Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen

Appendix D

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

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Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	British Uro-oncology Group (BUG)	Yes this is a very appropriate topic for NICE to consider and very timely	Comment noted. No action required.
	Janssen	Janssen believes this is an appropriate topic to refer to NICE for appraisal	Comment noted. No action required.
	Prostate Cancer Support Federation	It would definitely be appropriate to refer the use of Enzalutamide to Nice. Enzalutamide has been shown to be highly successful in trials and will be an important weapon in a area where not much else exists	Comment noted. No action required.
	Prostate Cancer UK	It would be appropriate to refer this topic to NICE. Treatment options for men with metastatic, castration-resistant prostate cancer following previous treatment with a docetaxel regimen 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 survival. Currently, abiraterone is the only treatment widely available on the NHS for men who have metastatic castration-resistant prostate cancer which has stopped responding to other hormone therapies and docetaxel chemotherapy. Cabazitaxel is licensed for use in this setting, but has not been recommended by NICE. The only other options are palliative/best supportive care. Therefore, Prostate Cancer UK welcomes NICE's proposed Single Technology Appraisal of enzalutamide. Should the proposed appraisal recommend that this agent is effective, it will help to provide standardised access and increased patient choice to	Comment noted. No action required.

Section	Consultees	Comments	Action
		a group of patients who currently have a limited range of treatments.	
	Astellas Pharma Ltd	Astellas supports the referral of enzalutamide to NICE for Single Technology Appraisal. Patients treated with enzalutamide have been shown to achieve a statistically-significant improvement in median overall survival compared to a placebo group (18.4 months versus 13.6 months respectively ($p < 0.0001$)), and positive guidance from NICE will facilitate access for both patients and physicians.	Comment noted. No action required.
Wording	British Uro-oncology Group (BUG)	Yes	Comment noted. No action required.
	Janssen	Janssen suggests that the wording of the remit should reflect the anticipated licence	Comment noted. The wording has been updated accordingly. Please note that following feedback received from stakeholders during scoping and appraisal consultations, NICE and the Department of Health have agreed that the term 'castration resistant prostate cancer' should be replaced with 'hormone relapsed

Section	Consultees	Comments	Action
			prostate cancer' (HRPC). This will be implemented for all prospective appraisals from January 2013 onwards. The scope has been updated accordingly.
	Prostate Cancer Support Federation	I think the wording is correct	Comment noted. No action required.
	Prostate Cancer UK	We would like NICE to consider use of the term 'castrate resistant prostate cancer' when providing information on this appraisal 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 small, survey of 27 of Prostate Cancer UK's supporters 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. The wording has been updated accordingly. Please note that following feedback received from stakeholders during scoping and appraisal consultations, NICE and the Department of Health have agreed that the term 'castration resistant prostate cancer' should be replaced with 'hormone relapsed

Section	Consultees	Comments	Action
			prostate cancer' (HRPC). This will be implemented for all prospective appraisals from January 2013 onwards. The scope has been updated accordingly.
	Astellas Pharma Ltd	No additional comments	Comment noted. No action required.
Timing Issues	British Uro-oncology Group (BUG)	This is an important development in the management of men with metastatic castration resistant prostate cancer and should be considered urgently as there are benefits to this group of patients with regards to overall survival and symptom control. This is also an extremely well tolerated therapy that can be prescribed in the out-patient setting without the needf or additional follow up tests and additional monitoring visits	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Prostate Cancer Support Federation	This is urgent, there are not many options for the group of patients this drug applies to. Many patients cannot toloerate either a Docetaxel or an Abiraterone regime due to the organ damage. This drug provides a less toxic path for such men and is urgently required.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.

Section	Consultees	Comments	Action
	Prostate Cancer UK	As there are limited treatment options for men with castrate resistant prostate cancer, once a licence is granted for enzalutamide we would like it to be appraised as soon as possible.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Astellas Pharma Ltd	Astellas support conducting this appraisal at the earliest opportunity to allow patients and physicians to access enzalutamide as close to the licensing date as possible. [*Commercial-in-confidence information removed*]	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
Additional comments on the draft remit	Janssen	No additional comments	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	British Uro-oncology Group (BUG)	Accurate and complete	Comment noted. No action required.
	Prostate Cancer Support Federation	Correct	Comment noted. No action required.
	Prostate Cancer UK	We note that the statisitics outlined in the background are based on 2008 figures. Cancer Research UK have produced new incidence and mortality statisitics. In 2009, 34,593 men were diagnosed with prostate cancer in England and 2,371 in Wales. The number of deaths from prostate cancer in 2010 were 9,082 in England and 547 in Wales. Prostate Cancer UK note that in the background section reference is made to 'around 55-65% of people with prostate cancer develop metastatic disease'. We believe it would be helpful if the evidence were reviewed to provide an updated figure. For example, the National Horizon Scanning Centre and CancerHelp UK now state that "metastatic disease occurs in 20-30% of men with prostate cancer, the majority of whom will eventually become resistant to hormone therapy", although we do not know the primary evidence source for this statistic.	Comment noted. The scope has been updated to incorporate the latest statics. According to our records, the figure for the development of metastatic disease is correct; it may be worth noting that at the time of writing the scope, the Cancer Research UK website stated that approximately 20-30% of men with primary prostate cancer *present* with incurable metastatic disease in the UK (that is, have metastatic disease at diagnosis rather than over the course of the disease). No change to the scope required regarding this point.
	Astellas Pharma Ltd	No additional comments	Comment noted. No action required.

Section	Consultees	Comments	Action
The technology/ intervention	British Uro-oncology Group (BUG)	Yes	Comment noted. No action required.
	Prostate Cancer Support Federation	Yes	Comment noted. No action required.
	Prostate Cancer UK	Yes.	Comment noted. No action required.
	Astellas Pharma Ltd	The brand name XtandiTM has been approved by EMA	Comment noted. No action required.
Population	British Uro-oncology Group (BUG)	Yes. This should consider all groups of men in this category	Comment noted. No action required.
	Janssen	Janssen believes that the population in the scope should reflect the anticipated licence. Additional relevant questions relate to, for example, the performance status of the studied population as well as average age.	Comment noted. No action required.
	Prostate Cancer Support Federation	Correct, no groups should be considered separately	Comment noted. No action required.
	Astellas Pharma Ltd	No additional comments	Comment noted. No action required.
Comparators	British Uro-oncology Group (BUG)	The 3 comparators are the standard therapies currently used in the UK. Following the Technology Appraisal No. 259, June 2012, 'Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen'. It is anticipated that abiraterone will be increasingly used in this group of patients who are to be treated with a further line of hormonal therapy. In a survey of 80 UK specilaist urological oncologists conducted by the British Urooncology Group (BUG) in 2010, mitoxantrone was	Comment noted. During the scoping workshop, the attendees agreed that mitoxantrone should be included as a comparator, as the most recent available evidence suggests that it is

Section	Consultees	Comments	Action
		used by 48% of participants compared with 39% who used docetaxel as second line chemotherapy. Although cabazitaxel is not recommended for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (NICE technology appraisal guidance 255), it is available through the Cancer Drugs Fund and is actively prescribed by oncologists. BUG has recently conducted a further survey on the prescribing of second line chemotherapy by dedicated urological oncologists in the UK and it is anticipated that these results will be available at the time of the full appraisal and may indicate the most appropriate comparator for those men who are treated with second line chemotherapy	still prescribed for this indication in the NHS. Cabazitaxel should not be included, as it has not been recommended by NICE for use in this indication.
	Prostate Cancer Support Federation	All correct	Comment noted. No action required.
	Prostate Cancer UK	The relevant clinical outcomes we would identify are those already set out 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.	Comment noted. Health related quality of life and adverse effects are included as outcomes in the scope. No action required.
	Astellas Pharma Ltd	Astellas consider that only abiraterone and best supportive care (BSC) are appropriate comparators based on their routine use, availability via NHS funding, and their support within NICE guidance. Recent expert advice has suggested that the most likely future prescribing decision will be whether to use abiraterone or enzalutamide before BSC.1 Alternative scenarios such as prescribing abiraterone and enzalutamide together, or considering options which are unlicensed or only available via the cancer drugs fund are highly	Comment noted. During the scoping workshop, the attendees agreed that mitoxantrone should be included as a comparator, as the most recent available evidence suggests that it is still prescribed for this

Section	Consultees	Comments	Action
		unlikely.[1] Mitoxantrone is not licensed for use in mCRPC. There is no relevant evidence that mitoxantrone has any benefits to patients with mCRPC.	indication in the NHS.
Outcomes	British Uro-oncology Group (BUG)	Yes	Comment noted. No action required.
	Janssen	Other outcomes may include time to initiation of cytotoxic therapies and time to opiate use. As well as HRQoL, pain response may be considered as one of the outcomes. Toxicity issues should be reflected in Adverse Events.	Comment noted. Scoping workshop attendees agreed that no change to the outcomes was required. The Committee may consider additional evidence on other outcomes if submitted.
	Prostate Cancer Support Federation	Yes	Comment noted. No action required.
	Prostate Cancer UK	Yes, these outcome measures are appropriate.	Comment noted. No action required.
	Astellas Pharma Ltd	Astellas propose the additional outcome measure of "time to first skeletal related event *(SRE)*"	Comment noted. Scoping workshop attendees agreed that no change to the outcomes was required. The Committee may consider additional evidence on other outcomes if submitted.

[1] Astellas advisory board held in Edinburgh on 23rd – 24th September 2012.

Section	Consultees	Comments	Action
Economic analysis	Prostate Cancer Support Federation	No Comment	
	Prostate Cancer UK	We do not have enough information to comment.	Comment noted. No action required.
	Astellas Pharma Ltd	Astellas intend to conduct a cost-effectiveness analysis based on the NICE reference case, reporting incremental cost-effectiveness (expressed as cost per QALY gained) versus abiraterone and BSC.	Comment noted. No action required.
Equality	Prostate Cancer Support Federation	No equality issues	Comment noted. No action required.
	Prostate Cancer UK	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. Eligible patients from these populations should not be 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. Issues related to differences in prevalence or incidence of a disease between population groups cannot be addressed in a technology appraisal. NICE is committed to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity. Full consideration will be given tof equality issues during the appraisal. No change to the scope required.

Section	Consultees	Comments	Action
	Astellas Pharma Ltd	Astellas do not envisage any equality issues surrounding enzalutamide.	Comment noted. No action required.
Other considerations	Prostate Cancer Support Federation	none	Comment noted. No action required.
	Astellas Pharma Ltd	No additional comments	Comment noted. No action required.
Innovation	British Uro-oncology Group (BUG)	Enzalutamide has demonstrated a sgnificant benefit in terms of overall survival, in the phase 3 AFFIRM study. The median overall survival was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group. The superiority of enzalutamide over placebo was shown with respect to all secondary end points: the proportion of patients with a reduction in the prostate-specific antigen (PSA) level by 50% or more (54% vs. 2%, P<0.001), the soft-tissue response rate (29% vs. 4%, P<0.001), the quality-of-life response rate (43% vs. 18%, P<0.001), the time to PSA progression (8.3 vs. 3.0 months; hazard ratio, 0.25; P<0.001), radiographic progression-free survival (8.3 vs. 2.9 months; hazard ratio, 0.40; P<0.001), and the time to the first skeletal-related event (16.7 vs. 13.3 months; hazard ratio, 0.69; P<0.001). This is also a very well tolerated drug and does not need additional hospital visits for monitoring.	Thank you for your comment. The Committee will consider the innovative nature of enzalutamide during the course of the appraisal. No amendment to the scope is required.
	Prostate Cancer Support Federation	This is a significant drug which is very well tolerated. It will save lives and improve the quality of life for both patients and their families. It is a step change in treatment because Enzalutimide has been shown to be very successful in trials and as it is non - steroidal in it's nature, there is less chance of toxicity and fewer adverse side affects than in the other comparitive treatments. This	Thank you for your comment. The Committee will consider the innovative nature of enzalutamide during the course of the appraisal. No

Section	Consultees	Comments	Action
		drug has outshone abiraterone in the US trial, delivering significantly longer survival times. The fact that it permits testosterone to flow and inhibits the activity of mutant receptors allows most men to have a more active life.	amendment to the scope is required.
	Prostate Cancer UK	Yes.	Thank you for your comment. The Committee will consider the innovative nature of enzalutamide during the course of the appraisal. No amendment to the scope is required.
	Astellas Pharma Ltd	Astellas believe that enzalutamide is an innovative technology and will provide a step-change in the management of mCRPC. Enzalutamide has a novel mode of action which inhibits androgen receptor signalling via three distinct mechanisms: 1) inhibition of androgen receptor binding, 2) inhibition of nuclear translocation, 3) inhibition of co-activator recruitment and DNA binding to the androgen receptor. Unlike currently available treatments for mCRPC, enzalutamide offers the flexibility to prescribe without concomitant steroids, the option of administering with or without food, and no additional monitoring requirements (for example liver function testing) versus comparator technologies.	Thank you for your comment. The Committee will consider the innovative nature of enzalutamide during the course of the appraisal. No amendment to the scope is required.
Questions for consultation		No questions for consultation were received from consultees or commentators.	No action required.
Additional comments on the draft scope	Janssen	No additional comments	Comment noted. No action required.
	Astellas Pharma Ltd	No additional comments	Comment noted. No action required.

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

Aberdeen HTA Group
Royal College of Pathologists
The Royal College of Nursing
Department of Health
Medicines and Healthcare products
Regulatory Agency (MHRA)

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
1.	Add: Astellas would like to propose the Men's Health Forum as a relevant stakeholder to be included.	Astellas		Added	This group meets the inclusion criteria and has been added to the matrix.

2.	Astellas believes that only manufacturers of licensed comparators should be included as stakeholders. As such, we propose removing all manufacturers of mitoxantrone.	Astellas		Noted	The list of comparators matches the scope. In the response to comments on the scope we note: "*During the scoping workshop, the attendees agreed that mitoxantrone should be included as a comparator, as the most recent available evidence suggests that it is still prescribed for this indication in the NHS.*"
3.	Please note that Prostate Cancer UK merged with Prostate Action in July 2012.	Astellas		Noted	Thank you for this comment. The matrix has been amended.