NATIONAL INSTITUTE FOR HEALTH and CLINICAL EXCELLENCE

Overview

Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (mHRPC)

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members prior to the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. In order to allow sufficient time for the overview to be circulated to Appraisal Committee members prior to the first Appraisal Committee meeting, it is prepared before the Institute receives Consultees' comments on the Assessment Report. These comments are therefore not addressed in the Overview.

A list of the sources of evidence used in the preparation of this document is given in Appendix A.

1 Background

1.1 The Condition

The prostate is a walnut-sized gland that is present only in men. It is located in the pelvis, just below the bladder exit, and surrounds the tube known as the urethra (through which urine flows from the bladder to the outside of the body). It is subdivided into three zones: central, transition and peripheral. The peripheral zone is located at the back of the prostate and is the part most susceptible to both prostate cancer and prostatitis. 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 it is either locally advanced and invading local adjacent structures, or has associated distant metastases. Approximately 22% of cases of prostate cancer will be diagnosed at stage IV, with a further 25% of patients developing metastases throughout the course of the disease.

The growth of most prostate cancers is stimulated by testosterone, and hormonal therapies which modify levels of, or responses to, testosterone are standard treatment for men with metastatic disease. Hormonal therapies are initially effective in the 80% of men with metastatic prostate cancer, but after around 18 months, the disease usually becomes unresponsive to hormone treatment and will progress. Metastatic hormone-refractory prostate cancer (mHRPC) is defined as either biochemically or clinically progressive metastatic disease despite castrate serum levels of testosterone.

The prognosis is poor for patients with mHRPC; survival of patients who have developed mHRPC is not expected to exceed between 9 and 12 months. The most important prognostic factor is the growth pattern or grade of the tumour assessed using the Gleason scoring system. Gleason scores range from <4 for less aggressive tumours to 8–10 for tumours that are more aggressive. Other important prognostic factors are prostate specific antigen (PSA) level and the extent of local tumour spread.

Prostate cancer is also associated with substantial morbidity that can have significant impact on the patients, families and carers. Prostate cancer was responsible for 39,283 hospital episodes in 2003–2004, although it is unknown how many of these related to patients with mHRPC. The symptoms of mHRPC 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. Over 90% of patients with late stage prostate cancer develop metastases to bone, and this can cause debilitating pain, pathological fractures and spinal cord compression. Patients can receive surgery, radiotherapy, steroids and analgesics as well as hormonal treatment and chemotherapy, and they could suffer adverse effects related to all of these.

The primary risk factor for prostate cancer is increasing age, with 90% of all cases occurring in men over 60 and 42% in men over 75. The highest worldwide rates are observed in Afro–American men, with much lower rates seen in men of Asian origin. The cause of prostate cancer probably involves multi-factorial environmental and genetic factors. As prostate cancer does not occur in castrated men, 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.

Data on the epidemiology of mHRPC are limited; therefore inferences must be drawn from available data for prostate cancer. Prostate cancer is the most common male cancer, excluding non-melanoma skin cancer in the UK. 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 the majority of such deaths are in patients with mHRPC.

1.2 Current management

Hormone-refractory metastatic prostate cancer cannot be cured. The aim of treatment is to improve symptoms, prolong life and slow progression of the disease.

There is no gold standard treatment for mHRPC in the UK. The clinical management of mHRPC is acknowledged to be multimodal rather than sequential and at any given time a patient may receive a combination of palliative treatments.

Treatment options include second-line hormonal therapy, chemotherapy with or without corticosteroids, and best supportive care. The choice of therapy is dependent on symptoms, site of relapse, performance status of the patient and the presence of other co-morbidities. 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 of the patients with prostate cancer are elderly and many have other medical problems.

Chemotherapy regimens that have been used to control the cancer include those based on mitoxantrone, estramustine and taxanes such as docetaxel. Mitoxantrone is widely used in the UK for mHRPC patients who are fit for chemotherapy, even though it is not licensed for this indication. Several consultees have advised that a combination of mitoxantrone and prednisolone has come to be accepted as the standard care for this group of patients.

NICE ‘Guidance on cancer services: improving outcomes in urological cancers: the manual (2002)’ states that chemotherapy should be considered for men with symptomatic hormone-refractory prostate-cancer and trials of chemotherapy supported, while palliative radiotherapy should also be considered as a treatment option. New guidelines prepared by the British Association of Urological Surgeons propose considering the use of docetaxel, for symptomatic patients who are fit for chemotherapy.

2 The technology

Table 1 Summary description of technology

Generic name	Docetaxel
Proprietary name	Taxotere®
Manufacturer	Sanofi-Aventis
Dose	75 mg/m^2 3-weekly
Acquisition cost ex. VAT (BNF edition 49)	0.5-ml vial = £162.75 2-ml vial = £534.75 40mg/mL (both with diluent)

Docetaxel (see Table 1) is licensed for use in combination with prednisone or prednisolone for treatment of patients with hormone refractory metastatic prostate cancer (Summary of Product Characteristics).

Prednisolone has a role in the palliation of symptomatic end-stage malignant disease when it may enhance appetite and produce a sense of well-being. It is unclear whether there is an alternative or additional rationale for combining docetaxel with prednisolone or prednisone. Prednisone is converted in the liver to prednisolone. The two drugs therefore have similar effects, and they are administered in the same dosage. Prednisone is not, however, used in the UK, therefore the scope for this appraisal defines the intervention as 'docetaxel in combination with prednisolone'.

Docetaxel is a member of 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.

The possible adverse effects of docetaxel include hypersensitivity reactions (presenting as flushing, skin reactions, hypotension and bronchospasm), bone marrow suppression (neutropenia, thrombocytopenia, anaemia), cutaneous reactions, fluid retention, peripheral neuropathy, mucositis, increase in liver enzymes, alopecia, cardiac irregularities and tiredness. Contraindications include severe allergic reaction, low white blood cell count due to bone marrow damage (myelosuppression), severe liver disease, pregnancy or breast-feeding. Pre-medication with a corticosteroid is usually recommended to help prevent allergic reaction.

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

3 The evidence

3.1 Clinical effectiveness

As mentioned in the previous section, the intervention as defined in the scope of this appraisal is 'docetaxel in combination with prednisolone'. It was decided at the protocol stage that due to the interrelationship between prednisone and prednisolone, evidence for the use of docetaxel in combination with prednisone would also be relevant.

Only one randomised controlled trial (RCT) (TAX327) which investigated docetaxel within its licensed indications was identified. No other trials were found that assessed the clinical effectiveness of docetaxel plus prednisone/prednisolone. Because TAX327 compared the intervention with mitoxantrone plus prednisone or prednisolone, it was important to consider other evidence that would inform a comparison against other potentially relevant comparators (for example, chemotherapy-based treatments and best supportive care). Therefore, the Assessment Group searched for all other treatments that were compared with mitoxantrone plus a corticosteroid.

Direct comparison between the intervention and a comparator

The key features of the TAX327 trial are summarised in Tables 2 and 3.

TAX327 was the 'registration study' featured in the sponsor submission. This was a multi-centre, open-label, randomised trial, stratified by baseline pain level and Karnofsky performance status score, comparing docetaxel plus prednisone/prednisolone in two different regimens with mitoxantrone plus prednisone/prednisolone. The results of this trial showed statistically significant improvements with 3-weekly docetaxel plus prednisone/prednisolone compared with mitoxantrone plus prednisone/prednisolone, in terms of overall survival, quality of life, pain response, and PSA decline. Docetaxel plus prednisone/prednisolone was associated with more grade 3 or 4 adverse events. However, this had no detrimental effect on quality of life.

The trial participants tended to be younger (median age 68 to 69) and of a higher performance status than the average mHRPC patient. The mean survival of patients with mHRPC has been estimated as 10 to 12 months, but for the control arm of TAX327 it was 16.5 months. In comparison, a study of the final year of life in men dying with prostate cancer showed a mean age of 77 years, and 7% of the men had impaired bone marrow function necessitating blood transfusion. The results of TAX327 may not therefore be generalisable to the whole patient population and this has implications for the identification of subgroups particularly suitable for the intervention.

Table 2 Key features of the TAX327 trial

Disease status of participants	Intervention	Control	Length of follow-up	Primary endpoint	Secondary endpoints
Men with metastatic prostate cancer, with disease progression during hormonal therapy. Karnofsky performance score at least 60%, stable levels of pain. Median age 68/69.	(1) Docetaxel 75 mg/m^2 3-weekly, or (2) docetaxel 30 mg/m^2 weekly plus prednisone or prednisolone 5 mg orally twice daily, premedication with dexamethasone	Mitoxantrone 12 mg/m^2 3-weekly plus prednisone or prednisolone 5 mg orally twice daily	(Median): Intervention (1): 20.8 months; Intervention (2): 20.7 months; Control: 20.7 months.	Overall Survival	Progression-free survival, response rate, PSA decline, adverse events, pain, health related quality of life

Table 3 Main results of the TAX327 trial

Health outcomes	Results (D+P vs M+P)
Mortality	166/335 (50%) vs 201/337 (60%)
	HR=0.76 (95% CI, 0.62 to 0.94)
Median Survival	18.9 months vs 16.5 months
	HR=0.76 (95% CI, 0.62 to 0.94)
Progression-free survival	Not reported
Response rate	17/141 (12%) vs 10/137 (7%)
	RR=1.65 (95% CI, 0.78 to 3.48)
Quality of life response	61/278 (22%) vs 35/267 (13%)
	RR=1.67 (95% CI, 1.14 to 2.45)
Pain response	54/153 (35%) vs 26/157 (22%)
	RR=1.58 (95% CI, 1.1 to 2.27)
PSA decline	131/291(45%) vs 96/300 (32%)
	RR=1.41 (95% CI, 1.14 to 1.73)
AE: Discontinued	11% vs 10%
AE: Grade 3/4	46% vs 35%
- Neutropenia	32% vs 22%
AE: Died	0.3% vs 1%

AE, adverse events; CI, confidence interval; HR, hazard ratio; PSA, prostate specific antigen; RR, relative risk; D, docetaxel; M, mitoxantrone; P, prednisone/prednisolone

Indirect comparison between the intervention and best supportive care

Key features of the trials discussed in this section are summarised in Appendix 1, with key results in Appendix 3.

The Assessment Group performed a meta-analysis of the results from three trials comparing mitoxantrone plus a corticosteroid with corticosteroid alone. The only outcome suitable for the pooling of results was overall survival. The pooled estimate of the hazard ratio for death of mitoxantrone plus corticosteroid versus corticosteroid was 0.99 (95% CI, 0.82 to 1.20). This was then compared indirectly with that from the TAX327 study, giving an indirect hazard ratio for death of docetaxel plus prednisone/prednisolone versus corticosteroid alone of 0.752 (95% CI, 0.567 to 0.999). Results of other health outcomes were not suitable for pooling, nor for quantitative indirect comparison, but it is notable that studies comparing mitoxantrone plus corticosteroid with corticosteroid alone resulted in improvements in various health outcomes other than mortality (see Appendix 3 for details); and that studies comparing docetaxel-based regimes with mitoxantrone plus prednisone/prednisolone resulted in improvements of various health outcomes in addition to mortality (see Appendix 4 for details). The Assessment Report notes that results of the adjusted indirect comparison need to be interpreted with caution because the underlying trials differed in patient population and methodology.

The Assessment Group also reviewed an RCT which compared mitoxantrone plus prednisone plus clodronate with mitoxantrone plus prednisolone (Ernst). This showed no significant differences in outcomes.

Trials comparing other docetaxel-containing regimens with mitoxantrone plus prednisone/prednisolone

Key features of the trials discussed in this section are summarised in Appendix 2, with key results in Appendix 4.

The Assessment Group found two other RCTs that investigated the effects of docetaxel in patients with mHRPC. One did not consider docetaxel within its licensed indications, and the other considered docetaxel in a regimen for which it is unclear whether it is within the licensed indications. The SWOG 9916 RCT compared docetaxel plus estramustine versus mitoxantrone plus prednisone. The Oudard RCT investigated docetaxel plus prednisone plus estramustine versus mitoxantrone plus prednisone. The results of the SWOG 9916 trial taken together with those of TAX327 have been interpreted in a number of submissions, including the sponsor's, to be evidence supporting the efficacy of docetaxel in terms of overall survival and quality of life and to suggest that the combination of docetaxel with estramustine is inferior to docetaxel regimes not containing estramustine because of increased toxicity.

Summary of Clinical effectiveness section

The Assessment Group found one trial that assessed the intervention under consideration – namely, docetaxel plus prednisone/prednisolone. This was in comparison with mitoxantrone plus prednisone/prednisolone (TAX327). This trial showed higher overall survival, quality of life, pain response and PSA decline in the docetaxel 3-weekly plus prednisone/prednisolone treatment arm compared with the mitoxantrone plus prednisone/prednisolone treatment arm, and the results were statistically significant. Docetaxel plus prednisone/prednisolone was associated with more grade 3 or 4 adverse events. However, this had no detrimental effect on quality of life.

The Assessment Group performed an adjusted indirect comparison between docetaxel plus prednisone/prednisolone versus prednisone/prednisolone alone, with mitoxantrone plus a corticosteroid as the common comparator. A meta-analysis of three trials that compared mitoxantrone plus a corticosteroid versus a corticosteroid alone showed very little difference in overall survival. The results of the adjusted indirect comparison showed that docetaxel seems to be superior to prednisone alone in terms of overall survival.

3.2 Cost effectiveness

Only Sanofi-Aventis and the Assessment Group provided estimates of cost-effectiveness, although some other consultees commented on economic issues. The Assessment Group developed their own economic model (section 6 of Assessment Report) and critiqued the model submitted by Sanofi-Aventis (section 5 of Assessment Report).

One consultee submission commented that it is not clear whether continuation of the drug beyond six cycles is significantly beneficial, and this should be considered along with patients' final 1 to 2 years life costs, which may already be increased by the addition of other palliative agents.

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

Overall description of the Sanofi-Aventis and Assessment Group models

Both models aim to consider the cost-effectiveness the technology from an NHS perspective. Both models reported their results as incremental cost-effectiveness ratios (ICERs) of docetaxel plus prednisone/prednisolone compared with mitoxantrone plus prednisone/prednisolone. As noted previously, mitoxantrone is not licensed in the UK for use for prostate cancer, although it is widely used.

The Sanofi-Aventis model estimates the incremental cost per life-year gained from docetaxel plus prednisone/prednisolone compared to mitoxantrone plus prednisone/prednisolone. The evaluation was 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 was considered in the analysis in keeping with the licensed recommended dose. No adjustment is made for quality of life. Two analyses are presented: Analysis 1 is based on within trial analysis (based on median survival), and Analysis 2 models extrapolation to lifetime survival (based on mean survival). Uncertainty is considered by way of two one-way sensitivity analyses, one related to the estimate of survival, and the other to that of costs per patient.

The Assessment Group model estimates the incremental cost per quality adjusted life year (QALY) gained of docetaxel plus prednisone/prednisolone compared to the least expensive strategy not excluded by dominance or extended dominance, of a number of treatment comparators. Two analyses were reported. Analysis 1 extends the comparators considered in the Sanofi-Aventis model to include best supportive care. The only suitable strategy to use in this respect was prednisone/prednisolone alone, given the results of the systematic review for clinical effectiveness. 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 ICER is that of docetaxel 3-weekly plus prednisone/prednisolone compared to mitoxantrone plus prednisone/prednisolone. Uncertainty is characterised by way of probabilistic sensitivity analysis, as well as three one-way sensitivity analyses, two reflecting changes to the utility estimate and the third a change of discount rate.

The comparators in the analyses of the two models are shown in Table 4 below. The structure, assumptions and characterisation of uncertainty of the two models are compared and contrasted in Appendix 5.

Table 4 Comparators in the two economic models

Sanofi-Aventis	Assessment Group
Analysis 1 and Analysis 2	**Analysis 1**
1. Docetaxel (75 mg/m^2 3-weekly) plus prednisone/prednisolone 2. Mitoxantrone plus prednisone/prednisolone	1. Docetaxel (75 mg/m^2 3-weekly) plus prednisone/prednisolone 2. Mitoxantrone plus prednisone/prednisolone 3. Prednisone/prednisolone alone
	Analysis 2 1. Docetaxel (75 mg/m^2 3-weekly) plus prednisone/prednisolone 2. Mitoxantrone plus prednisone/prednisolone 3. Prednisone/prednisolone alone 4. Docetaxel (30 mg/m^2 weekly)plus prednisone/prednisolone 5. Docetaxel (60–70 mg/m^2 3 weekly) plus estramustine 6. Docetaxel (70 mg/m^2 3-weekly) plus estramustine plus prednisone 7. Docetaxel (35 mg/m^2 twice every 3 weeks) plus estramustine plus prednisone 8. Mitoxantrone plus prednisone plus clodronate

Results

The base case results are shown in Table 5 below. Appendix 6 shows a breakdown of these results into their survival, quality of life, and cost components, and an approximate reconciliation between the base case ICERs from the two models. The main reason that the ICER using mean survival calculated by the Assessment Group is higher than that from the Sanofi-Aventis Model is that quality of life is adjusted for in the former but not in the latter.

Appendix 7 shows the ICERs resulting from one-way sensitivity analyses.

Table 5 Base case ICERs from the two economic models

	Sanofi-Aventis Model		**Assessment Group Model**	
	Incremental Cost per Life Year Gained		Incremental Cost per QALY	
	Analysis 1	Analysis 2	Analysis 1	Analysis 2
	(Median survival)	(Mean survival)	(Mean survival)	(Mean survival)
M+P	-	-	-	-
D+P (3-Weekly)	£30,280	£19,483	£32,706	£32,706
P	N/A	N/A	Dominated	Dominated
D+P (Weekly)	N/A	N/A	N/A	Dominated
D+E+P (70 mg/m^2)	N/A	N/A	N/A	Dominated
D+E+P (35 mg/m^2)	N/A	N/A	N/A	Dominated
D+E	N/A	N/A	N/A	Extended Dominance
M+P+C	N/A	N/A	N/A	Dominated

Key:

D	Docetaxel
M	Mitoxantrone
P	Prednisone or Prednisolone
E	Estramustine
Cl	Clodronate
N/A	Not Applicable
-	Cheapest non-dominated strategy

Summary of Cost-effectiveness section

The main result of the Sanofi-Aventis model was £19,483 as the incremental cost per life year gained from docetaxel plus prednisone/prednisolone over mitoxantrone plus prednisone/prednisolone. This changed to £30,280 if survival was estimated by the median rather than the mean.

The main results of the Assessment Group Model indicate that docetaxel plus prednisone/prednisolone appears cost-effective compared with other chemotherapy and non-chemotherapy regimens, as long as the NHS is willing to pay at least £32,706 per QALY. The use of prednisone/prednisolone alone appears to be dominated by mitoxantrone plus prednisone/prednisolone and hence the cost-effectiveness of docetaxel plus prednisone/prednisolone is most appropriately

informed by a comparison against mitoxantrone plus prednisone/prednisolone. Three one-way sensitivity analyses were undertaken to test the robustness of the model to alternative assumptions regarding discount rates, quality of life estimates and the impact of side effects. The ICER associated with docetaxel (3-weekly) plus prednisone/prednisolone remained fairly robust to these variations with estimates ranging from £28,019 to £33,298 per QALY (see Appendix 7 for details).

4 Issues for consideration

1. How generalisable are the results of TAX327? This issue has been raised in section 3.1 Clinical effectiveness.

2. How relevant to this appraisal for docetaxel in combination with prednisolone are trials investigating docetaxel in combination with estramustine and/or prednisone? This issue has been raised in section 3.1 Clinical effectiveness.

3. What is the clinical significance of the results? The Assessment Report states that while pain reduction and improvements in quality of life were achieved in substantial proportions of patients prior to the licensing of docetaxel for the treatment of mHRPC, survival did not appear to be prolonged. The sponsor submission states that docetaxel is unique in that it significantly extends life in patients with mHRPC, in addition to providing palliative benefits.

4. Can the evidence available inform the identification of subgroups for which the intervention would be particularly clinically effective or cost effective? All of the trials reviewed required patients to be of a minimum performance status in order to be recruited. TAX327, Oudard and SWOG 9916 stratified patients according to performance status (but by a different scale of measurement in each). It has been suggested in a consultee submission that the intervention could be considered after disease progression following at least two hormonal manipulations.

5. The role of steroids in combination with chemotherapy should be considered when discussing the clinical evidence. It is unclear how the selection (for example, dexamethasone or prednisolone), dosage and administration of premedication may have impacted on the clinical evidence.

6. Questions remain about how many cycles of docetaxel should optimally be given. This issue has been raised in section 3.2 Cost effectiveness, and discussion of this point may be of value.

5 Ongoing research

The Sanofi-Aventis submission notes that there are no ongoing phase III trials to investigate docetaxel in mHRPC in the UK, although a randomised phase II study is currently comparing docetaxel and prednisolone as standard therapy with other interventions; and that docetaxel is being used as a standard arm in several phase II and III trials of both early and advanced prostate cancer in Europe and North America.

The Assessment Report comments that it is difficult to make any recommendations for further research of docetaxel given that at the time of this assessment there were ongoing trials of docetaxel in which docetaxel plus prednisone or prednisolone was the standard treatment arm and used in combination with other therapies as the experimental arm(s).

The Assessment Group recommends that future research should include the assessment of quality of life associated with different treatments including adverse events of treatment, using generic quality of life instruments, which are suitable for the purposes of cost-effectiveness analysis.

6 Authors

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7 Appendix A. Sources of evidence considered in the preparation of the overview

A Assessment Report produced by CRD/CHE Technology Assessment Group, University of York:

Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, Birtle A, Palmer S and Riemsma R, *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 Submissions from the following organisations:

I Manufacturer/sponsors:

- Sanofi-Aventis

II Professional/specialist and patient/carer groups:

- Professor Jonathan Waxman, Professor of Oncology
- Mr Noel Clarke, Consultant Urologist
- Cancer BACUP
- Royal College of Nursing
- Royal College of Physicians } These organisations made a joint submission
- Association of Cancer Physicians }
- Royal College of Radiologists }
- Joint Collegiate Council for Oncology }

III Commentator organisations (without the right of appeal):

- None received

C Details of any additional references used:

- NICE 'Scope for Docetaxel for the treatment of hormone-refractory metastatic prostate cancer', December 2004

Appendix 1 Summary of RCTs reviewed in Assessment Report which investigated mitoxantrone-including regimens - please note subheadings

Name of trial	Study design	No.	Disease status of participants	Comparison			Length of follow-up	Primary endpoint	Secondary endpoints
Notes:				**Intervention**	**vs**	**Control**			
Dose and frequency of mitoxantrone and prednisone/prednisolone similar in all trials below.									
5 mg prednisone, 5 mg prednisolone and 20 mg of hydrocortisone are equivalent doses (BNF 49 page 357).									
The results for overall survival of the 3 RCTs below were pooled, and used for indirect comparision with docetaxel plus prednisone/prednisolone									
Berry et al (2002)	Phase III multi-centre, open-label RCT	120	Asymptomatic prostate cancer, about 80% of whom had bone metastases, about 20% of whom had lymph metastases. ECOG performance status of 0 to 2 to be eligible for trial.	Mitoxantrone plus prednisone	vs	Prednisone	Median: 21.8 months (range 2.4-50)	Time to failure of treatment - aggregate endpoint defined by the time between the start of treatment & occurrence of progression, removal from study or initiation of another treatment.	Overall survival, Response Rate, PSA decline, Adverse events, Pain, Health related QoL
CCI-NOV22 (key publication Tannock, 1996)	Phase III multi-centre, stratified open-label RCT	161	mHRPC. Patients were required to have symptoms of pain. Patients required to have ECOG performance status of 3 or better.	Mitoxantrone plus prednisone	vs	Prednisone	Not stated	Palliative response	Overall survival, Progression-free survival, PSA decline, Adverse events, Pain, Health related QoL
CALGB 9182 (key publication: Kantoff, 1999)	Phase III multi-centre, stratified open-label RCT	242	mHRPC. Patients required to have adequate hepatic, renal and bone marrow functions. Poorer prognosis patients were eligible to be included.	Mitoxantrone plus hydrocortisone	vs	Hydrocortisone	2-year follow-up after the accrual period, which lasted 3 years.	Overall Survival	Progression-free survival, Response Rate, PSA decline, Adverse events, Pain, Health related QoL
Other trials reveiwed by assessment group (not included in meta-analysis)									
Ernst (2003)	Phase III multi-centre, stratified double-blind RCT	227	mHRPC. ECOG performance status score of less than 3	Mitoxantrone plus prednisone	vs	Mitoxantrone plus prednisone plus clodronate	Not stated	Palliative response	Overall survival, Progression-free survival, PSA decline, Adverse events, Pain, Health related QoL

Appendix 2 Summary of RCTs reviewed in Assessment Report which investigated docetaxel-including regimens other than the docetaxel plus prednisolone/prednisone

Name of trial	Study design	No.	Disease status of participants	Comparison			Length of follow-up	Primary endpoint	Secondary endpoints
Notes:				**Intervention**	**vs**	**Control**			
Both these trials included a treatment arm with docetaxel close to (60 to 70 mg/m^2) the recommended dose.									
The Oudard trial also investigated a treatment arm with a lower dose of docetaxel given more frequently.									
Dose and frequency of mitoxantrone and prednisone/prednisolone were similar in both trials									
Oudard et al (2005)	Phase II multi-centre, open-label RCT, stratified by baseline PSA level and ECOG performance status score.	130	metastatic prostate cancer, with disease progression despite androgen deprivaiton. Performance status variable - ECOG score 0 to 2. Median age 68/70.	Docetaxel plus estramustine plus prednisone, pre-medication oral prednisolone 300mg. Also oral warfarin daily*	vs	Mitoxantrone plus prednisone*	Not stated	PSA decrease	Overall Survival, Progression-free survival, Response Rate, Adverse Events, Pain, Health related QoL
*All patients also given coumadin continuously									
SWOG 9916 (key publication Petrylak, 2004)	Phase III multi-centre, open-label RCT, stratified by type of progression (measurable versus PSA alone), grade of bone pain and SWOG performance status score.	770	metastatic prosate cancer, with disease progression despite androgen-ablative therapy and cessation of anti-androgen treatment. Patients required to have a SWOG performance status score of 0 to 2 (3 allowed if due to bone pain). Median age 70.	Docetaxel plus estramustine, pre-medication dexamethasone. Also 2 mg warfarin and 325 mg aspirin orally once daily after protocol change	vs	Mitoxantrone plus prednisone	Median: 32 months	Overall Survival	Progression-free survival, Response rate, PSA decline, Adverse events, Pain, Health related QoL

Appendix 3 Main results of the 3 RCTs reviewed in detail by the assessment group comparing mitoxantrone plus corticosteroid with corticosteroid alone, and 1 RCT which includes clodronate

Key to shading:

Significantly better outcome with M+C vs C alone	Significantly worse outcome with M+C vs C alone	Not statistically significant or not reported

Notes:

Dose and frequency of mitoxantrone and prednisone similar in all trials below.

5 mg prednisone, 5mg prednisolone and 20 mg of hydrocortisone are equivalent doses (BNF 49 page 357)

M, mitoxantrone; C, corticosteroid; P, prednisone; HC, hydrocortisone; Cl, clodronate; RCT, randomised controlled trial

Trial name	**Berry et al**	**CCI-NOV22**	**CALGB 9182**	**Ernst et al**
Treatments compared	M+P vs P	M+P vs P	M+HC vs HC	M+P+Cl vs M+P
Dose and frequency of mitoxantrone	12 mg/m^2 every 21 days	12 mg/m^2 every 21 days	14 mg/m^2 every 21 days	12 mg/m^2 every 21 days
Dose and frequency of corticosteroid	5 mg orally twice daily	5 mg orally twice daily	30 mg orally in the morning, 10 mg orally in the evening	5 mg twice daily
Health outcome	Mean (95% confidence interval)			
Mortality	43/56 (77%) vs 48/63 (76%)	43/77 56%) vs 60/70 (86%)	58/119 (49%) vs 68/123 (55%)	87/104 vs 89/105
	HR=1.13 (0.75 to 1.7)	HR=0.91 (0.69 to 1.19)	HR=1.05 (0.74 to 1.49)	HR=0.95 (0.71 to 1.28)
Median Survival	23 months vs 19 months	10 months vs 10 months	12.6 months vs 12.3 months	10.8 vs 11.5 months
	HR=0.89 (0.59 to 1.34)	HR=1.10 (0.84 to 1.45)	HR=0.95 (0.67 to 1.35)	HR=1.05 (0.78 to 1.42)
Progression-free survival	HR=0.64 (0.48 to 0.86)	HR=2.15 (1.46 to 3.17)	HR=1.502 (1.06 to 2.13)	HR=1.24 (0.93 to 1.64)
Response rate	RR=1.13 (0.20 to 6.24)	RR=2.33 (1.19 to 4.57)	RR=1.654 (0.56 to 4.91)	RR=1.14 (0.81 to 1.59)
QoL response	Not reported	Variety of measures - some improvements with Mitoxantrone	Variety of measures - some improvements with Mitoxantrone	RR=0.89 (0.64 to 1.25)
Pain response	Not reported			RR=1.27 (0.83 to 1.95)
PSA decline	RR=2.03 (1.21 to 3.40)	RR=1.5 (0.81 to 2.79)	RR=1.74 (1.14 to 2.66)	RR=1.04 (0.68 to 1.59)
AE: Discontinued	Not reported	11 vs 1	Reported for 286 (86%). More haematopoietic toxicities in M+P group	3 vs 2
AE: Grade 3/4	Not evaluable	22 vs 15		48 vs 44
AE: Died	None	Not reported		None

Appendix 4 Main results of the RCTs reviewed in detail by the Assessment Group which investigate docetaxel-containing chemotherapy regimens other than docetaxel plus prednisolone/prednisone

Key to shading:

Significantly better outcome with docetaxel-including regime vs M+P	Significantly worse outcome with docetaxel-including regime vs M+P	Not statistically significant or not reported

Notes:

Results only shown for doses of docetaxel close to dose recommended in license.
The Oudard trial also investigated a treatment arm
with a lower doses of docetaxel given more frequently.
Dose and frequency of mitoxantrone and prednisone/prednisolone similar in all trials.
D, docetaxel; M, mitoxantrone; P, prednisone/prednisolone; RCT, randomised controlled trial

Trial name	**SWOG 9916**	**Oudard et al**
Year of main publication	**2004**	**2005**
Comparators	D+E vs M+P	D+P+E vs M+P
Docetaxel dose	60-70 mg/m^2 3-weekly	70 mg/m^2 3-weekly
Health Outcomes:	Mean (95% confidence interval)	
Mortality	217/338 (64%) vs 235/336 (70%)	percentages not available
	HR=0.80 (0.67 to 0.97)	
Median Survival	17.5 months vs 15.6 months	18.6 months vs 13.4 months
	HR=0.80 (0.67 to 0.97)	HR=0.94 (0.29 to 1.02)
Progression-free survival	312/338 (92%) vs 311/336 (93%)	'Not enough data'
	HR=1.30 (1.11 to 1.52)	''
Response rate	17/103(17%) vs 10/93(11%)	9 vs 1
	RR=1.54 (0.74 to 3.18)	'Not enough data'
QoL response	Not reported	Not reported
Pain response	No significant difference	14/43 (33%) vs 9/42 (21%)
	- data not shown	RR=1.52 (0.74 to 3.13)
PSA decline	155/309 (50%) vs 82/303 (27%)	29/43 (67%) vs 7/42 (18%)
	RR=1.85 (1.49 to 2.30)	RR=4.05 (1.99 to 8.21)
AE: Discontinued	16% vs 10%	4 from all groups
AE: Grade 3/4	53% vs 33%	25* vs 27*
Haematological	64 vs 51	37% vs 48% (granulocytopenia)
AE: Died	2% vs 1%	1 in the docetaxel group

* may not be mutually exclusive

Appendix 5 Comparing and contrasting the economic models

Effectiveness

a) Survival

Structure

Both models estimate mean survival by fitting a Weibull distribution to the data of patient survival times for the docetaxel plus prednisone and mitoxantrone plus prednisone treatment arms of the TAX327 RCT. This allowed approximation of the 'tail' of survival times beyond the duration of the trial (analysis 2 of Sanofi-Aventis model, and Analyses 1 and 2 of Assessment Group model).

Both models thus derive the same estimate for mean survival without discounting. The Assessment Group model uses a two-state Markov model approach which allows the incorporation of discounting into the model, in accord with the NICE reference case. Discounting is unlikely to make a large difference in this appraisal due to the short time periods involved.

Parameter estimation

The parameters of the distribution of survival times for each treatment arm were estimated by Sanofi-Aventis using PROC LIFEREG in SAS (v9.1) software once it was established that a Weibull distribution was appropriate. Some parameters were reported in the sponsor submission and others were provided to the Assessment Group on request.

The effects on survival of treatments other than docetaxel plus prednisone/prednisolone and mitoxantrone plus prednisone/prednisolone considered in Analysis 2 of the Assessment Group model are estimated by applying indirect hazard ratios (with mitoxantrone plus prednisone/prednisolone as the common comparator, based on information from the RCTs reviewed in the clinical effectiveness section) to the absolute hazard rates estimated for mitoxantrone plus prednisone and docetaxel plus prednisone as appropriate.

Sensitivity analysis

Sanofi-Aventis also reported an ICER based on using the median (Analysis 1) of survival times observed within the trial rather than the estimated extrapolated mean (Analysis 2). A one-way, deterministic sensitivity analysis was undertaken using the estimates of the lower and upper bound (95% confidence interval) for mean survival for the docetaxel 3-weekly regimen.

The Assessment Group model base case assumes a discount rate for outcomes of 3.5%, and changes this to 1.5% for a one-way sensitivity analysis.

For the probabilistic sensitivity analysis carried out by the Assessment Group, a normal distribution for the estimated Weibull parameters was assumed, and the covariance between them was addressed based on data provided by Sanofi-Aventis. For indirect hazard rates estimated for Analysis 2, the log hazard is assumed to have a normal distribution.

b) Quality of Life

Structure

There is adjustment for the utility associated with health-related quality of life in the Assessment Group model, but not in the Sanofi-Aventis model.

Parameter estimation

For the base case, the Assessment Group model uses an estimate of quality of life during the last 12 months of life of patients with mHRPC derived from a published study which reported societal valuation using EuroQol EQ5D, a standardised and validated generic instrument. This was chosen after a systematic review of evidence reporting on the quality of life in patients with mHRPC. It should be noted that the model did not attempt to quantify, and therefore does not reflect any additional palliative benefits conferred by any individual chemotherapeutic regimen (over and above the increased benefits derived from gains in survival), and the same utility was used for quality adjustment of life years gained for all treatment strategies.

Sensitivity analysis

Two alternative approaches to estimating the quality of life adjustment for the Assessment Group model, are (1) the elicitation of preferences from the NHS Value in Health Panel with regard to health state descriptions based on FACT-P, a widely used and validated measure, and (2) the impact of adverse effects of treatment was estimated based on a meta-analysis of Grade III/IV event data, and the resulting utility decrements are assumed to have a gamma distribution for probabilistic sensitivity analysis.

Appendix 5 (continued) Comparing and contrasting the economic models

Costs

Structure	Both models consider the overall cost per patient to include the cost of study medication and administration per cycle multiplied by the estimated number of cycles, plus the estimated follow-up costs per patient, which include follow-up chemotherapy, supportive care drugs and hospitalisations.
Parameter estimation	Both models use an estimate of the mean number of cycles of chemotherapy received to estimate study medication costs. Both models estimate drug costs per cycle based on those in the *British National Formulary*, assuming that unused medication left in vials at the end of a session are discarded. The protocol doses are used in both models, with no adjustments made for dose-reduction for patients experiencing side-effects on either chemotherapy regimen. The Sanofi-Aventis model assumes a body surface area of 1.7 m^2, whereas the Assessment Group model uses 1.9 m^2. In the Sanofi-Aventis model, administration costs are estimated as the cost of a radiotherapy outpatient visit of £117, whereas the Assessment Group model uses a higher estimate of the cost of an oncology outpatient visit of £177. Follow–up costs in both models are based on within-trial treatment costs in the TAX327 multi-centre RCT. Further details are as follows: a) In the Sanofi-Aventis model, resource use data from all patients in the TAX327 trial were analysed and costed using UK unit costs to generate an average lifetime cost per patient within each arm of the trial, and data for the 'follow-up phase' ('other in-trial costs') were presented separately from costs of the 'first-line chemotherapy phase' (study medication drug acquisition and administration costs). To estimate the incremental differences between the costs of the docetaxel and mitoxantrone arm of the TAX327 trial, analysis was undertaken based on patient-level data. b) The Assessment Group model uses the Lin method to estimate follow-up costs, to ensure that censoring was appropriately considered. In the absence of patient level data it was not possible to conduct a detailed analysis of the resource use and costs associated with the component parts of the follow-up costs considered. As a result, costs were modelled using aggregate data and as such the potential impact of the different treatments on these separate components could not be reflected in the subsequent analyses. An adjustment based on a published cost-effectiveness study was used to estimate the follow up cost for patients receiving prednisone alone.
Sensitivity analysis	The Assessment Group report two one-way sensitivity analyses based on the Sanofi-Aventis model: one using the median, rather than mean number of cycles; the other using a higher assumption for body surface area and applying the costs of pre-medication oral dexamethasone. Sanofi-Aventis investigated a sensitivity analysis around the estimation of costs using the Lin method, and report that the different methods result in similar values, but the resulting ICER is not presented. A one-way sensitivity analysis on the Assessment Group model uses a discount rate of 6.5% for costs, rather than the 3.5% used in the base case. A probabilistic sensitivity analysis was carried out taking into account the spread around the mean number of cycles, and assuming a gamma distribution for follow-up costs.

Appendix 6 Breakdown and Reconciliation of Base case ICERs from the two models						
Abbreviations:						
AR=Assessment Report	**Docetaxel plus**		**Mitoxantrone plus**		**Difference (D+P - M+P)**	
AG=Assessment Group	**prednisone/prednisolone**		**prednisone/prednisolone**			
S-A=Sanofi-Aventis	**S-A**	**AG**	**S-A**	**AG**	**S-A**	**AG**
Expected Cost per patient	£15,767	£15,883	£9,711	£10,834	£6,056	£5,049
Estimated Mean Survival (Months)	22.38	-	18.65	-	3.73	3.48
Estimated Mean Survival (Years)	-	1.80	-	1.51	0.31	0.29
Estimated Median Survival	18.90	-	16.50	-	2.40	0.20
Quality Adjusted Life Years gained	-	0.96801	-	0.81364	-	0.1544
Health QoL utility used from AR (p.138/9)		0.538				
Results						
ICER of D+P vs M+P	**S-A**	**AG**				
With survival estimated by mean (S-A Analysis 2; AG Analyses 1 and 2)	£19,483	£32,706				
With survival estimated by median (S-A Analysis 1)	£30,280					
Approximate reconciliation between Sanofi-Aventis ICER to Assessment Group ICER						
Start with Sanofi-Aventis ICER from Analysis 2…		£19,483				
Quality adjust the life years gained	=19483/0.538	£36,214				
Use AG estimated difference in mean costs instead	=36214x5049/6056	£30,192				
Use AG estimated mean survival that incorporates discounting, rather than S-A estimate which does not	=30192x3.73/3.48	£32,360	…which is close to AG ICER of £32,706. Quality adjusting results in a substantial increase in the ICER, different cost estimation reduces it somewhat, and discounting mean survival increases it a little.			

Appendix 7 Description of sensitivity analyses, and resulting ICERs						
	Sanofi-Aventis Model			**Assessment Group Model**		
Overview of charactersation of uncertainty	Analysis 1 and Analysis 2 use different methods to estimate extrapolated survival. Two one-way sensitivity analyses are investigated, as described below.			This table shows ICERs resulting from 3 one-way sensitivity analyses described below. Probabilistic Sensitivity Analysis was also done, and results for the reference case are shown in the Assessment Report pp.146-9.		
		Analysis 1	Analysis 2		Analysis 1	Analysis 2
Base Case ICER	Analysis 1 uses median of within trial survival; Analysis 2 estimated extrapolated	£30,280	£19,483	Analysis 1 compares 3 treatment strategies (D+P, M+P and P); Analysis 2 compares 8 treatment strategies	£32,706	£32,706
Sensitivity analyses	**Change from Base case**	**New ICER (D+P vs M+P)**		**Change from Base case**	**New ICER (D+P vs M+P)**	
Effectiveness a) Survival	(No Discounting)			Discount rate 1.5% rather than 3.5% (and 6.5% for costs as below)	£31,674	£31,890
	A one-way, deterministic sensitivity analysis was undertaken using the estimates of the lower and upper bound (95% confidence interval) for mean survival for the docetaxel 3-weekly regimen, while keeping the mean survival estimate for mitoxantrone constant.	lower bound survival	£42,007			
		upper bound survival	£12,173			
Effectiveness b) Health QoL Utility	(No quality of life adjustment made)			Alternative method of estimating utility: FACT-P & NHS Value - In-Health Panel	£28,019	£29,436
				Adjustment to utility values for adverse events. Estimated using a meta-analysis of Grade III/IV adverse event data using a hierarchical Bayesian model.	£33,298	£33,298
Cost	A sensitivity analysis around the estimated is costs was investigated using the Lin Method, which resulted in similar values.	No resulting ICER is presented				
	Median number of cycles instead of mean (done by Assessment Group)	£46,095	£29,659			
	Body surface area 1.9 rather than 1.7 m2, and the costs of pre-medication oral dexamethasone were applied (done by Assessment Group)	£32,285	£20,773			
	(No Discounting)			Discount rate 6.5% rather than 3.5% (and 1.5% for outcomes as above)	£31,674	£31,980