NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Docetaxel for the treatment of hormone-refractory metastatic prostate cancer

Response to consultee, commentator and public comments on the ACD

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
Sanofi-Aventis		We believe that all the relevant evidence has been taken into account, and that the summaries of clinical effectiveness are reasonable interpretations of the available evidence with the following caveats:	Noted.
	1.3	The ACD discusses when repeat cycles of docetaxel may not be recommended including following relapse after initial response. Clarification on the definition of relapse may be required, as there may be confusion. It is not uncommon for patients to have intermittent chemotherapy breaks, which are not due to relapse. Therefore disease progression relapse is distinct from a treatment break.	Amended to: 'Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.'
	2.11	The ACD implies that the British Association of Urological Surgeons (BAUS) guidelines for second-line treatment of hormone-resistant disease recommend use in just asymptomatic patients; however, their recommendation actually includes all "fit patients". The BAUS guidelines, therefore, state "Docetaxel improves pain, patient quality of life, and overall survival and should be considered in all patients with mHRPC who are sufficiently fit for chemotherapy". This is an important clarification as "fit" patients will be defined regardless of whether they are symptomatic or	Amended to: 'There are a number of guidelines produced by professional organisations.'

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		asymptomatic. The recent MDT (Multi-disciplinary Team) Guidance for Managing Prostate Cancer Produced by BAUS, British Uro-oncology Group (BUG) and British Prostate Group (BPG) also recommends chemotherapy in patients who are metastatic and hormone-refractory. Stating 'Those who do not respond to maximal second-line hormonal therapy are considered to have hormone-refractory disease and are candidates for chemotherapy, novel therapies and/or symptomatic local treatments". In addition, the European Association of Urology guidelines also support the use in *all* mHRPC patients, specifically recommending docetaxel use in patients with mHRPC as being the reference treatment.	
Sanofi-Aventis	4.3.4	The ACD reviews both the TAX-327 study and a pooled meta-analysis in their review of docetaxel. In order to avoid potential confusion we would suggest clarifying that the Quality of Life (QoL) conclusion covered in Section 4.3.4 is highlighted as referenced to the pooled meta-analysis, i.e.:"there was insufficient evidence *at present based on the pooled metanalysis* to support the assertion that docetaxel provides benefits in quality of life and palliation over and above those associated with the use of mitoxantrone". However, in the randomised study TAX-327, docetaxel has shown significant QoL benefits in terms of pain response and prostate-specific symptoms, compared to mitoxantrone. This benefit has	Now addressed in paragraph 4.3.7 and amended to: '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

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		been recognised in section 4.1.5.	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 benefits results in an ICER lower than £32,700.'
Sanofi-Aventis	4.3.5	We agree with the comments made in Section 4.3.5. We would like to highlight that most centres will have a pro-active side-effect management protocol; and either prophylactically prevent side effects occurring with docetaxel in prostate cancer, or pro-actively brief patients on what can be expected, giving docetaxel a manageable and predictable side effect profile in Prostate Cancer.	Noted.
	4.3.6	We are pleased that the committee accepted the extrapolation of clinical data beyond the trial period, and find both the manufacturer and assessment group models acceptable.	Noted.
	5.1	The MRC Study (STAMPEDE) and other trials such as TRAPEZE review docetaxel in combination with bisphosphonates and radio-isotopes, These studies incorporate quality of life (QOL) assessments and have study populations in line with, and representative of, the	Noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		wider patient population in terms of age, performance status and co-morbidity, and will therefore, serve to enhance the volume of information available for this product in this licence indication for the future. To conclude, we consider that the provisional recommendations of the Appraisal Committee, in line with the additional comments suggested, are sound and constitute a suitable basis for the preparation of guidance to the NHS.	Noted.
British Prostate Group		We consider that this is a good document, that has taken into account the available evidence, and that the provisional recommendations are a sound basis for guidance to the NHS. We would echo some previous comments regarding the difficulty faced by non-health economists in evaluating complex health economic assessments, but would stress that this is a general point and not intended as a critique of this particular ACD. We would be delighted to provide any further assistance if required.	Noted.
The Royal College of Pathologists		The only comment I had regarding this health technology assessment was a correction of fact concerning the importance of Gleason grading. In paragraph 2 of page 30, it is stated that "the most important prognostic factor is the growth pattern or grade	Clarification noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		of the tumour assessed using the Gleason scoring system." This is true for hormone naive prostate cancer i.e. at presentation in untreated patients, but it is not true once tumours have metastasised and been treated by and become refractory to hormones. This does not affect the health technology assessment as such.	
The Prostate Cancer Charity		We agree with the Appraisal Committees preliminary recommendations on the use and prescription of the drug, as we feel that Docetaxel is an important addition to the medical arsenal against prostate cancer. Men with HRPC have a terminal condition and, though Docetaxel will not save their lives, it can extend and improve the quality of their lives remaining.	Noted.
The Prostate Cancer Charity	4.2.7	Cost effectiveness is important, but we note with concern the use of equivocal phrase "as long as the NHS is willing to pay at least £32,706 per QALY" on page13, point 4.2.7. We will scrutinise any attempts to ration this drug which might arise as a result of this equivocation. This may have the effect of permitting some Trusts to make Docetaxel 'unavailable' because it is deemed too expensive. This does not also make it cease to exist. A	Amended to: 'In the base-case results of the Assessment Group model the ICER of docetaxel (3-weekly) 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.' The Secretary of State's Direction on the funding of NICE Technology Appraisals can be accessed via http://www.nice.org.uk/page.aspx?o=294356 .

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		choice may be denied for a group of men who, up until now, have had few choices anyway, and it goes against your clear recommendation in favour. There may be an unintentional [and, admittedly, uncommon] discrimination against some disabled men, with an unqualified blanket application of the 60% Karnofsky rule. We agree that the cut off is largely 'reasonable' but want to flag up that a man in a wheelchair, for example, with some level of disability related to a pre existing condition e.g. spinal injury, might fall below that cut off in their pre cancer lives - and then not get treatment should they get HRPC later. This would be discrimination on the grounds of his disability, not on his likely response to treatment. He may, in all other senses, be fit. This could, I imagine, be easily adjusted in the wording.	The Committee's discussion on this issue is described in paragraph 4.3.9 : '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.' Appendix C has been amended correspondingly.
NHS Quality Improvement Scotland Reviewer 1		1. Whether you consider that all the relevant evidence has been taken into account. *Yes* 2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are	Noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		appropriate. *Yes* 3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. *Yes*	
NHS QIS Reviewer 2		1. I did enjoy reading the documents and was very impressed. They are clear and well-reasoned and I did not have cause to disagree with any of the recommendations. They recommend docetaxel as a treatment option for patients who are asymptomatic and have only laboratory or radiological evidence of progression. This group of patients were also included in the TAX 327 study and so the evidence base is there. Where chemotherapy is palliative some consultants advise using it in patients with symptoms from their disease and not necessarily using it in patients who are asymptomatic and whose quality of life is already good. The guidance, by calling it a treatment option does allow for treatment to be given immediately when there is biochemical evidence of progressive disease or deferred until symptoms develop. In relation to my clinical practice the guidelines are extremely welcome because at present use of docetaxel is not permitted for prostate cancer but I may use	Noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
NHS QIS Reviewer 2		mitoxantrone (outside its licence). It is clear that for most patients docetaxel has superior efficacy and I have been very keen to use it in selected patients with good performance status especially those with symptoms. 2. This is as usual a comprehensive review of the limited available literature, but it does rely very heavily on a single randomised trial. This did show advantages for docetaxel, but the advantage in median survival, while statistically significant, was only 2.4 months. There were benefits in quality of life and pain too, but a significantly greater risk of major adverse events which were more likely to be associated with longer term morbidity. Although described as 'cost-effective' the figures provided by the company and the assessment group are at the upper limit of usual acceptability and exceed £30k. In the absence of any effective treatment for this condition there will be very considerable pressure to make even a marginally effective treatment available, but this ACD does not seem to follow its own logic in the conclusions reached. A conclusion that docetaxel is marginally effective, toxic and expensive would seem to be equally supported by the evidence reviewed. Additional supporting evidence would seem to be necessary if the conclusion of the ACD is to be the outcome of the FAD in due course.	The Committee discussed this comment and related amendments have been made to section 4.3 of the FAD: Consideration of the evidence.
NHS QIS Reviewer 3	Overview	OVERVIEW – Issues for consideration 1. How generalisable are the results of TAX327? This issue has been raised in section 3.1 Clinical	Noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		effectiveness. *I believe they are, for appropriate groups* 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. *Difficult to advise. Probably best ignored* *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. *Survival issue is important – only treatment shown to improve survival in this group of patients, and will form the basis for future research trials* a. 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	

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		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. *Suggested requirements reasonable. Intervention should be considered after failure to respond to hormones – number of agents irrelevant. If a patient consistently shows responses to hormone manoeuvres, Docetaxel would not be appropriate till they stop. If they fail to respond to first line hormone, further hormone treatments are a waste of time.*	
NHS QIS Reviewer 3		b. 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. *Can't say, but little effect. Ignore*	
NHS QIS Reviewer 3		c. 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. *Depends on response. For most patients in UK, will*	

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
		probably receive maximum of 6 cycles, but will depend on clinical situation and response. The use of 10 cycles in the TAX 327 trial had more to do with Mitoxantrone use, particularly in US practice	
Institute of Cancer Research		We consider that all relevant evidence has been taken into account in the production of this comprehensive and thorough report. The summaries of clinical and cost effectiveness, as mentioned in the report, are limited by a lack of ability to include the results of the quality of life analysis using the FACT-P instrument in these estimates. It may well be that benefits in quality of life are, in fact, underestimated and the cost effectiveness analyses therefore overestimate the cost per QALY. It should also be noted that the comparison is made with chemotherapy using mitoxantrone and prednisolone rather than prednisolone alone. Although mitoxantrone is widely used within the UK, it does not have a product licence for hormone-refractory prostate cancer. Mitoxantrone is certainly not routinely offered to all men in the UK with hormone refractory disease and a Karnofsky performance status of 60% or more. The report notes that mitoxantrone and prednisolone are more cost effective that prednisolone alone. A secondary conclusion from the report could therefore be that, even without the new studies with docetaxel, that mitoxantrone should have been made more widely available to UK patients.	Noted. The Committee discussed this comment and related amendments have been made to section 4.3 of the FAD: Consideration of the evidence. In particular paragraph 4.3.7 has been amended to: '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.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
			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 benefits results in an ICER lower than £32,700.'
Institute of Cancer Research		The change in service provision needed to give chemotherapy with either docetaxel or mitoxantrone are fairly similar. In our opinion, such facilities should be more widely available to men with hormone-refractory prostate cancer. The consultation document would support our views that mitoxantrone should have been more widely available. The realisation that chemotherapy is a valuable management option for men with hormone-refractory disease will require the reconfiguration of service provision in that many men with hormone-refractory disease have not had adequate access to oncology rather than urology services in the past and Cancer Networks will need to design suitable patient pathways to ensure that chemotherapy provision can be made.	The NICE Implementation Directorate develop implementation support materials. This issue has been brought to their attention for consideration during the development of any relevant materials.
		We consider that the provisional recommendations are sound and a good basis for preparation of guidance to the NHS. We would also recommend, however, that due emphasis be given, in the future, to developing further studies to assess both the optimal timing and duration of treatment and the most appropriate management for men who have recurred after docetaxel treatment either because of primary lack of response to the drug or who relapse after initial response.	Noted.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
Welsh Assembly Government		We are content with the technical detail of the evidence supporting the provisional recommendations and have no further comments to make at this stage.	Noted.
Clinical Expert		I was very impressed with the thoroughness and quality of the review, and was pleased to note that the committee has recommended the use of docetaxel for fit patients who have recurrent prostate cancer.	Noted. The guidance section has been amended to: 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 (see appendix D) 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.'

Reply received but no comments:

- Department of Health

Comments received from website consultation:

- No comments received