PUBLIC SUMMARY DOCUMENT
Product: CABAZITAXEL, injection set containing 1 single use vial concentrate for I.V. infusion, 60 mg (anhydrous) in 1.5 mL with 1 single use vial diluent 4.5 mL, Jevtana®
Sponsor: Sanofi-Aventis Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application
The submission sought an Authority required listing for treatment of hormone refractory metastatic carcinoma of the prostate (mHRPC), in combination with prednisolone, in patients previously treated with a docetaxel-containing regimen.

2. Background
This drug had not previously been considered by the PBAC.

3. Registration Status
Cabazitaxel was TGA registered on 8 December 2011 for use in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

4. Listing Requested and PBAC's View
Authority Required
Treatment of hormone refractory metastatic carcinoma of the prostate in a patient previously treated with a docetaxel-containing regimen.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Prostate cancer is the most common cancer in Australian men and the second leading cause of male deaths due to cancer. The initial treatment choice is hormone therapy, however the disease often develops into metastatic hormone-refractory prostate cancer (mHRPC) as the tumour becomes androgen independent (hormone refractory). Docetaxel is currently used first line in the treatment of patients with mHRPC. Due to the nature of the disease, disease progression after initial chemotherapy treatment occurs frequently. Treatment options for mHRPC include secondary hormonal manipulations, palliative radiotherapy, chemotherapy and best supportive care. The submission states that mitozantrone is the most widely used drug in the second line setting. The submission proposed that cabazitaxel would provide an additional treatment option for second line therapy for mHRPC.

6. Comparator
The submission nominated mitozantrone as the main comparator. The PBAC agreed that this was appropriate.

7. Clinical Trials
The basis of the submission was one open-label randomised trial (TROPIC) comparing cabazitaxel 25 mg/m^2 once every three weeks plus prednisolone 10 mg daily with mitozantrone 12 mg/m^2 once every three weeks plus prednisolone 10 mg daily in patients with mHRPC with disease progression post docetaxel chemotherapy.

Publication details of the TROPIC trial and associated reports presented in the submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
TROPIC	A randomised, Open Label Multicenter Study of XRP6258 at 25mg/m^2 in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere®-containing regimen.	
De Bono JS, et al	Prednisolone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial.	*Lancet* 2010; 376: 1147-54.
Bouchet BP, et al	Cabazitaxel, a new taxane with favourable properties.	*Drugs of Today* 2010; 46(10): 735-742.

8. Results of Trials

The table below summarises the primary outcome of the TROPIC trial, overall survival.

Overall survival (ITT) in TROPIC

	Cabazitaxel/prednisolone (n=378)	Mitozantrone/prednisolone (n=377)
Number of deaths (%)	234 (61.9)	279 (74.0)
Number of patients censored (%)	144 (38.1)	98 (26.0)
Median OS (months) [95% CI]	15.1 (14.1–16.3)	12.7 (11.6–13.7)
Kaplan-Meier estimates for OS		
6 month estimate [95% CI]	**85.0% [81%, 89%]**	**80.0% [76%, 84%]**
12-month estimate [95% CI]	**64.0% [59%, 68%]**	**53.0% [48%, 58%]**
18-month estimate [95% CI]	**39.0% [33%, 44%]**	**28.0% [23%, 33%]**
Hazard Ratio: TPF/PF [95% CI]	**0.70 [0.59, 0.83]**	
Log-rank p value	<0.0001	

Bolded typography indicates statistically significant differences between treatment groups

Median overall survival was statistically significantly longer for patients treated with cabazitaxel than for those treated with mitozantrone (15.1 months versus 12.7 months; an incremental overall survival of 2.4 months ($p<0.0001$)). The hazard ratio was 0.70 (95% CI: 0.59, 0.83) in favour of cabazitaxel, corresponding to a 30% reduction in risk of death.

The table below summarises the adverse events reported in the TROPIC trial.

Summary of adverse events in the TROPIC trial

TROPIC Trial	CP N=371 n (%)	MP N=371 n (%)	RR (95% CI)
Patients with any TEAE	355 (95.7%)	328 (88.4%)	**1.08 (1.04,1.13)**
Patients with grade ≥3 TEAE	213 (57.4%)	146 (39.4%)	**1.46 (1.25, 1.70)**
Patients with any serious TEAE	145 (39.1%)	77 (20.8%)	**1.88 (1.49, 2.38)**
Patients discontinuation due to TEAE	68 (18.3%)	31 (8.4%)	**2.19 (1.47, 3.27)**
Patients with any TEAE leading to death	19 (5.1%)	17 (4.6%)	1.12 (0.59, 2.12)
- AE other than disease progression	18 (4.9%)	7 (1.9%)*	**2.57 (1.09, 6.08)**
- Disease progression reported as AE	1 (0.3%)	9 (2.4%)	**0.11 (0.01, 0.87)**
- Disease progression, hepatic failure	0 (0.0%)	1 (0.3%)	0.33 (0.01, 8.16)
Patients with AE of grade ≥1	355 (95.7%)	328 (88.4%)	**1.08 (1.04,1.13)**
Patients with AE of grade ≥2	316 (85.2%)	258 (69.5%)	**1.22 (1.13, 1.33)**
Patients with AE of grade ≥3	213 (57.4%	146 (39.4%)	**1.46 (1.25, 1.70)**
Patients with AE of grade ≥4	99 (26.7%)	47 (12.7%)	**2.11 (1.54, 2.89)**
Patients with AE of grade ≥5**	19 (5.1%)	17 (4.6%)	1.12 (0.59, 2.12)

TEAE = Treatment Emergent Adverse Event; CP = Cabazitaxel + Prednisone/Prednisolone;
MP = Mitozantrone + Prednisone/Prednisolone

* Five patients died due to disease progression coded as adverse events and one patient died because of a motor vehicle accident. ** TEAE including Disease Progression reported as an AE

A statistically significantly greater number of patients treated with cabazitaxel reported treatment emergent adverse reactions (TEAEs), TEAEs grade ≥3, serious TEAEs and TEAEs leading to discontinuation. A significantly higher incidence of neutropenia (RR=3.04; 95% CI: 2.00, 4.62), febrile neutropenia (RR=5.60; 95% CI: 2.19, 14.34) and diarrhoea (RR=23.00; 95%CI: 3.12, 169.43) was reported in patients treated with cabazitaxel.

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

9. Clinical Claim

The PBAC considered that the submission's claim that cabazitaxel is superior in terms of comparative effectiveness and inferior in terms of comparative safety over mitozantrone was reasonable.

10. Economic Analysis

The submission presented a stepped economic evaluation, based on the TROPIC trial. The type of economic evaluation presented was a cost-utility analysis.

The submission presented a 5-state Q-TWiST analysis of patient level data to determine the time spent in each of the five health states during the clinical trial period:

- Time with treatment response and toxicity;
- Time with treatment response without toxicity;
- Time without response or progression but with toxicity;
- Time without response or progression or toxicity; and
- Disease progression.

Treatment response in the Q-TWiST was defined as PSA (Prostate Specific Antigen) response and disease progression was defined as the earliest occurrence of pain, PSA increase or tumour progression from the trial data.

Overall survival was extrapolated by fitting Weibull distributions to patient level data in each arm of the TROPIC trial.

Quality-adjusted time spent in each health state was derived by applying utilities relevant to each health state to the time spent in that state

The costs included in the modelled economic evaluation included:

- second-line drug and administration costs;
- second-line adverse event costs - only costs associated with hospitalisation of adverse events of grade 3 or greater;
- second-line non-drug costs (excluding from adverse events);
- third-line chemotherapy costs.

The results of the base case modelled economic evaluation showed that cabazitaxel was associated with an incremental cost per extra quality adjusted life year (QALY) gained of between $75,000 and $105,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated in the submission to be in the range of $10–30 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC acknowledged that there was a clinical need for cabazitaxel for the second line treatment of hormone refractory metastatic prostate cancer in patients who have failed docetaxel and agreed that mitozantrone was the appropriate comparator.

The PBAC considered that the requested restriction should stipulate use of cabazitaxel in combination with prednisone/prednisolone, progression or intolerance to docetaxel rather than "patients previously treated with a docetaxel containing regimen", WHO status of 2 or less, no use of cabazitaxel beyond progression and no return to docetaxel after progression on cabazitaxel.

The key clinical trial in the submission was TROPIC, an open-label randomised trial comparing cabazitaxel 25 mg/m^2 once every three weeks plus prednisolone 10mg daily with mitozantrone 12 mg/m^2 once every three weeks plus prednisolone 10mg daily in patients with mHRPC with disease progression post docetaxel chemotherapy. The PBAC noted that the median survival was significantly longer for patients treated with cabazitaxel (15.1 months) than for those treated with mitozantrone (12.7 months), with an incremental overall survival of 2.4 months ($p<0.0001$). The hazard ratio was 0.70 (95% CI: 0.59, 0.83) in favour of cabazitaxel, corresponding to a 30% reduction in risk of death.

A statistically significantly greater number of patients treated with cabazitaxel reported treatment emergent adverse reactions (TEAEs), TEAEs grade ≥3, serious TEAEs and TEAEs leading to discontinuation. A significantly higher incidence of neutropenia (RR=3.04; 95% CI: 2.00, 4.62), febrile neutropenia (RR=5.60; 95% CI: 2.19, 14.34) and diarrhoea

(RR=23.00; 95%CI: 3.12, 169.43) was reported in patients treated with cabazitaxel. The PBAC noted that the submission did not include the costs of other PBS therapies likely to be co-administered and/or prescribed for the treatment of adverse events with cabazitaxel and that the cost of cabazitaxel is therefore likely underestimated in the submission.

Cabazitaxel is associated with higher rates of neutropenia and patients on cabazitaxel are much more likely to require G-CSF. Without G-CSF, the treatment outcomes are also likely to be less favourable. Inclusion of G-CSF costs is likely to increase the ICER. Further there were differences across trial sites in the deaths due to neutropenic complications, with these being less in settings where neutropenia was managed with G-CSF. The cost of treating neutropenic complications was not factored into the model and this would also potentially increase the ICER

There was an early inflexion in the Kaplan Meier curve of cabazitaxel as a result of several early deaths due to neutropenic complications. More cycles of cabazitaxel were given compared with mitozantrone (5.96 versus 4.6) and greater toxicity is seen with cabazitaxel. The PBAC noted that the trial protocol allowed only one dose reduction but that this did not reflect current clinical practice where further dose reductions are likely to occur or treatment may be delayed. The PBAC noted that this is not captured in the sensitivity analysis, and that this increased uncertainty in relation to the estimated survival advantage. the PBAC noted that the number of cycles is likely to be higher in the Australian setting and as the economic model is sensitive to the number of treatment cycles, the PBAC considered that the ICER is likely to be higher than estimated in the submission.

The PBAC agreed that the clinical claim that cabazitaxel is superior in terms of comparative effectiveness and inferior in terms of comparative safety over mitozantrone is reasonable.

The PBAC noted that the economic evaluation presented a Q-TWiST analysis of patient level data to determine the time spent in each of the five health states during the clinical trial period. Overall survival was extrapolated by fitting Weibull distributions to patient level data in each arm of the TROPIC trial. The PBAC considered that the incremental median survival of 2.4 months captured the early toxicity and death. However, the PBAC considered that the cabazitaxel Weibull function appeared to overestimate the extrapolated incremental mean overall survival (4.26 months) which was attributed to difference in progression-free survival. At the 30 month time point all patients had progressed at the end of the trial and few patients were alive (16.9% of cabazitaxel and 8.9% mitozantrone). The average survival gain per patient over 30 months was 3.18 months. The PBAC noted that the mean within-trial survival for cabazitaxel (3.2 months) presented in the sponsor's Pre-PBAC Response is quite different from the median (2.4 months), unlike the mean and median within-trial survival for docetaxel in the first-line mHRPC setting, which is very similar (2.3 months versus 2.4 months respectively). The PBAC concluded that the Weibull function appears to underestimate survival in some parts of the curve and over-estimate in other parts, and therefore is relatively uncertain. The PBAC noted that the extrapolation of the model from 30 months to lifetime has a huge impact on the ICER.

The extrapolated incremental mean overall survival gain of second-line mHRPC cabazitaxel versus mitozantrone (4.26 months) is also compared with that of first-line mHRPC docetaxel versus mitozantrone (3.73 months) in the sponsor's Pre-PBAC Response. However, most of the 4.26 months for patients receiving cabazitaxel is spent in the progressive disease state

(3.14 months) which was not the case for patients treated with docetaxel, where the greatest proportion of the 3.73 months gain in extrapolated mean overall survival was spent in the TWIST state (no toxicity and no progression). Therefore, the PBAC considered that most of the gain with cabazitaxel is beyond the trial period and is based on time spent in the terminal or end of life phase of the disease.

In the TROPIC trial no G-CSF was given in the first cycle of treatment and was administered at the discretion of the treating clinician for subsequent cycles. Neutropenic complications were lower in centres that used G-CSF. The PBAC considered that without G-CSF supportive therapy, efficacy may be reduced due to lower starting and subsequent doses of cabazitaxel being administered to reduce the likelihood of toxicity. Alternatively, a larger number of patients receiving cabazitaxel in the Australian setting would be co-prescribed G-CSF. However, as G-CSF is currently not PBS subsidised for patients receiving chemotherapy for prostate cancer the PBAC noted that there may be issues with equity of access.

The sponsor's Pre-PBAC response addressed the issue regarding the inclusion of G-CSF in the modelled economic evaluation which increased the ICER by about 1%. However, as the early adverse events due to neutropenic complications, and neutropenia adverse events and complications were less common when G-CSF was used, the PBAC considered that the addition of this trial based cost may understate the impact on the ICER, as G-CSF use was reported in TROPIC to be in 10.9% of cycles and use is likely to be considerably higher in clinical practice in Australia.

The PBAC considered that the utility states may also be overestimated as the utility values are derived from vignettes designed for first-line mHRPC patients and there may be key quality of life differences between first- and second-line therapy that will not be captured in these vignettes (the study was conducted in a general population sample). The PBAC noted that the ICER is very sensitive to the QALY weights as evidenced by the large difference in the incremental cost per life year gained ($45,000 - $75,000) and incremental cost per quality-adjusted life year gained ($75,000 - $105,000). In view of the issues raised above, the PBAC considered these ICERs to be uncertain.

The PBAC considered that it was highly likely that lower doses would be required in clinical practice due to toxicity and therefore considerable wastage would result from only a 60mg vial being available.

The PBAC considered that the 43% uptake rate of cabazitaxel is an overestimation and that the increase in significant adverse events for many patients will limit the suitability of this treatment.

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

The PBAC also acknowledged and noted the consumer comments received in its consideration of cabazitaxel.

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

Sanofi is disappointed by this decision but is committed to continuing to work with the PBAC to ensure that Jevtana is made available on the PBS for Australian men who have prostate cancer.