NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Docetaxel for the treatment of hormone-refractory metastatic prostate cancer

1 Guidance

1.1 Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory metastatic prostate cancer only if their Karnofsky performance-status score is 60% or more.

1.2 It is recommended that treatment with docetaxel should be stopped:

- at the completion of planned treatment of up to 10 cycles, or
- if severe adverse events occur, or
- in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies.

1.3 Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.

2 Clinical need and practice

2.1 The prostate gland is present only in men. It is located just below the bladder exit, surrounding the urethra, and is subdivided into three zones: central, transition and peripheral. The peripheral zone, at the back of the prostate, is the part most susceptible to prostate cancer. The extent of prostate cancer is classified into stages I–IV. At stages I and II the disease is confined to the prostate. At stage III the tumour is more locally advanced and at stage IV either it is locally advanced and invading local adjacent structures, or it has associated distant metastases.

2.2 The growth of most prostate cancers is stimulated by testosterone, and hormonal therapies that modify levels of, or responses to, testosterone are

standard treatment for men with metastatic disease. Hormonal therapies are initially effective in 80% of men with metastatic prostate cancer, but after around 18 months the disease usually becomes unresponsive to hormone treatment and will progress.

2.3 Hormone-refractory metastatic prostate cancer is defined on the basis of biochemical testing (prostate-specific antigen, PSA), findings of imaging studies, or using clinical criteria of progressive metastatic disease despite castrate serum levels of testosterone.

2.4 Data on the epidemiology of hormone-refractory metastatic prostate cancer are limited; therefore inferences must be drawn from available data for prostate cancer. In the UK, prostate cancer is the most common male cancer, excluding non-melanoma skin cancer. In 2001 there were 26,067 new cases in England and 1746 in Wales, giving age-standardised incidence rates of 89.8 and 92.6 per 100,000 men respectively. Prostate cancer is the second most common cause of male cancer deaths, accounting for 13% of them. In 2003 there were 8582 deaths in England and 579 in Wales from prostate cancer, giving age-standardised mortality rates of 27.3 and 28.6 per 100,000 men respectively. It has been estimated that most of the deaths are in patients with hormone-refractory metastatic prostate cancer.

2.5 Prostate cancer is associated with substantial morbidity that can have a significant impact on the patients, and on their families and carers. Prostate cancer was responsible for almost 40,000 hospital episodes in the 2003–04 financial year, although it is unknown how many of these related to patients with hormone-refractory metastatic prostate cancer. The symptoms of hormone-refractory metastatic prostate cancer may be related to compression of the urethra, metastases to bone and other sites, and adverse effects of treatment. Urinary symptoms include difficulty starting the flow of urine, passing urine more often, and discomfort while passing urine. More than 90% of patients with late-stage prostate cancer develop metastases to bone, and this can cause debilitating and sometimes uncontrollable pain, pathological

fractures and spinal cord compression. Patients may receive surgery, radiotherapy, steroids and analgesics as well as hormonal treatment and chemotherapy, and they may suffer adverse effects related to all of these.

2.6 The primary risk factor for prostate cancer is increasing age: 90% of cases are in men older than 60, and 42% in men older than 75. Worldwide, the highest rates are observed in African-American men, with much lower rates seen in men of Asian origin. The cause of prostate cancer is probably multifactorial, involving environmental and genetic factors. Prostate cancer does not occur in castrated men, so testosterone is implicated. High levels of insulin-like growth factor (IGF-1), a protein involved in cell metabolism, may also be involved. About 9% of cases are thought to have a genetic component. Diets high in animal fats and dairy products appear to be associated with increased risk of prostate cancer.

2.7 The prognosis is poor for patients with hormone-refractory metastatic prostate cancer: survival is not expected to exceed between 9 and 12 months. Hormone-refractory metastatic prostate cancer cannot be cured. The aim of treatment is to improve symptoms, prolong life and slow progression of the disease.

2.8 There is no gold standard treatment for hormone-refractory metastatic prostate cancer in the UK. Clinical management is acknowledged to be multimodal rather than sequential and patients may receive a combination of palliative treatments.

2.9 Treatment options include second-line hormonal therapy, chemotherapy with or without corticosteroids, and best supportive care. The choice of therapy depends on the symptoms, the site of relapse, the performance status (see appendix D) of the patient and the presence of other comorbidities. Best supportive care can be provided with radiotherapy, bisphosphonates, steroids and analgesics, and is the only option for patients who are too ill to tolerate further active intervention. Tolerability of chemotherapy is of concern,

particularly because most patients with prostate cancer are elderly and many have other medical problems.

2.10 Chemotherapy regimens that have been used to treat the cancer include those based on mitoxantrone, estramustine and taxanes such as docetaxel. Mitoxantrone is widely used in the UK for hormone-refractory metastatic prostate cancer patients who are fit for chemotherapy, even though it is not licensed for this indication. The Institute has been informed by several consultees that a combination of mitoxantrone and prednisolone has come to be accepted as the standard care for this group of patients.

2.11 NICE's cancer service guidance 'Improving outcomes in urological cancers' states that chemotherapy should be considered for men with symptomatic hormone-refractory prostate cancer, trials of chemotherapy should be supported, and that palliative radiotherapy should also be available. There are a number of guidelines produced by professional organisations.

3 The technology

3.1 Docetaxel (Sanofi-Aventis) is an anti-neoplastic drug that belongs to a class of drugs known as taxanes. It works by disrupting the microtubular network that is essential for mitotic and interphase cellular functions, causing inhibition of cell division and cell death.

3.2 Docetaxel is licensed for use in combination with prednisone or prednisolone for the treatment of patients with hormone-refractory metastatic prostate cancer.

3.3 Docetaxel is administered as a 1-hour infusion once every 3 weeks. The recommended dose is 75 mg/m^2, with twice daily oral administration of prednisone or prednisolone at a dose of 5 mg.

3.4 Reported adverse effects of docetaxel include hypersensitivity reactions (presenting as flushing, skin reactions, hypotension and bronchospasm), bone marrow suppression (neutropenia, thrombocytopenia and anaemia),

cutaneous reactions, fluid retention, peripheral neuropathy, alopecia, cardiac disorders and tiredness. Contraindications include severe allergic reaction, low white blood cell count due to bone-marrow damage (myelosuppression), or severe liver disease. Premedication with a corticosteroid is usually recommended to help prevent allergic reaction. For full details of side effects and contraindications see the summary of product characteristics.

3.5 The net price of docetaxel (40 mg/ml) is £162.75 for a 0.5 ml vial and £534.75 for a 2 ml vial (excluding VAT; 'British national formulary', 50th edition). The cost per patient, assuming an average of seven cycles of treatment, would be approximately £8000. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 One randomised controlled trial (RCT) that investigated docetaxel within its licensed indications was identified (TAX327). In TAX327, docetaxel plus prednisone or prednisolone was compared with mitoxantrone plus prednisone or prednisolone.

4.1.2 TAX327 was an international, multicentre, open-label, phase III RCT. The trial enrolled 1006 men with metastatic prostate cancer with disease progression during hormonal therapy. The men were randomised to three chemotherapy arms, all of which received prednisone or prednisolone 5 mg orally twice daily. The chemotherapy regimens were: docetaxel at 75 mg/m^2 administered every 3 weeks (335 patients); docetaxel at 30 mg/m^2 administered weekly for the first 5 weeks in a 6-week cycle (334 patients); and mitoxantrone 12 mg/m^2 administered every 3 weeks (337 patients). Up to 10 cycles of treatment were planned for the 3-weekly docetaxel group and the mitoxantrone group, and up

to five cycles (of 6 weeks each) in the weekly docetaxel group. Patients in the docetaxel groups also received premedication with dexamethasone.

4.1.3 Patients were required to have a Karnofsky performance-status score (see appendix D) of at least 60%, and stable levels of pain for at least 7 days before randomisation. The median length of follow-up was 20.8 months for the 3-weekly docetaxel group and 20.7 months for the other two groups. The planned treatment was delivered to 98% of patients in the 3-weekly docetaxel group, 96% of patients in the weekly docetaxel group and 99% in the mitoxantrone group. There was a high level of crossover between groups; 27% of patients randomised to the 3-weekly docetaxel group received mitoxantrone and 20% of patients randomised to the mitoxantrone group received docetaxel.

4.1.4 Overall survival was the primary end point for the trial and was defined as the time from the date of randomisation to the date of death from any cause, or censored at the date of last contact. There was a statistically significant benefit in terms of overall survival for the 3-weekly docetaxel group compared with the mitoxantrone group, with a hazard ratio for death of 0.76 (95% confidence interval [CI], 0.62 to 0.94, p = 0.009). At the time of analysis 166/335 (50%) patients receiving 3-weekly docetaxel and 201/337 (60%) of patients receiving mitoxantrone had died. The median survival was 18.9 months (95% CI, 17.0 to 21.2) in the 3-weekly docetaxel group compared with 16.5 months (95% CI, 14.4 to 18.6) in the mitoxantrone group. There was no statistically significant difference in overall survival between the weekly docetaxel group and the mitoxantrone group, with a hazard ratio for death of 0.91 (95% CI, 0.75 to 1.11).

4.1.5 Quality of life response was defined as a 16-point improvement in score on the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire, compared with baseline, on two measures at least 3 weeks apart. There was a statistically significant benefit in terms of quality of life response observed for both the 3-weekly docetaxel group (22% [61/278]

response; 95% CI, 17 to 27%) and the weekly docetaxel group (23% [62/270] response; 95% CI, 18 to 28%) compared with the mitoxantrone group (13% [35/267] response; 95% CI, 9 to 18%), giving a relative risk of 1.67 (95% CI, 1.14 to 2.45, p = 0.009) for the 3-weekly docetaxel group, and 1.75 (95% CI, 1.20 to 2.56, p= 0.005) for the weekly docetaxel group. The responses to the FACT-P questionnaire were not mapped to utility values.

4.1.6 In TAX327 there was a statistically significant benefit in terms of pain response observed for the 3-weekly docetaxel group (35% [54/153] response; 95% CI, 27 to 43%) compared with the mitoxantrone group (22% [35/157] response, 95% CI, 16 to 29%), giving a relative risk of 1.58 (95% CI, 1.1 to 2.27).

4.1.7 In TAX327 a statistically significant benefit in terms of PSA response was observed for the 3-weekly docetaxel group (45% [131/291] response; 95% CI, 40 to 51%) compared with the mitoxantrone group (32% [96/300] response; 95% CI, 26 to 37%), giving a relative risk of 1.41 (95% CI, 1.14 to 1.73).

4.1.8 In TAX327 a higher proportion of grade 3 or 4 adverse events was reported in the 3-weekly docetaxel group (45.8%) than in the mitoxantrone group (34.6%). Adverse events were measured using the Common Toxicity Criteria of the US National Cancer Institute, version 2, and were reported for all 997 patients who received their planned treatment.

4.1.9 To allow for a comparison between docetaxel and relevant comparators other than mitoxantrone plus corticosteroid (for example, other chemotherapy regimens and best supportive care), the Assessment Group searched for RCTs in which other treatments were compared with mitoxantrone plus a corticosteroid, which could then be used as the common comparator. The Assessment Group performed a meta-analysis of the results from three RCTs comparing mitoxantrone plus a corticosteroid with corticosteroid alone. Although various health outcomes other than mortality were measured in those studies (including health-related quality of life and pain response in two of them), the only outcome suitable for the pooling of results was overall

survival. The pooled estimate of the hazard ratio for death for mitoxantrone plus corticosteroid versus corticosteroid was 0.99 (95% CI, 0.82 to 1.20). This was then compared indirectly, using appropriate statistical analysis, with that from the TAX327 study, giving an indirect hazard ratio for death for docetaxel plus a corticosteroid (prednisone or prednisolone) versus corticosteroid alone (prednisone, prednisolone or hydrocortisone), of 0.752 (95% CI, 0.567 to 0.999). The Assessment Report notes that results of the adjusted indirect comparison should be interpreted with caution because the underlying trials differed in patient population and methodology.

4.1.10 Two other RCTs that investigated the effects of docetaxel in combination with estramustine in patients with hormone-refractory metastatic prostate cancer were submitted in support of the efficacy of docetaxel and included in the Assessment Report. SWOG 9916 compared docetaxel plus estramustine versus mitoxantrone plus prednisone. A statistically significant benefit, in terms of overall survival, was observed for the docetaxel plus estramustine group compared with the mitoxantrone plus prednisone group, with a hazard ratio for death of 0.80 (95% CI, 0.67 to 0.97). Oudard and coworkers investigated two different regimens of docetaxel plus prednisone plus estramustine versus mitoxantrone plus prednisone. There was a non-statistically significant reduction in the relative risk of death for patients in the docetaxel groups. The median survival was longer in the docetaxel groups than in the mitoxantrone group, but the difference was not statistically significant.

4.2 Cost effectiveness

4.2.1 The manufacturer (Sanofi-Aventis) and the Assessment Group provided estimates of cost effectiveness. Some consultees commented on economic issues. The Assessment Group developed its own economic model and critiqued the model submitted by Sanofi-Aventis.

4.2.2 The Assessment Group's literature search did not yield any suitable cost-effectiveness studies of docetaxel-based treatment regimens. One study was

found that compared mitoxantrone and prednisone with prednisone alone and was based on the CCI-NOV-22 RCT. That study was used to inform the follow-up costs of the Assessment Group's economic model.

Summary of evidence of cost effectiveness from the manufacturer

4.2.3 The Sanofi-Aventis model estimates the incremental cost per life-year gained (LYG) from docetaxel plus prednisone or prednisolone compared with mitoxantrone plus prednisone or prednisolone. No adjustment is made for quality of life. The evaluation is based on an analysis of patient-level data derived from prospective collection of resource use and patient outcome data from the TAX327 trial. Only the 3-weekly regimen of docetaxel is considered in the analysis, in keeping with the licensed recommended dose. Two analyses are presented: the preliminary analysis uses the difference in median survival within the TAX327 trial as the measure of clinical benefit, and the base case uses an estimate of the mean difference in survival extrapolated beyond the trial period; data extrapolation is used to characterise the survival of patients beyond the period of follow-up in the trial. The sponsor submission states that in economic valuation, mean survival times are preferred to medians to provide the best estimate of relative cost effectiveness between two competing interventions. Uncertainty is considered using two different one-way sensitivity analyses, one related to the estimate of survival, and the other to that of costs per patient.

4.2.4 The base-case result of the Sanofi-Aventis model was £19,483 as the incremental cost per life year gained from docetaxel plus prednisone or prednisolone over mitoxantrone plus prednisone or prednisolone. In the preliminary analysis, the incremental cost per life year gained was £30,280.

Summary of economic evaluation undertaken by the Assessment Group

4.2.5 The Assessment Group model estimates the incremental cost per quality-adjusted life year (QALY) gained by using docetaxel plus prednisone or prednisolone compared with the least expensive of a number of treatment comparators not excluded by dominance or extended dominance. It is a

probabilistic model that was run for a time horizon of 15 years. A Markov model was used to estimate mean survival and incorporate discounting. Resource utilisation and cost data were estimated from the perspective of the NHS, based on the drug acquisition and administration costs for each intervention and subsequent follow-up costs including the management of side effects, further chemotherapies and palliative care. The Assessment Group undertook a systematic review of literature on measurement of the utility associated with the health-related quality of life of patients with hormone-refractory metastatic prostate cancer, and used this review to inform inputs to the model.

4.2.6 Two analyses were reported. Analysis 1 compares 3-weekly docetaxel plus prednisone or prednisolone, mitoxantrone plus prednisone or prednisolone, and best supportive care in the form of prednisone or prednisolone alone. Analysis 2 extends this comparison to include the full range of potential comparators identified in the clinical effectiveness review. In both base cases, and all reported sensitivity analyses, the relevant resulting incremental cost-effectiveness ratio (ICER) is that of 3-weekly docetaxel plus prednisone or prednisolone (the licensed regimen) compared with mitoxantrone plus prednisone or prednisolone (the cheapest non-dominated strategy). Uncertainty is characterised using probabilistic sensitivity analysis, as well as three different one-way sensitivity analyses.

4.2.7 In the base-case results of the Assessment Group model the ICER of 3-weekly docetaxel plus prednisone or prednisolone compared with mitoxantrone plus prednisone or prednisolone is estimated to be £32,700 per QALY, with all other strategies compared in both analyses dominated by mitoxantrone plus prednisone or prednisolone. Three one-way sensitivity analyses were undertaken to test the robustness of the model to alternative assumptions about discount rates, utility associated with health-related quality of life and the impact of adverse effects on quality of life. The ICER associated with 3-weekly docetaxel plus prednisone or prednisolone

remained fairly robust to these variations, with estimates ranging from £28,000 to £33,000 per QALY.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of docetaxel for hormone-refractory metastatic prostate cancer, having considered evidence on the nature of the condition and the value placed on the benefits of docetaxel by people with hormone-refractory metastatic prostate cancer, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee noted that prednisone was used as an alternative to prednisolone in the RCTs. It was aware that prednisone is a pro-drug of prednisolone, and that in the UK prednisolone has historically been preferred to prednisone on the grounds that it does not require conversion to the active substance. The Committee concluded that in practice the difference between prednisone and prednisolone was not clinically significant, and it therefore accepted the relevance of the results of international studies to the appraisal.

4.3.3 The Committee understood from the testimony of the clinical experts that docetaxel is the first treatment to show survival benefit in men with hormone-refractory metastatic prostate cancer. The Committee was persuaded that there was a significant survival advantage for the 3-weekly docetaxel regimen over treatment with mitoxantrone, as opposed to the weekly regimen, for which there was no statistically significant difference. It also considered that this differential effect between the two docetaxel regimens was biologically plausible. The Committee considered evidence from the SWOG 9916 trial and noted that although the regimen was not licensed, its results added weight to the evidence of the effect on overall survival of a 3-weekly regimen of docetaxel compared with treatment with mitoxantrone.

4.3.4 The Committee carefully considered the adverse events related to docetaxel, and the differential adverse events associated with a 3-weekly docetaxel regimen as opposed to a weekly regimen were discussed. The clinical experts indicated that patients receiving weekly docetaxel are more likely to experience painful and debilitating nail dystrophia, whereas this is less common in those receiving the drug 3-weekly. However the 3-weekly regimen was associated with a higher incidence of neutropenia. Additionally the Committee heard from both the clinical experts and the patient representatives that many patients feel that the benefits of treatment with docetaxel outweigh the side effects. The Committee concluded that the adverse events related to docetaxel, when weighed against the potential for beneficial effects, should not preclude recommendation of the use of docetaxel in patients with hormone-refractory metastatic prostate cancer.

4.3.5 The Committee considered the economic models put forward by the manufacturer and the Assessment Group. The structure of the Assessment Group model was discussed and it was accepted as suitable and adequate for this appraisal. The Committee discussed the base-case assumptions in the Assessment Group model for patients' extrapolated mean survival, drug and administration costs per cycle, follow-up costs, terminal care costs and the number of cycles received per patient. The Committee accepted these as reasonable assumptions and noted that they were similar to those used in the manufacturer's economic model.

4.3.6 The Committee discussed the way in which life years survived were adjusted for health-related quality of life in the Assessment Group model, noting that this had not been done in the manufacturer's model. The Committee noted that no information on utilities had been collected in TAX327 and that, in order to adjust life years survived for health-related quality of life, the Assessment Group had used an assumption based on a study found through a systematic literature review. The Committee further noted that the same utility assumption had been used for all treatment strategies and concurred that it was likely to be a reasonable estimate because it had been derived from a

study in a large sample using appropriate methodology. Furthermore, the Committee noted that an ICER of £28,000 had resulted from a one-way sensitivity analysis using a utility assumption derived from the elicitation of preferences of the NHS Value in Health Panel.

4.3.7 The Committee considered the potential for quality of life benefits associated with docetaxel treatment over and above mitoxantrone treatment. The Committee discussed the results observed for quality of life response in TAX327 based on the FACT-P questionnaire, and noted that this was the only evidence available and it had not been possible to relate those results to utility values. The Committee agreed with the Assessment Group's conclusion that indirect comparisons of quality of life and pain responses could not have been undertaken because of differences in the definitions and measurements. The Committee concluded that although there is potentially a quality of life benefit of docetaxel over mitoxantrone treatment, it was appropriate not to include it in the base-case assumptions of the economic model because the evidence was insufficient to support doing so. However, the Committee recognised that this approach was conservative and was satisfied by the additional analyses that indicated the inclusion of any quality of life benefit results in an ICER lower than £32,700. Furthermore, the Committee noted that the base-case ICER in the Assessment Group model was robust to a sensitivity analysis in which the reductions in quality of life of the different adverse effects associated with docetaxel and mitoxantrone were modelled.

4.3.8 In summary of the Committee's considerations of the cost-effectiveness evidence, it considered the methodology used in Assessment Group's model to be sound, and the base-case assumptions to be either reasonable or conservative. It noted that the base-case ICER of £32,700 had been robust to the one-way sensitivity analyses presented. The Committee therefore concluded that docetaxel within its licensed indications was acceptably cost-effective based on the evidence available at the time of this appraisal.

4.3.9 The Committee discussed the uncertainty surrounding the generalisability of the evidence from the RCT to everyday clinical practice. It was aware that the patients enrolled into the pivotal trial (TAX327) generally were younger and had a higher performance status than those who typically present for treatment in the UK. The Committee heard from the clinical experts that performance status, as defined by the Karnofsky score, was an important predictor of the likelihood of benefit from treatment for individual patients, irrespective of age. The Committee therefore decided that the recommendation on the use of docetaxel for patients with hormone-refractory metastatic prostate cancer should be limited to patients who have a Karnofsky score of 60% or more, an entry requirement of the TAX327 RCT. The experts agreed that such an approach would be appropriate. Additionally the Committee considered the potential for the Karnofsky performance-status score to be interpreted in such a way as to potentially discriminate against men who were disabled in a manner unrelated to their likelihood of benefit or harm from docetaxel treatment for prostate cancer. The Committee concluded that for disabled men the restriction in the guidance to a minimum Karnofsky performance-status score should be interpreted on an individual basis at the discretion of the clinician.

4.3.10 The Committee also discussed the lack of evidence and the uncertainty surrounding the generalisability of the results of the TAX327 RCT with regard to duration of treatment. The Committee heard testimony from the experts that in clinical practice the duration of treatment is determined by the balance of clinical benefit against the occurrence of adverse events, and in practice it is rare for patients to receive more than six cycles of 3-weekly docetaxel therapy. The Committee therefore concluded, in agreement with the experts and in accordance with the stopping rules of the TAX327 RCT, that treatment should be stopped either in the presence of progression of disease (as evidenced by clinical or laboratory criteria, or by imaging studies) or the presence of severe adverse events, and that patients should not receive more than a maximum of 10 cycles of treatment. Further, the Committee discussed

repeat cycles in the event of disease recurrence after completion of the planned course of docetaxel treatment. It considered that there was no evidence to support a recommendation for further cycles of docetaxel therapy if the disease recurs (as evidenced by clinical or laboratory criteria, or by imaging studies) after completion of the planned course of chemotherapy.

4.3.11 The Committee heard testimony from clinical experts that the diagnosis of hormone-refractory metastatic prostate cancer may vary in clinical practice in terms of the number and type of hormonal treatments the patient has previously received. The Committee was therefore satisfied that it was not appropriate to limit the recommendation to patients who had received a particular number of hormonal manipulations.

4.3.12 In summary, the Committee considered that the use of docetaxel in hormone-refractory metastatic prostate cancer was both clinically and cost effective on the basis of the above considerations and where the treatment protocol was that which was shown to be clinically effective in the pivotal RCT (TAX327), namely the 3-weekly docetaxel regimen administered for a maximum of 10 cycles only.

5 Recommendations for further research

5.1 The Committee noted that there are ongoing trials, which include the MRC STAMPEDE study, and trials in which docetaxel plus prednisone or prednisolone is the standard treatment arm and is used in combination with other therapies such as zoledronic acid, strontium-89 and bevacizumab, in the experimental treatment arm.

5.2 The Committee identified a need for research to assess the quality of life associated with different treatments for hormone-refractory metastatic prostate cancer using generic quality of life instruments that are suitable for the purposes of cost-effectiveness analyses. The Committee also identified a need for research on the effects of docetaxel over a longer follow-up period, and in a patient group that is more representative of a wider patient

population in terms of age, performance status and comorbidity, than in the RCTs considered in this appraisal.

6 Implications for the NHS

The NICE Costing Unit is currently developing this section. A costing template and report will be available at the time of publication of the final guidance.

7 Implementation and audit

7.1 NHS organisations and clinicians who care for men with prostate cancer should review their current practice and policies to take account of the guidance set out in section 1.

7.2 Local guidelines, protocols or care pathways that refer to the care of men with prostate cancer should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in appendix C.

7.3.1 A man with hormone-refractory metastatic prostate cancer is offered docetaxel, within its licensed indications, as a treatment option only if his Karnofsky performance-status score is 60% or more.

7.3.2 For a man with hormone-refractory metastatic prostate cancer who is treated with docetaxel, treatment with docetaxel is stopped when any of the following circumstances occur:

- planned treatment of up to 10 cycles is completed, or
- the man experiences a severe adverse event, or
- there is evidence of progression of disease.

7.3.3 Repeat cycles of treatment with docetaxel are not provided if the disease recurs after completion of the planned course of chemotherapy.

8 Related guidance

8.1 NICE has commissioned the National Collaborating Centre for Cancer to develop a guideline on the diagnosis and treatment of prostate cancer. Publication expected early 2008.

8.2 The following technology has been referred to NICE for appraisal:

- atrasentan for hormone-refractory prostate cancer.

8.3 NICE has issued the the following related guidance on cancer services:

- Improving outcomes in urological cancers. *NICE cancer service guidance* (2002). Available from www.nice.org.uk/CSGUC

9 Review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

9.2 The guidance on this technology will be considered for review in April 2009.

David Barnett
Chair, Appraisal Committee
April 2006

Appendix A Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St George's Hospital, London

Professor A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Representative

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital

Professor Christopher Eccleston

Director Pain Management Unit, University of Bath

Dr Paul Ewings

Statistician, Taunton and Somerset NHS Trust, Taunton

Professor Terry Feest

Professor of Clinical Nephrology, Southmead Hospital, Bristol

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical

Ms Linda Hands

Consultant Surgeon, John Radcliffe Hospital, Oxford

Dr Elizabeth Haxby

Lead Clinician in Clinical Risk Management, Royal Brompton Hospital, London

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital, Uxbridge

Dr Catherine Jackson

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre, Angus, Scotland

Professor Richard Lilford

Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne

Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson

Independent Research Consultant

Mrs Kathryn Roberts

Nurse Practitioner, Hattersley Group Practice, Cheshire

Professor Philip Routledge

Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Debbie Stephenson

Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens (Vice Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, Associate Professor, Department of Primary Care and General Practice, University of Birmingham

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

Dr David Winfield

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

B. NICE project team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Helen Chung

Technical Lead

Sarah Garner

Technical Advisor

Alana Miller

Project Manager

Appendix B Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Systematic Reviews Centre for Reviews and Dissemination, University of York:

Collins R, Fenwick E, Trowman R et al. *A systematic review and economic model of the effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer,* September 2005.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document. Consultee organisations are provided with the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsors:

- Sanofi-Aventis.

II Professional/specialist and patient/carer group:

- British Association of Urological Nurses
- British Association of Urological Surgeons
- British Geriatrics Society
- British Oncological Association
- British Oncology Pharmacy Association (BOPA)
- British Prostate Group
- British Psychosocial Oncology Society (BPOS)
- Cancer Research UK
- Cancer Voices
- CancerBACUP
- Department of Health

- Erewash PCT
- Greenwich PCT
- Long-term Medical Conditions Alliance
- Macmillan Cancer Relief
- Marie Curie Cancer Care
- National Cancer Alliance
- National Council for Hospice and Specialist Palliative Care Services
- Prostate Cancer Charity
- Prostate Cancer Support Association
- Prostate Help Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians' Medical Oncology Joint Special Committee
- Royal College of Radiologists
- Royal College of Surgeons
- Royal Pharmaceutical Society
- Tenovus Cancer Information Centre
- Welsh Assembly Government.

III Commentator organisations (without the right of appeal):

- Baxter Healthcare
- Board of Community Health Councils in Wales
- British National Formulary
- Institute of Cancer Research
- Mayne Pharma
- MRC Clinical Trials Unit
- National Cancer Research Institute
- National Collaborating Centre for Cancer

- National Coordinating Centre for Health Technology Assessment
- National Public Health Service for Wales
- NHS Centre for Reviews & Dissemination –York
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Pfizer
- Prostate Cancer Guideline Development Group
- Wyeth Pharmaceuticals.

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on docetaxel for the treatment of hormone-refractory metastatic prostate cancer by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the appraisal consultation document:

- Mr Noel Clarke, Consultant Urologist, British Association of Urological Surgeons, MRC Clinical Trials Unit – Clinical Specialist.
- Professor Jonathan Waxman, Professor of Oncology, Imperial College of Science Technology and Medicine, nominated by the Prostate Cancer Charity – Clinical Specialist.
- Mr Ian Gooding, nominated by Tenovus Cancer Information Centre – Patient Expert.

D The following individual representing the National Collaborating Centre responsible for developing the Institute's clinical guideline on prostate cancer was invited to attend the Appraisal Committee's meetings on the appraisal consultation document and final appraisal determination to contribute as an advisor.

- Dr John Graham, Consultant in Clinical Oncology, Beatson Oncology Centre, Western Infirmary, Glasgow

Appendix C Detail on criteria for audit of the use of docetaxel for the treatment of hormone-refractory metastatic prostate cancer

Possible objectives for an audit

An audit could be carried out to ensure the appropriateness of use of docetaxel in men with hormone-refractory metastatic prostate cancer.

Possible patients to be included in the audit

An audit could be carried out on men with hormone-refractory metastatic prostate cancer who are seen in a reasonable time period for audit, for example, 6 months to 1 year. It may be useful to include men who were diagnosed and treated sufficiently long ago that the disease may have recurred after completion of the planned course of chemotherapy.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of docetaxel for the treatment of hormone-refractory metastatic prostate cancer are as follows.

Criterion	Standard	Exception	Definition of terms
1. A man with hormone-refractory metastatic prostate cancer is offered docetaxel, within its licensed indications, as a treatment option only if his Karnofsky score is 60% or more	100% of men with hormone-refractory metastatic prostate cancer	A. The man has a contraindication to docetaxel	Hormone-refractory metastatic prostate cancer is defined either on the basis of biochemical testing (prostate-specific antigen, PSA), findings of imaging studies, or using clinical criteria of progressive metastatic disease despite castrate serum levels of testosterone. Clinicians will need to agree locally on how hormone-refractory metastatic prostate cancer is diagnosed and how the offer of docetaxel as a treatment option are documented, for audit purposes. Karnofsky score of 60% or more means that at least the man is able to care for himself but requires occasional assistance. If the man is disabled in a manner unrelated to his likelihood of benefit or harm from docetaxel treatment of prostate cancer, the Karnofsky score should be interpreted on an individual basis at the discretion of the clinician. See appendix D for more information on the Karnofsky

			performance score. For details of contraindications, see the Summary of Product Characteristics.
2. For a man with hormone-refractory metastatic prostate cancer who has been treated with docetaxel, treatment with docetaxel is stopped when any of the following occur: a. the planned treatment of up to 10 cycles is completed **or** b. the man experiences a severe adverse event **or** c. there is evidence of progression of disease	100% of men being treated with docetaxel for metastatic prostate cancer and for whom a or b or c occur	None	Adverse events are measured using the Common Toxicity Criteria of the US National Cancer Institute, version 2. Evidence of progression of disease is by imaging studies or by clinical or laboratory criteria, which clinicians will need to agree locally, for audit purposes.
3. Repeat cycles of treatment with docetaxel are offered to a man with hormone-refractory metastatic prostate cancer if the disease recurs after completion of the planned course of chemotherapy	0% of men with hormone-refractory metastatic prostate cancer in whom the disease recurs after completion of the planned course of chemotherapy	None	Clinicians will need to agree locally how men in whom the disease recurs after completion of the planned course of chemotherapy are identified, for audit purposes.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the } \textbf{criterion} \textit{ } \textbf{\textit{plus}} \text{ number of patients who meet any } \textbf{exception} \text{ listed}}{\text{Number of patients to whom the } \textbf{measure} \text{ applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

Appendix D Karnofsky Performance-Status Scores

100%	The patient has no complaints and is without evidence of disease.
90%	The patient has minor signs/symptoms, but is able to carry out his or her normal activities.
80%	The patient demonstrates some signs/symptoms and requires some effort to carry out normal activities.
70%	The patient is able to care for self, but is unable to do his or her normal activities or active work.
60%	The patient is able to care for self, but requires occasional assistance.
50%	The patient requires medical care and much assistance with self care.
40%	The patient is disabled and requires special care and assistance.
30%	The patient is severely disabled and hospitalisation is indicated; death is not imminent.
20%	The patient is very ill with hospitalisation and active life-support treatment necessary.
10%	The patient is moribund with fatal process proceeding rapidly.
0%	Dead.