

**Economic Evaluation of cabazitaxel (Jevtana<sup>®</sup>) for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with docetaxel-containing treatment regimen.**



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1. Cabazitaxel (Jevtana<sup>®</sup>), in combination with prednis(ol)one, is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer (mHRPC) previously treated with a docetaxel-containing treatment regimen. Cabazitaxel is suitable for in-hospital administration only. In November 2011, Sanofi submitted an economic evaluation on the cost-effectiveness of cabazitaxel to the National Centre for Pharmacoeconomics (NCPE).
2. The submission evaluates the cost-effectiveness of cabazitaxel (in combination with prednis(ol)one 10mg daily) for the treatment of patients with mHRPC previously treated with docetaxel-containing treatment regimen. Cost-effectiveness is demonstrated using a cohort Markov model. Efficacy and safety data were based directly from the TROPIC trial <sup>[1]</sup>. Parametric functions were fitted to trial event rates to extrapolate overall survival (OS) and progression free survival (PFS) beyond the trial cut-off date to a lifetime horizon (14.4 years).
3. TROPIC was an open-label randomised phase III trial in men ( $\geq 18$  years) with mHRPC who had received previous hormone therapy, but whose disease had progressed during or after treatment with a docetaxel-containing regimen. Participants were randomized to receive 10 mg/day of prednisone with three-weekly mitoxantrone 12 mg/m<sup>2</sup> or three-weekly cabazitaxel 25 mg/m<sup>2</sup>. In total 755 men (ECOG performance score = 0-2) were included in the intention-to-treat analysis (377 mitoxantrone, 378 cabazitaxel). Median follow-up was 12.8 months. Median number of treatment cycles was six for cabazitaxel and four for mitoxantrone. The primary endpoint was OS; secondary endpoints included PFS, response rate, pain measures and safety. At the cut-off date for analysis, 234 and 279 deaths had occurred in the cabazitaxel and the mitoxantrone groups respectively. The median OS was 15.1 months with cabazitaxel and 12.7 months with mitoxantrone (hazard ratio (HR) =0.70; 95%CI 0.59, 0.83;  $p < 0.0001$ ). Median PFS was 2.8 months (95% CI 2.4, 3.0) in the cabazitaxel group and 1.4 months (95% CI 1.4, 1.7) in the mitoxantrone group (HR=0.74; 95%CI 0.64, 0.86;  $p < 0.0001$ ).

The most frequent clinically significant grade 3/4 adverse events were neutropenia (cabazitaxel (82%) vs. mitoxantrone (58%)) and diarrhoea (6% vs. <1% respectively). Febrile neutropenia occurred in 8% and 1% of the cabazitaxel and mitoxantrone groups respectively. Death within 30 days of the last infusion occurred in 4.8% and 2.4% of the cabazitaxel and mitoxantrone groups respectively. The most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences <sup>[1]</sup>. An updated analysis performed almost six months after the trial cut-off date, when 585 deaths had occurred, reported median OS values similar to the previous analyses (HR for death 0.72; 95%CI 0.61, 0.84; p < 0.0001) <sup>[2]</sup>.

4. The basecase ICERs (full TROPIC population; ECOG performance score = 0-2) were €120,084/QALY and €81,474/LYG. The probability that cabazitaxel is cost-effective over the threshold range €20,000-€45,000/QALY is zero.
5. In clinical practice the drug may not be offered to patients with an ECOG performance score of 2 as they may not be well enough to tolerate the drug. The ICER fell to €113,766/QALY (€77,126/LYG) in the sub-group analysis of TROPIC patients with ECOG performance = 0-1 (who had received  $\geq 225$  mg/m<sup>2</sup> docetaxel).
6. The model result was particularly sensitive to the time horizon; the ICER reached €605,185/QALY when the time horizon was decreased to 1 year. The NCPE review group highlighted concerns in relation to the events in TROPIC being extrapolated to 14.4 years in the basecase evaluation.
7. The review team raised concerns that the utility values for the 'stable disease' (0.763) and 'progressive disease' (0.659) states appear to be high for patients with mHRPC given that the sex-matched/age-matched utility value observed in the UK general population is 0.78 <sup>[3]</sup>. A 20% decrease in the utility value for the progressive disease state increased the ICER to €140,486/QALY. Similarly the ICER increased to €127,310/QALY when the utility value of the 'stable disease' state was decreased by 20%.

The review team investigated the impact of giving greater weight to the QALYs achieved (assuming that the extended survival period is experienced at the full Health Related Quality of Life (HRQoL) anticipated for a healthy individual of the same age); a revised ICER of €105,734/QALY was obtained.

8. A decrease in the average cabazitaxel wastage per patient from 25% (in the original analysis) to 0% decreased the ICER to €90,995/QALY. The review team note that the concentrate and solvent vials must be used immediately once opened <sup>[4]</sup>. Hence, vial sharing may not be feasible in practice.
9. A pricing sensitivity analysis was presented. The incremental cost ranged from €99,979/QALY to €140,189/QALY (€67,837/LYG to €92,120/LYG) when the ex-factory price of cabazitaxel was varied by  $\pm 20\%$ .
10. The pharmacoeconomic evaluation included a budget impact (BI) estimate. The BI model estimated that a total of 22 mHRPC patients would be treated with cabazitaxel in 2012 increasing to 34 in 2016. The gross BI would increase from about €0.84 million in 2012 to about €1.3 million in 2016 (cumulative about €5.60 million). The net BI would increase from approximately €0.8 million in 2012 to about €1.2 million in 2016 (cumulative in the region of €5.02 million). The NCPE believe that the BI presented may be an underestimate.
11. On review, the NCPE believe that, at the submitted price, cabazitaxel is not cost-effective for the treatment of patients with mHRPC previously treated with a docetaxel-containing treatment regimen. The ICER remains well above both the €20,000/QALY and €45,000/QALY thresholds even when a greater weight to the QALYs is applied (assuming a full sex-matched/age-matched HRQoL).

## References

1. de Bono, J.S., et al., *Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial*. *The Lancet*, 2010. **376**(9747): p. 1147-1154.
2. de Bono, J.S., et al., *Cabazitaxel or mitoxantrone with prednisolone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC)*. *ASCO Annual Meeting. Chicago, USA, 2010*. 2010.
3. Kind, P., G. Hardman, and S. Macran, *UK population norms for EQ-5D, Working Papers 172chedp, Centre for Health Economics, University of York*. 1999.
4. *Jevtana® (cabazitaxel). Summary of Product Characteristics. Sanofi-Aventis. Available at <http://www.medicines.org.uk/emc/medicine/24431/SPC/jevtana/> [Accessed 2012 February 28]*.