC did not result in a statistically significant difference in overall survival for the ITT population. With the exclusion of 13 patients who did not meet the trial inclusion or exclusion criteria from the analysis, the comparison of vinflunine + BSC and BSC resulted in:
- Approximately 2.6 months difference in median overall survival (November 2008 data cut-off).

- 6.19 On the basis of the head to head trial presented, vinflunine + BSC is more likely to cause serious adverse events; per 100 patients treated, 15 are more likely to have a serious adverse event. The events included febrile neutropenia, infections with severe neutropenia and myocardial infarction/ischaemia.

Clinical claim

- 6.20 The re-submission described vinflunine + BSC as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC. The PBAC previously (Sections 9 and 12, pp4-6, November 2011, PBAC PSD, item 5.3):
- ‘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’;
 - ‘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’;
 - ‘agreed that vinflunine is inferior in terms of comparative safety over BSC’.
- 6.21 The re-submission described vinflunine + BSC as superior in terms of comparative efficacy and similar in terms of comparative safety over active chemotherapy, although it also noted that it is not possible to provide a reliable therapeutic claim for vinflunine versus active chemotherapy due to a lack of clinical evidence. The clinical claim is not adequately supported.
- 6.22 The PBAC noted the following issues:
- Superior efficacy of vinflunine versus active chemotherapy is not supported by the evidence. There are only single arm studies for the active chemotherapy comparator;
 - A systematic comparison of the safety of vinflunine and active chemotherapy was not presented in the re-submission, but was addressed in the PSCR, as discussed above. The ESC considered that the safety of vinflunine was likely to be similar to active chemotherapy.

Economic analysis

- 6.23 The economic evaluation included in the November 2011 submission was a cost-utility decision analysis comparing vinflunine + BSC with BSC alone. The re-submission presented a cost-utility analysis using a Markov model. However, a Markov process was not used to assign the cohort to the health states and the costs were calculated separately to the model. Thus the model presented in the re-submission is essentially the same as that presented in the November 2011 submission.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	Based on data from Study 302 with no extrapolation. In the model all patients were dead by 4.4 years in the vinflunine + BSC arm and by 3.9 years in the BSC arm.
Outcomes	LYG and QALYs
Methods used to generate results	Mean survival (PFS and OS) calculated from Kaplan Meier plots for Study 302. The estimates differed marginally compared with those in the November 2011 submission.
Health states	Progression free disease, progressive disease, death
Cycle length	21 days
Transition probabilities	Partitioned survival analysis used to calculate proportion of patients in each health state

Source: compiled during the evaluation

6.24 The key model drivers are summarised in Table 8 below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
mITT population	13 patients were excluded from the analysis population post hoc because they did not fulfil the key trial inclusion or exclusion criteria. The ESC considered that the ITT rather than the mITT was the appropriate analysis for determining cost-effectiveness.	High, favours vinflunine +BSC
Utility values – mapping algorithm	Utility values estimated by transforming the EORTC QLQ-C30 scores from Study 302 using the Rowen 2011 algorithm. <ul style="list-style-type: none"> • PFS for vinflunine + BSC: 0.75; PFS for BSC: 0.78 • Progressive disease: 0.71 In the November 2011 submission a different algorithm was used to transform the EORTC QLQ-C30 scores (McKenzie 2009). A justification for using the values derived using the Rowen algorithm was not included in the re-submission. These values are higher than those using the McKenzie algorithm. The ESC considered that the data from Rowen et al. is likely to be more sensitive to changes in quality of life, and is probably the better approach.	High, favours vinflunine+ BSC
Adverse Events - costing	Based on difference in the proportion of patients hospitalised in Study 302. Cost for treating AEs: Vinflunine + BSC = \$█████; BSC = \$█████ The cost of treating AEs associated with vinflunine has been underestimated because: <ul style="list-style-type: none"> • The proportion of patients hospitalised rather than the number of hospitalisations was used. • The costs for treating the more serious events were not included. • A higher cost has been used for AEs associated with BSC compared with AEs for vinflunine. • Only the cost of specialist visits has been included for AEs treated outside the hospital setting. The PSCR (p4) noted that this difference in costs was based on trial data which found the complexity and subsequent cost of hospitalisation was higher for BSC than vinflunine, e.g. due to more admissions for malignant neoplasm (30% vs 6% respectively). The ESC remained concerned that the uncertainty in cost favours vinflunine,	High, favours vinflunine + BSC
Utility values – pooling post-progression	Utility values in the vinflunine arm are pooled with those not receiving vinflunine post-progression. The appropriateness of pooling of utilities post-progression has not been adequately justified, and not pooling the utility values increases the ICER	Moderate, favours vinflunine + BSC

Source: compiled during the ESC and evaluation, Table D.6.1, of the commentary. Abbreviations: AE, adverse event; BSC, best supportive care; ITT, intention to treat; PFS, progression free survival.

- 6.25 The results of the economic evaluation for the re-submission and November 2011 submission are presented in the Table 9.

Table 9: Results of the stepped economic evaluation

Step and component	Vinflunine + BSC	BSC	Increment
Step 1: trial-based costs and outcomes (ITT population)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY	0.8484	0.7367	0.1117
Incremental cost/extra LY gained			\$ [REDACTED]
Step 2: trial-based costs and outcomes (mITT population)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY	0.8558	0.6399	0.2159
Incremental cost/extra LY gained			\$ [REDACTED]
Step 3: modelled evaluation (transformation of LYs to QALYs)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
QALY	0.6214	0.4692	0.1522
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 4: modelled evaluation (inclusion of costs for vinflunine administration, laxatives, PRT, treatment of AEs and specialist visits)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	0.8558	0.6399	0.2159
QALY	0.6214	0.4692	0.1522
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
November 2011 submission			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	0.849	0.643	0.207
QALY	0.495	0.380	0.115
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Table D.5.3, of the commentary. Abbreviations: LY, life years; QALY, quality of life years; BSC, best supportive care; PRT, palliative radiotherapy; AEs, adverse events.

The redacted table above shows a base case incremental cost of \$45,000 - \$75,000 per extra quality adjusted life years (QALY) gained.

- 6.26 The incremental LYG for the mITT population (Step 2, 0.2159) was almost double that for the ITT population (Step 1, 0.11), and consequently the cost/LYG was approximately halved for the mITT population (\$ [REDACTED] vs \$ [REDACTED]).
- 6.27 The cost/LYG in the resubmission (\$ [REDACTED]) was higher than in the 2011 submission (\$ [REDACTED]) primarily due to the higher incremental cost. The cost/QALYG in the re-submission (\$45,000 – \$75,000) was substantially lower than in the 2011 submission (\$ [REDACTED]) due to the higher utility values for the PFS (0.75/0.78 vs 0.61/0.64) and the progressive disease period (0.71 vs 0.56).
- 6.28 The sensitivity analyses indicated that the ICER is most sensitive to:

- The Study 302 population. Use of the ITT population rather than the mITT population increased the cost/QALYG from \$45,000 – \$75,000 to \$75,000 - \$105,000.
- The average number of vinflunine cycles. Reducing the average number of cycles from 4.2 to 3 reduced the cost/QALYG to \$15,000 - \$45,000. Increasing the average number of cycles to 6 increased the cost/QALYG to \$75,000 - \$105,000.
- The cost of treating AEs. Doubling the cost of treating AEs associated with vinflunine + BSC (from \$█████ to \$█████) but not changing the cost of treating BSC AEs (\$█████), increased the cost/QALYG to \$45,000– \$75,000.
- The utility values used. Use of the utility values from the November 2011 submission increased the cost/QALYG to \$45,000– \$75,000.
- The ESC considered pooling of utility data post-progression may not be inappropriate, and in this case bias the results in favour of vinflunine. Treatment-specific utility weights cause the ICER to increase to \$45,000– \$75,000/QALYG.

6.29 The BSC arm of the economic model was modified to estimate the cost/QALYG for vinflunine versus active chemotherapy. Assuming the PFS and OS with active chemotherapy is the same as for BSC, and safety of active chemotherapy is the same as for vinflunine, the cost/QALYG was \$15,000 - \$45,000. There are no clinical data to support the assumption of no difference in PFS and OS between active chemotherapy and BSC. While it is correct to compare vinflunine relative to active chemotherapy, the ESC considered that there was inadequate amount of data to give an informative assessment of the cost-effectiveness compared to active chemotherapy. Assuming the incremental gains in PFS and OS for active chemotherapy vs BSC are 50% of that for vinflunine vs BSC, the cost/QALYG was \$75,000 - \$105,000. If the incremental gains in PFS and OS with active chemotherapy are the same as for vinflunine, active chemotherapy dominates vinflunine.

Drug cost/patient/per year (average 4.2 cycles): \$█████

6.30 The dispensed cost per cycle for vinflunine is \$█████ based on the effective ex-manufacturer vial prices, the dose from Study 302 and 75% use in private hospitals ($1.56^1 \times \$█████ + 1.94^1 \times \$█████ + 0.75 \times \$█████ + 0.25 \times \$█████$).

6.31 The cost per patient per year was estimated in the November 2011 submission to be \$█████. This was based on the average vinflunine dose in Study 302, funding being capped at 3 cycles per patient and no wastage. A █████% price reduction was offered in the pre-PBAC Response for the November 2011 submission (p8, November 2011, PBAC Minutes, item 5.3).

Estimated PBS usage & financial implications

6.32 The submission was considered by DUSC.

¹ Mean number of vials estimated based on a dose of 289 mg/m² and a BSA of 1.86 m². The averages for the number of vials have not been rounded in the calculations.

- 6.33 The re-submission used an epidemiological approach to estimate the financial implications of listing vinflunine on the PBS. The approach used was the same as for the November 2011 submission although a number of the assumptions and inputs were revised.
- 6.34 The 6th Community Pharmacy Agreement which took effect on 1 July 2015, made some changes to the way chemotherapy preparation fees are paid under the Section 100 Efficient Funding of Chemotherapy (EFC) arrangement.

In addition, some chemotherapy compounders will be paid a smaller fee and the DPMA that is published in the schedule will only include that smaller fee.

Under the finalised new arrangements:

- a) The preparation fees paid to compounders who are licensed by the TGA to undertake such compounding are higher than those paid to compounders who are not licensed by the TGA, recognising that TGA licensed compounders incur additional costs in complying with the TGA's licensing requirements, as compared to chemotherapy compounders who are not TGA licensed;
- b) The preparation fee paid to TGA licensed compounders remains the same as under the 5th CPA at \$102.67* (indexed price for 2014/2015);
- c) The preparation fees paid to a s90 Community Pharmacy (incl s92 approved practitioners) and a s94 Approved Private Hospital Authority are the same as those paid to TGA licensed compounders to recognise the specialist nature of preparing chemotherapy medicines;
- d) The preparation fee paid to non-TGA licensed compounders is \$20 less at \$82.67.
- e) Where applicable, the \$20 portion of the preparation fee will be paid directly to the compounder through Australian Healthcare Associates (AHA); and.
- f) The \$20 is not currently captured by the DMPA that is published in the Schedule of Pharmaceutical Benefits.

As the majority of chemotherapy preparations are compounded in settings where the \$102.67 fee applies, this fee should continue to be used in PBAC submissions.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated (90% uptake)					
Number treated, Nov 2011 (90% uptake)					
Vials					
Vials, Nov 2011					
Estimated net cost to PBS/MBS					
Net cost to PBS (incl. cost offset for substituted therapies; excl. co-pay) ^a	\$	\$	\$	\$	\$
Net cost to PBS Nov 2011 (no cost offset for substituted therapies, excl. co-pay)	\$	\$	\$	\$	\$
Net cost to MBS ^b (for chemotherapy administration and PRT)	-\$313,767	-\$319,195	-\$324,607	-\$329,998	-\$335,376
Net cost to MBS, Nov 2011 (for chemotherapy administration only) ^c	\$144,819	\$146,698	\$148,821	\$151,198	\$153,839

Public Summary Document – November 2015 PBAC Meeting

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated total net cost					
Net cost to PBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/MBS, Nov 2011	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the evaluation. Tables E.2.3 and E.5.1, of the commentary. Note: a revised based on October 2015 price for gemcitabine, the number of cycles was reduced to 3.15, number of doses per cycle was increased to 3; b Includes the cost of PRT based on the MBS benefit (85% of the fee); c the November 2011 submission costed PRT based on AR-DRG cost weights and was not included with the MBS costs.

The redacted table above shows that the number of patients treated with vinflunine is estimated to be less than 10,000 per year at a net cost to the PBS of less than \$10 million per year.

- 6.35 The uptake for vinflunine (90%) has not been reduced from that in the November 2011 submission despite the additional restriction criteria of a PS ≤ 1 and no prior neoadjuvant/adjuvant chemotherapy. A substantial proportion of patients may have previously received neoadjuvant/adjuvant chemotherapy (estimated to be approximately 40% in the commentary) and hence the number of patients may be overestimated. Reducing the uptake to 50% reduces the net cost to the PBS in year 5 to \$ [REDACTED] less than \$10 million.
- 6.36 The November 2011 submission assumed that 50% of patients with advanced/metastatic TCCU are clinically fit for first-line chemotherapy. This was increased to 80% in the re-submission. Both of these estimates were informed by Expert Opinion, and the estimates being different highlight the uncertainty. Reducing the proportion to 50% reduces the net cost to the PBS in year 5 to \$ [REDACTED] m.
- 6.37 The net PBS cost was also sensitive to the average number of vinflunine cycles and the estimated proportion of patients progressing from local/regional to advanced/metastatic TCCU. The number of cycles was based on Study 302. The estimates in the published literature regarding the proportion of patients that progress vary widely (5-48%, the re-submission used 30%).
- 6.38 The estimated net PBS cost was lower in the re-submission compared with the November 2011 submission primarily due to including the cost-offset associated with the reduction in use of active chemotherapy (based on the cost of gemcitabine). At year 5, the estimated number of patients was [REDACTED] less than 10,000 and the net cost to the PBS would be \$ [REDACTED] less than \$10 million.
- 6.39 The DUSC considered that:
- There is potential for the number of eligible patients to be less than estimated in the re-submission because:
 - The declining incidence of bladder cancer in Australia was not accounted for.
 - The estimate for the proportion of patients with advanced/metastatic TCCU who are clinically fit for first-line chemotherapy was increased substantially from the November 2011 submission without justification (from 50% to 80%).

- The net PBS cost was sensitive to the estimated proportion of patients progressing from local/regional to advance/metastatic TCCU. The primary source of the estimate of 30% progression was not supplied and could not be verified.
- The proportion of patients with advanced/metastatic TCCU who are clinically fit for first-line chemotherapy, the proportion with a PS ≤ 1 and the vinflunine uptake are based on a survey of 3 oncologists. These estimates are uncertain. Thus, as noted by the PBAC for the 2011 submission, the estimated patient numbers are uncertain.
- The uptake for vinflunine (90%) has not been reduced from that in the November 2011 submission despite the additional restriction criteria of a PS ≤ 1 and no prior neoadjuvant/adjuvant chemotherapy. Thus the patient numbers may be overestimated.
- Additional sources of uncertainty include the number of treatment cycles per patient, the number of palliative radiotherapy episodes and net costs of best supportive care and adverse events, which were considered to be underestimated.

6.40 Overall, the DUSC considered that there is potential for the net cost/year for the PBS to be less than the estimate in the submission given that the number of eligible patients has potentially been overestimated. However, countering this, the PBS costs associated with treating vinflunine adverse events were not considered.

Quality Use of Medicines

6.41 The re-submission did not identify any issues relating to the quality use of medicines.

6.42 The DUSC identified that minimising risk of adverse events and hospitalisations may be an important consideration for patients in the context of a treatment with an adverse event pattern suggestive of high toxicity and a relatively small overall survival gain of less than three months.

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

Financial Management – Risk Sharing Arrangements

6.43 The re-submission stated a risk share agreement may be proposed to limit government exposure, particularly relating to vinflunine use beyond the proposed restriction in patients previously treated with neoadjuvant or adjuvant chemotherapy.

6.44 Relative to the previous submission, the re-submission has not included a proposed cap on the number of cycles of vinflunine received per patient. The previous submission proposed a cap of three cycles, compared to 4.2 per patient in Study 302. The ESC noted the change, but was not overtly concerned of substantial effect on cost-effectiveness or utilisation.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the Section 100 (Efficient Funding of Chemotherapy) listing of vinflunine (as ditartrate) for treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU) after failure of a prior platinum-containing regimen, on the basis of insufficient evidence of comparative clinical benefit compared to alternative treatments and a high and highly uncertain incremental cost-effectiveness ratio.
- 7.2 The PBAC noted the proposed restriction in the resubmission. The PBAC considered the clinical criterion of 'Patient must have failed a platinum-containing regimen for this condition' would more closely align with the TGA indication for vinflunine than the proposed wording. The PBAC recalled that patients who had received neoadjuvant or adjuvant treatment were excluded from the trial (Study 302). As neoadjuvant/adjuvant chemotherapy is recommended for the treatment of localised muscle-invasive tumours, the PBAC noted that this criterion would likely exclude otherwise eligible patients who may derive a benefit from the treatment with vinflunine.
- 7.3 In regards to the comparator, the PBAC noted that the ESC considered that comparisons against both active chemotherapy and BSC were relevant. The PBAC reiterated their view from November 2011 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.
- 7.4 The PBAC noted that the resubmission presented one randomised, unblinded trial (Study 302), as in the November 2011 submission, comparing vinflunine (280mg/m² or 320mg/m² 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.
- 7.5 The PBAC recalled at the November 2011 consideration that the Committee 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 patient's age (likely to be older in clinical practice), any previous radiotherapy, and impaired performance status may adversely affect 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 and at best less than 3 months, and this benefit is at the expense of significant toxicity. Therefore, the PBAC considered that there is insufficient evidence of a clinical place for vinflunine.

- 7.6 The PBAC reiterated their view from November 2011 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 ITT population more closely approximates the likely PBS population.
- 7.7 The PBAC considered that the resubmission had not supported a claim of superior efficacy of vinflunine versus active chemotherapy. The PBAC noted that:
- There are only single arm studies for the active chemotherapy comparator.
 - The patient populations in the 20 included studies varied with respect to chemotherapy regimens and criteria regarding prior treatment.
 - The median OS in the comparator studies (3.1 to 12.6 months) overlapped with the range reported for vinflunine (6.9 to 10 months).
- 7.8 The PBAC agreed with the ESC that the safety of vinflunine was likely to be similar to active chemotherapy.
- 7.9 In the economic analysis, the PBAC considered that the assumption of no difference in PFS and OS between active chemotherapy and BSC would likely overestimate the comparative efficacy of vinflunine in the model. In addition, the PBAC noted that the model was sensitive to the population used in the analysis. The PBAC recalled their view from the November 2011 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. In this resubmission, the PBAC noted that the use of the ITT population in a sensitivity analysis increased the cost/QALYG from \$45,000 - \$75,000 to \$75,000 - \$105,000.
- 7.10 The PBAC also noted the concerns of the ESC about the inputs of costs for treating adverse events into the model. The PBAC noted the toxicity profile of vinflunine and that doubling the cost of treating AEs associated with vinflunine + BSC (from \$ [REDACTED] to \$ [REDACTED]) but not changing the cost of treating BSC AEs (\$ [REDACTED]), increased the cost/QALYG from \$ [REDACTED] to \$ [REDACTED].
- 7.11 The PBAC noted that the resubmission estimated that [REDACTED] less than 10,000 patients would be treated over 5 years at a cost to PBS/MBS of \$10 - \$20 million. The PBAC noted that the DUSC considered that there is potential for the net cost/year for the PBS to be less than the estimate in the resubmission given that the number of eligible patients has potentially been overestimated, based on the proposed restriction. However, countering this, the PBS costs associated with treating vinflunine adverse events were not considered.
- 7.12 The PBAC considered that the following would need to be addressed in a major resubmission: assessment of the comparative clinical effectiveness and cost

effectiveness of vinflunine versus best supportive care using the ITT trial population, more rigorous assessment of the comparative clinical effectiveness and cost effectiveness of vinflunine versus active chemotherapy, updating the economic evaluation and revised financial estimates addressing the concerns of ESC and DUSC, particularly in regards to the cost of treating adverse effect associated with vinflunine. The PBAC considered, given uncertainty of clinical benefit compared to BSC and active chemotherapy, that a lower ICER/QALY would likely result in vinflunine being considered acceptably cost-effective.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

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

Pierre Fabre will continue to work with PBAC toward a listing for vinflunine.