National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Abiraterone for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy

Responses to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Commissioning Support Appraisals Service	This topic is appropriate.	Comment noted
	Janssen	We believe that this is an appropriate topic to refer to NICE for appraisal.	Comment noted
	Prostate Cancer Charity	It would be appropriate to refer this topic to NICE. Treatment options for men with metastatic, castration-resistant prostate cancer following previous cytotoxic chemotherapy are limited and it would be desirable to increase the range of effective treatments available for these patients, particularly if this leads to extended overall and progression-free survival. There is currently no approved agent for men with metastatic, castration-resistant prostate cancer that has progressed during or after a docetaxel-based treatment. Should the proposed appraisal recommend that abiraterone is effective for the above indication, it will help to provide standardised access and increased patient choice to a group of patients who currently have a restricted range of treatments available once their cancer progresses following docetaxel treatment.	Comment noted
	British Uro-oncology Group (BUG)	Yes it is appropriate to review this product now.	Comment noted
Wording	Commissioning Support	Yes.	Comment noted

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	Appraisals Service		
	Janssen	We propose the wording of the remit to be as follows: "To appraise the clinical and cost effectiveness of abiraterone within its licensed indication for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a taxane."	Comment noted. Following the scoping workshop, consultees agreed that “castration-resistant” should be changed to “castrate-resistant”, and that this change would be concurrently reflected in the wording of the population.
	Prostate Cancer Charity	We would like NICE to consider use of the term ‘castrate resistant prostate cancer’, particularly when providing information to patients. Although we acknowledge that this is a clinically accurate term used amongst health professionals, we know that people affected by prostate cancer are generally detered by it. A recent, small, survey of 27 of the Charity's Prostate Cancer Voices network found that 24 of the respondents said they would prefer to see a different phrase used to describe this type of prostate cancer. 21 respondents said they found the phrase "castration" was an unhelpful way of describing the treatments or type of prostate cancer.	Comment noted. Following the scoping workshop, consultees agreed that “castration-resistant” would be changed to “castrate-resistant”, and that this change would be concurrently reflected in the wording of the population. The scope has been amended accordingly.
	British Uro-oncology Group (BUG)	The pivotal trial was conducted in men who had all received prior docetaxel, but we think this wording is more appropriate for clinical practice.	Comment noted
Timing Issues	NHS Bradford and Airedale	We are not convinced that there is an urgent need to appraise this treatment now. The benefit, albeit from an as yet unpublished research, is hardly convincing. Though there would seem to be an improvement in overall survival - 4 months is hardly startling for prostate cancer. We have concerns about the affordability of the drug if positively appraised by NICE. PCTs cannot afford to introduce new treatments without first removing other treatments from the care pathway - this rarely happens in practice. The net result is usually that PCTs are required (as a result of a positive NICE TA) to make investments in less cost effective therapies, and thus make later disinvestments in more cost effective interventions -	Comment noted. NICE is expected to produce guidance on the use of new technologies within 6 months from when the marketing authorisation is granted. If this topic is referred to NICE by the Department of Health for a technology appraisal, the

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		thus representing a net loss of health to their population. This is not palatable and many find it unacceptable. Increasingly PCTs will seek to remove this funding as close to the treatment concerned as possible - therefore we would seek reductions elsewhere in the prostate cancer spend. The view we have picked up from local clinicians is that this is not high on any wish lists.	Committee will consider both the clinical and cost-effectiveness of the treatment before making its recommendation. A positive recommendation will only be made if the Committee is convinced by the available evidence that the technology represents a cost-effective use of NHS resources.
	Commissioning Support Appraisals Service	The drug does not currently have marketing authorisation in the UK	Comment noted
	Janssen	Please see the response from Janssen under "Comment 4: regulatory issues".	Comment noted
	NHS Hertfordshire (previously EAST & North Hertfordshire PCT)	This technology has not been raised as a priority in our prioritisation exercise with our clinicians. Hence, we do not believe there to an urgent need to appraise this treatment now. From the unpublished research, there appears to be some benefit. However, this benefit does not appear to convincing for the following reasons: - Most people do not die of prostrate cancer. - the proposed improvement in overall survival is not impressive for prostrate cancer. An STA only adds treatment to a pathway and does not look at the overall treatment pathway and comparable cost-effectiveness of treatments in the pathway. In the current NHS climate of diminishing resources, PCTs can only afford new treatments by disinvestment elsewhere. Unless NICE considers this as part of its technology review (which is not within the scope of the review) this will not happen in practice. Hence, a positive	Comment noted. NICE is expected to produce guidance on the use of new technologies within 6 months from when the marketing authorisation is granted. If this topic is referred to NICE by the Department of Health for a technology appraisal, the Committee will consider both the clinical and cost-effectiveness of the treatment before making its recommendation. A positive recommendation will only be made if the Committee is convinced by the available

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		recommendation from NICE would impact on PCTs being able to afford delivery of more cost-effective interventions. In the scenario we are in now, this invariably results in disinvesting from more cost-effective interventions (especially those that would keep people at home) - thus representing a net loss of health to our population. This is not palatable and many find it unacceptable.	evidence that the technology represents a cost-effective use of NHS resources.
	Prostate Cancer Charity	The timing appears appropriate, however it should be noted that treatment options for this patient population are limited. The results of the appraisal could significantly improve treatment choice for these patients (should abiraterone be considered effective) and so should be conducted promptly.	Comment noted
	British Uro-oncology Group (BUG)	This is an urgent issue as patient's clinical condition changes rapidly and any delays will limit the number of men who may benefit.	Comment noted
Additional comments on the draft remit	Janssen	No additional comments.	Comment noted
	NHS Hertfordshire (previously EAST & North Hertfordshire PCT)	The draft review is very narrow and in line with the potential licensing of the drug. As NICE is aware, there is an increasing need to consider all treatments in the pathway of the condition as a multiple technology assessment.	Comment noted. Following the scoping workshop, consultees agreed that, for reasons of timeliness (as the technology appraisal of cabazitaxel for the second-line treatment of hormone-refractory, metastatic prostate cancer has already been scheduled into the work programme) abiraterone should be appraised through the STA process.
	Prostate Cancer Charity	None.	Comment noted

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Commissioning Support Appraisals Service	This is complete	Comment noted
	Janssen	Under the 3rd paragraph in this section, we would like to add the following statement after the last sentence. "At the present time, there are no licensed medicines and there is no standard of care for treating these patients."	Comment noted. The scope has been amended to indicate that there are currently limited treatment options for these patients.
	Prostate Cancer Charity	Important additional information that should be provided is the number of men with prostate cancer who will go on to develop metastatic disease. It is estimated that 55-60% of patients will do so, and once they become resistant to hormone therapy their prognosis becomes extremely poor (Source: National Horizon Scanning Centre April 2009). This information should provide a better context to assess the need for this technology and the number of patients who may be eligible.	Comment noted. The background of the scope is only intended to provide a brief overview of the disease and its current clinical management. A more thorough description of the clinical aspects of the disease will be included in the manufacturer's submission. The scope has been amended to state that "it is estimated that 55-60% of men with prostate cancer will develop metastatic disease".
	British Uro-oncology Group (BUG)	Paragraph 2, line 2 - propose changing this to 'NICE Guideline 2008 states that men with localised disease should be managed with active surveillance, surgical removal of the prostate (prostatectomy) or high dose radical radiotherapy' Paragraph 3, line 1 - would say that the response rate to initial hormone therapy is >90% Paragraph 4 - last line: management options include mitoxantrone with or without steroids, further hormonal therapies and bone targeted therapies but none have been shown to improve survival.	Comment noted. The scope has been amended in order to reflect these proposed changes. Mitoxantrone is included as a comparator.

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The technology/ intervention	NHS Bradford and Airedale	At this stage the data seems limited, but when the key trial is published it should be enough to support a licence.	Comment noted
	Commissioning Support Appraisals Service	Yes	Comment noted
	Janssen	Please note that as of September 2010, the company name has been changed to Janssen. Under "The Technology" section, we would like to revise the first two paragraphs to the following for accuracy: "*Abiraterone (Brand name unknown, Janssen) is an oral selective androgen biosynthesis inhibitor that potently blocks CYP17, a critical enzyme in testosterone synthesis, theraby blocking persistent androgen synthesis generated by the adrenals, prostate, and within the tumour.* *Abiraterone does not have a UK marketing authorization. It has been studied in clincal trials in combination with prednisone or prednisolone compared with placebo plus prednisone or prednisolone in men who had previously received cytotoxic chemotherapy (docetaxel). These men have had prior medical and/ or surgical castration and whose disease has progressed."* Under "The Intervention", we would like to revise the statement to: "*Abiraterone in combination with prednisone or prednisolone*". This wording reflects the information submitted in the European Medicines Agency (EMA) Marketing Authorization Application (MAA).	Comment noted. The "Technology" section of the scope has been amended slightly. This section is only intended to provide a brief description of the technology. A complete description will be provided by the manufacturer in their evidence submission. Following the scoping workshop, consultees agreed that, since prednisone and prednisolone are, respectively, the US and UK counterparts of one another, the scope would only include the version used in the UK (prednisolone). The intervention in the scope has not been changed.
	NHS Hertfordshire (previously EAST & North Hertfordshire PCT)	The description appears to be in line with the PHASE III study - so we assume this is how the drug would be licensed. However, the data of this study is limited.	Comment noted

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	Prostate Cancer Charity	It is difficult to comment on the technology at present as the results of the relevant phase 3 clinical trial/s have not yet been published in a peer reviewed journal. It is hoped that this evidence will shortly be available and will not significantly delay consideration of this technology.	Comment noted
	British Uro-oncology Group (BUG)	The trial compared abiraterone and predisone/prednisolone with placebo and prednisone/prednsiolone.	Comment noted. The technology section of the scope has been updated accordingly.
Population	NHS Bradford and Airedale	PCTs will seek a very clear articulation of the size of the likely population to be treated. This should be at as early a stage as possible. Toxicity is an issue with this drug, as such - patients tend to get docetaxel first – those that fail tend to be quite elderly/poorly at this stage and so a toxic treatment would be an option only for a minority. We would view that the TA should place this treatment ONLY after docetaxel therapy.	Comment noted. Following the scoping workshop, consultees agreed that the impact of both toxicity and treatment-related symptom changes would be captured in the measure of health-related quality of life. The Committee will consider the most appropriate place for the technology in the current clinical pathway for prostate cancer, after assessing the licensed indication of the treatment, advice from clinical experts and the available evidence.
	Commissioning Support Appraisals Service	Yes.	Comment noted

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	Janssen	We would like to revise the statement to the following: "*For the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a taxane*."	Comment noted. NICE can only appraise technologies within their licensed indications and has amended the population in line with the indication as specified in the CHMP positive opinion.
	NHS Hertfordshire (previously EAST & North Hertfordshire PCT)	At the scoping stage, PCTs would like the size of the population to be articulated clearly. It is not clear from the unpublished research of the performance status of the studied population or average age. Those that fail docetaxel tend to quite poorly at this stage. Hence, impact on QoL with the treatment is of paramount importance. We would view that the TA should place this treatment ONLY after docetaxel therapy.	Comment noted. The Committee will consider the most appropriate place for the technology in the current clinical pathway for prostate cancer, after assessing the licensed indication of the treatment, advice from clinical experts and the available evidence.
	Prostate Cancer Charity	No comments.	Comment noted
	British Uro-oncology Group (BUG)	Consider limiting the use to men who have progressed after the use of cytotoxic chemotherapy metastatic castrate refractory prostate cancer (as opposed to those who received it adjuvantly ie within STAMPEDE).	Comment noted. The Committee will consider the most appropriate place for the technology in the current clinical pathway for prostate cancer, after assessing the licensed indication of the treatment, advice from clinical experts and the available evidence.
	Royal College of Physicians (RCP)	Within the contexts of the available data, this is the appropriate population to consider. The evidence for patients who are not fit for docetaxol chemotherapy is not available; but there is no reason why these patients should respond to abiraterone in a different way.	Comment noted

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Comparators	NHS Bradford and Airedale	We feel this would be more appropriately framed as a MTA. This drug and cabazitaxel are in competition, though the key licensing trials had different comparators. Abiraterone did better, it was up against an easier comparator. Mitoxantrone (which also carries a high toxicity risk) would also be a suitable comparator.	Comment noted. Following the scoping workshop, consultees agreed that, for reasons of timeliness (as the technology appraisal of cabazitaxel for the second-line treatment of hormone-refractory, metastatic prostate cancer has already been scheduled into the work programme) abiraterone should be appraised through the STA process. Mitoxantrone is included as a comparator.
	Commissioning Support Appraisals Service	Best supportive care is an appropriate comparator for castration- and cytotoxic-resistant prostate cancer. Mitoxantrone plus prednisolone is an appropriate comparator. In June 2006 TA101 warned that 'Mitoxantrone is widely used in the UK for hormone-refractory metastatic prostate cancer patients who are fit for chemotherapy…combination of mitoxantrone and prednisolone has come to be accepted as the standard care for this group of patients'. The current level of mitoxatrone use as an alternative to docetaxel should be assessed.	Comment noted.
	Janssen	We agree with the listed comparator, "mitoxantrone in combination with prednisolone". We propose that the comparator, "Best Supportive Care (BSC)" be omitted as the use of the supportive care regimens mentioned here (may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics) are employed across all comparators in this patient population. These best supportive care measures are given on an as needed basis in order to address the complications of the disease, regardless of the main	Comment noted. It was stated by clinical experts at the scoping workshop that best supportive care is symptom-driven and complementary. It was clarified that best supportive care should include: radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal

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		comparator used to treat the prostate cancer. We suggest the addition of prednisone or prednisolone (given as daily therapy) as a comparator in this patient population. When prednisone or prednisolone is given as a daily therapy in this manner, it is viewed as an active comparator that has an effect on PSA (prostate specific antigen) response (Tannock et al. 1996) in patients with prostate cancer. The Abiraterone Phase III Study COU-AA-301 uses daily prednisone or prednisolone as a comparator and has BSC regimens allowed for both study arms when needed. Reference: Tannock IF et al (1996). Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. JCO 1996;14:1756-1764	therapies, and corticosteroids. The description of best supportive care in the scope has been amended accordingly. The comparators in the scope are intended to reflect current routine clinical practice in the UK for patients with metastatic, castration-resistant prostate cancer, and have been defined based on clinical literature and advice from clinical experts. Consultees did not consider that prednisolone is currently given as monotherapy for this patient population.
	NHS Hertfordshire (previously EAST & North Hertfordshire PCT)	We feel this would be more appropriately framed as a MTA as NICE is also undertaking an STA of cabazitaxel. Even though the key licencing trials had different comparators for these two treatments, they are indicated at the same stage in the pathway. The placebo arm in Abiraterone trials was an easier comparator compared to that used in Cabazitaxel trial. Mitoxantrone (which also carries a high toxicity risk) would also be a suitable comparator.	Comment noted. Following the scoping workshop, consultees agreed that, for reasons of timeliness (as the technology appraisal of cabazitaxel for the second-line treatment of hormone-refractory, metastatic prostate cancer has already been scheduled into the work programme) abiraterone should be appraised through the STA process. Mitoxantrone is included as a comparator.

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	Prostate Cancer Charity	In best supportive care (this may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics) there is scope for slowing disease progression with corticosteroids, but none of the other treatments available offer the same apparent advantage as abiraterone.	Comment noted.
	British Uro-oncology Group (BUG)	Yes - we think all of these are used except oxygen and antibiotics! BSC care also includes radioisotopes, zoledronic acid and additonal hormonal manoeuvres including diethylstilboestrol and ketoconazole, and second line docetaxel None of these can be considered best - treatment is highly individualised	Comment noted. It was stated by clinical experts at the scoping workshop that best supportive care is symptom-driven and complementary. It was clarified that best supportive care should include: radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids. The description of best supportive care in the scope has been updated accordingly.
	Royal College of Physicians (RCP)	Bisphosphonates (typically Zoledronic Acid) should also be considered. Radiotherapy would include radioisotope therapy (Strontium, Samarium). Second-or third-line hormone therapy would include Bicalutamide or Stilboestrol. All of the above comparators are routinely used, as well as those listed in the draft scope. It is not possible currently to identify subgroups who are most likely to benefit. Previous response to taxane treatment would also be relevant.	Comment noted. It was stated by clinical experts at the scoping workshop that best supportive care is symptom-driven and complementary. It was clarified that best supportive care should include: radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids. The description of best supportive care in the scope has been updated accordingly.

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Outcomes	NHS Bradford and Airedale	Toxicity is a significant issue and this should be reflected in the measurement of outcomes, and factored into the economic analysis - both on the cost of treating toxicity related events, and in the measurement of quality of life. Side effects included altered liver function, cardiac function and fluid retention - we would seek that there is a quantification of these (and all other side effects) are incorporated into the analysis NHSBA notes that the as yet unpublished study (presented at EMSO conference) finds that Abiraterone plus low-dose prednisone/prednisolone treatment was associated with a 35% reduction in the risk of death (HR=0.65; 95% CI: 0.54 to 0.77; p<0.0001) and a 36% increase in median survival (14.8 vs. 10.9 months) vs. placebo + prednisone/prednisolone. Our view is that median survival often overestimates MEAN treatment effect in the whole population. The distribution of outcome measures are usually left skewed - i.e. there are a significant cohort of the treated population that have little benefit, but the median survival is skewed by a few outliers whom survive a very long time indeed. Thus from a commissioning perspective we would wish to see a MEAN survival - or log transformation of the median data to get an estimate of mean survival. Commissioners are interested in the whole population - those that do well and those that do not do well.	Comment noted. Following the scoping workshop, consultees agreed that the impact of both toxicity and treatment-related symptom changes would be captured in the measure of health-related quality of life. No changes to the scope required.

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	NHS Hertfordshire (previously EAST & North Hertfordshire PCT)	Toxicity is a significant issue and this should be reflected in the measurement of outcomes, and factored into the economic analysis - both on the cost of treating toxicity related events, and in the measurment of quality of life. Side effects included altered liver function, cardiac function, sodium levels and fluid retention - we would seek that there is a quantification of these (and all other side effects) are incorporated into the analysis It is noted that the yet unpublished study finds that Abiraterone plus low-dose prednisone/prednisolone treatment was associated with a 35% reduction in the risk of death (HR=0.65; 95% CI: 0.54 to 0.77; p<0.0001) and a 36% increase in median survival (14.8 vs 10.9 months) vs placebo + prednisone/prednisolone. As Commissioners are interested in the likely benefit to the whole treated population - those that do well and those that do not do well, we would wish to see a MEAN survival - or log transformation of the median data to get an estimate of mean survival. Our view is that median survival often overestimates MEAN treatment effect in the whole population. The distributiuon of outcome measures are usually left skewed - ie there are a significant cohort of the treated population that have little benefit, but the median survival is skewed by a few outliers who survive a very long time indeed.	Comment noted. Following the scoping workshop, consultees agreed that the impact of both toxicity and treatment-related symptom changes would be captured in the measure of health-related quality of life. No changes to the scope required.
	Commissioning Support Appraisals Service	Affect upon symptoms could be considered as an additional outcome	Comment noted. Following the scoping workshop, consultees agreed that the impact of both toxicity and treatment-related symptom changes would be captured in the measure of health-related quality of life. No changes to the scope required.

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	Janssen	We would like to recommend that the following outcome measures be considered: - Overall survival - Radiographic Progression Free Survival - Time to Prostate Specific Antigen (PSA) Progression - PSA Response Rate - Adverse effects of treatment - Health-related quality of life	Comment noted. Following the scoping workshop, consultees agreed that the outcome measures to be considered are: - overall survival - progression-free survival - response rate - prostate specific antigen (PSA) response - adverse effects of treatment - health-related quality of life For an STA, the manufacturer is responsible for providing the evidence submission for the Committee to consider. Additional outcomes can be included for the Committee to consider at the manufacturer's discretion.

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	Prostate Cancer Charity	The relevant clinical outcomes we would identify are those already identified in the draft scope. However, it is important that health-related quality of life and adverse effects are considered with an equal standing to the other outcomes. Patient-reported outcomes should also be considered, to ensure that the agent is not only clinically effective but also improves outcomes of importance to this patient population. Health-related quality of life is particularly crucial at this point in the cancer journey for a man with castrate resistant disease. Aspects that relate to quality of life should be specifically considered, including the impact of the treatment regimen on number of hospital appointments, method of delivering treatment (e.g. oral, intravenous etc.) and side effects. For example, as abiraterone is an oral agent, its administration is likely to be comparatively more straightforward and can offer a man with advanced disease greater flexibility to lead a more 'normal' life for the period of benefit.	Comment noted
	British Uro-oncology Group (BUG)	As long as pain improvement and prolongation of developing new pain is captured.	Comment noted
Economic analysis	Janssen	No comment.	Comment noted
	British Uro-oncology Group (BUG)	Appropriate.	Comment noted
	Prostate Cancer Charity	We do not evidence to enable us to comment on this area.	Comment noted
Equality and Diversity	Commissioning Support Appraisals Service	There are no issues.	Comment noted

Section	Consultees	Comments	Action
	Janssen	No comment.	Comment noted
	Prostate Cancer Charity	It will be important to ensure that access to this technology is equitable and discrimination does not occur solely on the basis of age, ethnicity or socio-economic status. Prostate cancer is more common in men aged over 60 and African Caribbean men are three times more likely to develop prostate cancer than white men of the same age in the UK. Furthermore, men from lower socioeconomic backgrounds are less likely to survive prostate cancer than men from more affluent backgrounds. It will be important to ensure that eligible patients from these populations are not denied access to this technology (if approved) because of factors related to their age, ethnicity and socio-economic status. Information and communication strategies must also be considered and patients consulted to ensure that access can be as equitable as possible.	Comment noted. The Committee will be expected to assess whether any of their decision restrict access to the technology for any people with the protected characteristics outlined in the current Equalities legislation. During consultation on the scope, no evidence was received of differential access to therapy or prognosis in this group. The fact has been noted for the Committee to consider, but no changes to the scope are required.
	British Uro-oncology Group (BUG)	There should not be any issues regarding equality as patients will alll be under the care of specialist oncologists.	Comment noted
Innovation	Royal College of Physicians (RCP)	This technology is believed by the international community to represent a 'step change' in the management of this condition.	Comment noted. The Committee will consider the innovative nature of abiraterone, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No changes to the draft scope required.

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Other considerations	NHS Bradford and Airedale	This trial was stopped early, with a relatively high degree of publicity. We are not able to discern what the reason for the early cessation of the trial was. NHSBA would seek a VERY CLEAR articulation of why the trial was stopped early and what benefit this has. A 2005 systematic review in JAMA highlighted an increasing trend towards stopping stopped RCTs early. Trials stopped early often fail to adequately report relevant information about the decision to stop early, and show implausibly large treatment effects, particularly when the number of events is small. These findings suggest clinicians should view the results of such trials with scepticism. JAMA. 2005;294:2203-2209 This drug seems to display some of these characteristics, therefore we would seek a full explanation of the technical reasons of why this trial was stopped. It seems entirely possible that the trial was truncated in order to bring the drug to market as soon as possible - whilst this is commendable if a treatment truly is innovative and truly incrementally better that what it replaces (we remain to be convinced in this particular case) truncation of a trial limits the ability of the trial to properly test the a priori hypothesis about treatment efficacy and safety, thus we might not truly know quite how good a treatment is because all the data that was planned to be collected was not. Until the data is published in full, in a peer reviewed journal, it is simply impossible to make any kind of judgement as to whether the truncation of THIS trial was justified by bringing an important treatment forward. We would be particularly interested in whether the trial was truncated before it had recruited all of the planned patients (i.e. possibility of underpowered) or whether it was truncated and outcomes / adverse events measured with a too short timescale to allow full judgement of the population impact of the treatment. The JAMA systematic review found an increasing prevalence of RCTs reported to have stopped early for benefit, with clustering of publication in the top general medical journals. Many RCTs evaluated cardiovascular or cancer interventions and were funded by for-profit agencies. The JAMA systematic review found that truncated trials can lead to over estimating	Comment noted. For an STA, the manufacturer is responsible for providing the evidence submission for the Committee to consider. The submission will provide a comprehensive assessment of the clinical evidence, including detailed descriptions of all of the pivotal clinical trials.

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	NHS Hertfordshire (previously EAST & North Hertfordshire PCT)	This drug has attracted a high degree of publicity as the trial is funded in part of Cancer Research UK. We note that the trial was stopped early and patients from placebo arm moved to treatment arm. We are not able to discern what the reason for the early cessation of the trial was. NHS Hertfordshire would seek a VERY CLEAR articulation of why the trial was stopped early and what benefit this has. A 2005 systematic review in JAMA highlighted an increasing trend towards stopping RCTs early. Trials stopped early often fail to adequately report relevant information about the decision to stop early, and show implausibly large treatment effects, particularly when the number of events is small. These findings suggest clinicians should view the results of such trials with skepticism. JAMA. 2005;294:2203-2209 This drug seems to display some of these characteristics, therefore we would seek a full explanation of the technical reasons of why this trial was stopped. It seems entirely possible that the trial was truncated in order to bring the drug to market as soon as possible - whilst this is commendable if a treatment truly is innovative and truly incrementally better that what it replaces (we remain to be convinced in this particular case) truncation of a trial limits the ability of the trial to properly test the a priori hypothesis about treatment efficacy and safety, thus we might not truly know quite how good a treatment is because all the data that was planned to be collected was not. Until the data is published in full, in a peer reviewed journal, it is simply impossible to make any kind of judgement as to whether the truncation of THIS trial was justified by bringing an important treatment forward. We would be particularly interested in whether the trial was truncated before it had recruited all of the planned patients (ie possibility of underpowered) or whether it was truncated and outcomes / adverse events measured with a too short timescale to allow full judgement of the population impact of the treatment. the JAMA sytematic review found found an increasing prevalence of RCTs	Comment noted. For an STA, the manufacturer is responsible for providing the evidence submission for the Committee to consider. The submission will provide a comprehensive assessment of the clinical evidence, including detailed descriptions of all of the pivotal clinical trials.

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		reported to have stopped early for benefit, with clustering of publication in the top general medical journals. Many RCTs evaluated cardiovascular or cancer interventions and were funded by for-profit agencies.The JAMA systematic review found that truncated trials can lead to over estimating the treatment effect, sometimes considerably, especially when the number of events is small (<200).	
	Commissioning Support Appraisals Service	These are appropriate.	Comment noted
	Janssen	The following is commercial in confidence information: **Confidential information has been removed**	Comment noted
	British Uro-oncology Group (BUG)	Comparison with cabazitaxel.	Comment noted. It was noted by clinical experts at the scoping workshop that although both agents are intended for use in broadly similar populations, abiraterone would likely be used to defer the use of cabazitaxel until a later stage. Cabazitaxel is not currently in routine use in the UK and therefore is not considered as an appropriate comparator to abiraterone at this time.
Questions for consultation	NHS Bradford and Airedale	Not strictly a question for NICE, but we note that this drug is being supplied free of charge pre licence currently - and that all patients starting treatment within this pre licence phase will remain free.	Comment noted

Section	Consultees	Comments	Action
	Commissioning Support Appraisals Service	As covered above	Comment noted
	Janssen	Abiraterone has a mechanism of action not found in currently licensed medications. Abiraterone is an oral selective androgen biosynthesis inhibitor that potently blocks CYP17, a critical enzyme in testosterone synthesis, thereby blocking androgen synthesis generated by the adrenal, prostate and within the tumour. Abiraterone demonstrated an overall survival benefit in the Phase III Study COU-AA-301 trial. The adverse event profile for abiraterone consisted of predominantly Grade 1 or 2 events with a low rate of drug discontinuation. Abiraterone has the potential to make a significant and substantial impact on health-related benefits compared to using corticosteroids alone. This represents a step-change for the management of metastatic castration resistant prostate cancer patients. Patients at this late stage of their disease have progressive disease for which there are no licensed medicines or standard of care available. Since abiraterone is an oral medication that is well tolerated, there may be health-related benefits like patient preference which may not be included in the QALY calculation. The nature of the data will be taken from the Phase III Study COU-AA-301 for abiraterone.	Comment noted. The Committee will consider the innovative nature of abiraterone, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No changes to the draft scope required.
	NHS Hertfordshire (previously EAST & North Hertfordshire PCT)	Not strictly a question for NICE, but we note that this drug is being supplied free of charge pre licence currently - and that all patients starting treatment within this pre licence phase will remain free.	Comment noted

Section	Consultees	Comments	Action
	British Uro-oncology Group (BUG)	Yes, this is a significant additional therapy that has the potential to prolong survival for a large number of men As a tablet it can be dispensed immediately and will have relativley little impact on clinics Results from PIVOTAL phase III trial COU-AA-301, pre-planned interim results presented in 2010, with full paper submitted to NEJM 2011	Comment noted
	Royal College of Physicians (RCP)	The results of the COU-AA-301 (in press, NEJM) are the major source of evidence. The previous publications by de Bono and colleagues and by Attard and colleagues give further background from the phase I and II studies, and which illustrate the benefits well.	Comment noted
Additional comments on the draft scope.	Janssen	No comment.	Comment noted

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Medicines and Healthcare products Regulatory Agency
NHS Quality Improvement Scotland
Public Health Wales NHS Trust
Prostate Action
Welsh Government
Marie Curie Cancer Care
Royal College of Nursing