# Sponsor submission to the National Institute for Health and Clinical Excellence:

# Taxotere® (docetaxel) in Metastatic Hormone Refractory Prostate Cancer (mHRPC)

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# 1 EXECUTIVE SUMMARY

- With over 30,000 cases in 2001, prostate cancer is now the most common cancer affecting men in the UK [a]. In 2003, around 10,000 deaths were attributed to prostate cancer making it second only to lung cancer as a cause of cancer-specific death [a]. It is a disease that largely affects older men with more than 60% of cases diagnosed in patients over 70 [a].

- Hormonal therapy is the cornerstone of treatment for advanced or metastatic prostate cancer but it becomes increasingly ineffective and most patients will develop metastatic hormone refractory prostate cancer (mHRPC) [b, c]. Once progression has occurred, prognosis is dismal [c] and there is no current treatment option other than palliation of symptoms.

- There is a clear unmet need for an active treatment that can extend the survival between failure of hormonal therapy and terminal stages of the disease.

- Metastatic HRPC has long been regarded as a disease that is unresponsive to chemotherapy [c]. However, studies with mitoxantrone have demonstrated that chemotherapy can provide effective palliation [d, e]. Phase II studies demonstrated that docetaxel is highly active in mHRPC and consequently large, randomised phase III studies were initiated.

- The registration study (TAX 327) compared the combination of docetaxel plus prednisone with the current international standard, mitoxantrone plus prednisone [f]. The supporting study, performed by the South West Oncology Group (SWOG 9916), compared docetaxel plus estramustine with the same standard therapy [g]. Overall survival was the primary endpoint of both trials, which also examined other important clinical features such as pain control, quality of life, PSA response and time to progression.

- The TAX 327 trial demonstrated a 24% reduction (95% confidence interval 0.62 to 0.94, p=0.009) in the risk of death for patients who received docetaxel 75 mg/m2 every three weeks compared with patients who received the standard mitoxantrone based therapy, which equates to an extra 2.4 months of life. Median survival was 18.9 months in the 3-weekly docetaxel group compared with 16.5 months in the mitoxantrone group. At 2 years the survival rate for patients in the docetaxel 3-weekly regimen was nearly 40% compared with less than 30% in the mitoxantrone arm [f]. The results from the SWOG 9916 study supported the findings from TAX 327 [g].

- Pre-defined levels of pain reduction were seen in 35% vs 22% of patients in the 3-weekly docetaxel and mitoxantrone groups, respectively (p=0.01). PSA responses of >50% reduction were seen in 45% of patients in the 3-weekly docetaxel group compared to just 32% in the mitoxantrone group (p<0.001). The stringent health-related quality of life assessment showed that the docetaxel 3-weekly regimen provided significant improvements in a greater number of patients compared with the standard mitoxantrone therapy (22% vs 13%, respectively [p=0.009]) [f].

- In both phase III studies adverse event reporting was increased in the docetaxel treatment groups. However adverse events, including neutropenia, nausea and vomiting, were manageable with standard clinical interventions [f, g].

- Existing treatments for mHRPC offer palliative relief and some health-related quality of life benefits. The TAX 327 study demonstrates that docetaxel is unique; in addition to providing palliative benefits, it significantly extends survival and improves health-related quality of life compared with the international standard of mitoxantrone-based therapy [f].

- An economic evaluation is included based on the patient population of the clinical study which is representative of the population likely to receive docetaxel in clinical practice in the UK.

- The perspective of this analysis is that of the UK NHS, and therefore only direct costs are considered. The objective of the economic evaluation described here is to evaluate the incremental cost-effectiveness of docetaxel plus prednisone compared to mitoxantrone plus prednisone in the UK, using an estimate of the mean difference in survival benefit.

- The efficacy data used are based on the TAX 327 clinical trial. Resource use data from all patients in the trial were analysed and costed using UK unit costs to generate an average lifetime cost per patient within each arm of the clinical trial. The differences in total costs were then used within the incremental cost-effectiveness ratio (ICER) calculation to generate a cost per life-year gained.

- From an economic perspective, the analysis presented suggests that in this context and in terms of cost per life-year gained, docetaxel plus prednisone offers reasonable value for money compared to using mitoxantrone plus prednisone, assuming the NHS is willing to pay £19,483 per life-year gained.

- Conclusion:

  — Prostate cancer is the most common cancer affecting men in the UK today and the second largest cause of cancer-related deaths. Hormone therapy is used to treat advanced and metastatic prostate cancer but in most cases it becomes ineffective and the patient develops refractory disease. mHRPC is currently managed by palliative measures and there is an unmet clinical need for therapies that can relieve symptoms, improve health-related quality of life and extend survival at the same time. Patients with prostate cancer generally have a poor experience compared with those with other cancers and the NHS prioritised prostate cancer within the NHS Cancer Plan [h]. A recent report from the National Audit Office shows that this situation has not yet improved [i]. New technologies will provide opportunities to improve the treatment of patients with prostate cancer.

  — Large randomised phase III clinical trials have demonstrated that docetaxel is highly effective and well tolerated in men with mHRPC. In addition to the palliation of symptoms, docetaxel improves health-related quality of life and extends survival compared with existing treatments.

  — Guidelines that are currently being drafted by the British Association of Urological Surgeons [j] specifically recommend the use of docetaxel as first-line treatment for patients with mHRPC. Patient opinion indicates that 80% consider improved survival to be the most important aspect of treatment [k] and groups within the NHS [l] have also recognised the benefits that docetaxel provides to patients with mHRPC. Several current clinical trials in mHRPC are using docetaxel as the standard arm.

— The data presented here demonstrate that docetaxel in combination with prednisone represents the best possible therapy for patients with advanced or metastatic prostate cancer who have failed hormonal therapy. Use of docetaxel in combination with prednisone is cost effective compared to treatment with mitoxantrone and prednisone and offers symptomatic control, maintenance of health-related quality of life and an extension to life expectancy. Consequently, docetaxel should be recommended for the treatment of patients with mHRPC.

*Reference material for the Executive Summary:*


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f Tannock I.F., de Wit R., Berry W.R., Horti J., Pluzanska A., Chi K.N., Oudard S., Theodore C., James N.D., Turesson I., Rosenthal M.A. & Eisenberger M.A. (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*, **351,** 1502.g Petrylak et al 2004

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i National Audit Office (2005) Tackling Cancer: Improving the Patient Journey.

j BAUS (2005) (British Association of Urological Surgeons) Proposed guidelines or treatment of prostate cancer.

k Prostate cancer research campaign UK (2005), Data on file.

l London Cancer New Drugs Group (2005) http://www.druginfozone.nhs.uk/.