National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Apalutamide for treating non-metastatic, hormone-relapsed prostate cancer [ID1174]

Response to consultee and commentator comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	No. Janssen suggests the wording of the remit should reflect the anticipated license as follows: To appraise the clinical and cost effectiveness of apalutamide within its marketing authorisation for treating adult men with non-metastatic castration-resistant prostate cancer who are at a high risk of developing metastatic disease.	Comment noted. The remit has been left broad to ensure that if apalutamide receives a marketing authorisation in the UK for this indication, the appraisal covers the whole licensed population. As detailed in the scope, the term 'hormone

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			relapsed prostate cancer' is preferred.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
	Prostate Cancer UK	Our understanding is that apalutamide is being considered for the treatment of non-metastatic hormone-relapsed prostate cancer, not localised hormone-relapsed prostate cancer. Non-metastatic prostate cancer includes locally advanced prostate cancer which has spread to the lymph nodes in the pelvic region (N1 vs. N0). It is likely that the license will also only apply to 'high-risk' non-metastatic hormone-relapsed prostate cancer. 'High risk' is defined in the SPARTAN trial a PSA doubling time of less than 10 months for men receiving hormone therapy.	Comments noted. 'Localised' has been removed from the text. The scope has been left broad to ensure that the appraisal covers the population in the marketing authorisation.
Timing Issues	Astellas Pharma	No Comment	Comment noted. No action required.
	Bayer	There are currently no licensed treatments for this stage of prostate cancer but three treatments (apalutamide, enzalutamide and darolutamide) are likely to be licensed within the next two years.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10377. No action required.

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	Janssen-Cilag	There is no licensed medication in this disease setting despite the known risk of rapid progression to metastasis which impacts patients significantly. There is therefore an unmet need.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10377. No action required.
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
	Prostate Cancer UK	Men with localised and locally advanced prostate cancer, whose PSA levels indicate that they are no longer hormone sensitive will, if no visible metastases are identified have no treatment options available to them. They must wait, receiving periodic scans, to determine whether their prostate cancer has metastasised before any further treatment options are open to them. Current imaging used to diagnose advanced prostate cancer is limited in its ability to detect metastases. This means that men can be left in limbo without access to treatment and the potential to gain additional months of life from the treatments available for castrate-resistant metastatic prostate cancer. Apalutamide gives these men the opportunity to access a treatment that can delay progression. Further research is needed to determine whether, for those men with undetected metastases, this treatment could also provide clinical benefit.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10377. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit	Bayer	No comments.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	The epidemiology data in this section relates to a population with non-metastatic prostate cancer; whereas apalutamide will be indicted for a smaller subgroup of this population namely adult men with non-metastatic castration-resistant prostate cancer who are at a high risk of developing metastatic disease. Clarifications included in bold below 3rd paragraph: Hormone-relapsed prostate cancer is diagnosed by rising prostate-specific antigen levels **despite treatment with ADT or orchidectomy**. 5th paragraph: stopping hormone therapy completely would increase testosterone levels and **decrease** the likely time to metastatic disease	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal. The text has been amended as suggested.

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	NCRI-ACP-RCP-RCR	Satisfactory	Comment noted. No action required.
	Prostate Cancer UK	In the UK, men with hormone sensitive intermediate or high risk non-metastatic prostate cancer should not be offered hormone therapy alone. These men will be offered radical treatment and will only receive hormone therapy alone if they are unable to receive radical treatment. However, it is correct that men will become castrate-resistant after taking hormone therapy.	Comments noted. This information has been included in the background section.
The technology/ intervention	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	The description of the technology is accurate. Janssen suggests the following wording in line with the anticipated license: Apalutamide does not currently have a marketing authorisation in the UK for the treatment of high-risk non-metastatic castration-resistant prostate cancer.	The wording in this section is aligned with the remit for consistency. Please see the response above relating to the wording of the remit.
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.
	Prostate Cancer UK	Yes	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	Astellas Pharma	Patients for inclusion to the pivotal phase 3 study for apalutamide (SPARTAN)* were classified as 'high-risk' defined in terms of PSA doubling time and Astellas Pharma Ltd would recommend that the appraised population reflects this. *Ref. Mathew R. Smith et al. Apalutamide Treatment and Metastasis-free Survival in prostate cancer. N Engl J med 2018;378:1408-18	The scope has been left broad to ensure that the appraisal covers the population in the marketing authorisation.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	The words 'localised' and 'non-metastatic' are used interchangeably in the draft scope. Localised disease tends to refer to an earlier stage in the prostate cancer pathway than the indication under review. Janssen proposes use of non-metastatic for consistency, and in line with other NICE technology appraisals in this disease setting. As noted in the background section, the words 'hormone-relapsed' and 'castration-resistant' are also used interchangeably in the literature. Janssen proposes the use of castration-resistant for consistency with the anticipated license. The population under consideration is: Adult men with non-metastatic castration-resistant prostate cancer who are at a high risk of developing metastatic disease. There are no groups within this population that should be considered separately.	Comments noted. 'Localised' has been removed and 'non-metastatic' has been added to the description. As detailed in the scope, the term 'hormone relapsed prostate cancer' is preferred.

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	NCRI-ACP-RCP-RCR	Yes: Typographical error – adults with non-metastatic hormone (sensitive? Missing) relapsed localised prostate cancer Within the population consideration to histology (adenocarcinoma) and how aggressively prostate cancer is (in studies, PSA doubling time used)	Comments noted. 'Hormone-relapsed' refers to prostate cancer that no longer responds to hormone therapy. Our understanding is that most prostate cancers are adenocarcinomas so it is not clear that a subgroup based on histology would add value. PSA doubling time in less than 10 months is defined as 'high risk' in the trial and so is likely to already be accounted for in the evidence. No action required.
	Prostate Cancer UK	It will primarily be men who are non-metastatic castrate-resistant who receive this treatment. This includes men with locally advanced disease which has spread to lymph nodes in the pelvic region. To avoid confusion the word 'localised' should be removed. More advanced imaging modalities give increased diagnostic scanning accuracy. It is possible that the men in this indication already have	Comments noted. 'Localised' has been removed from the description.

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		advanced prostate cancer, but current imaging techniques are unable to identify metastases.	
Comparators	Astellas Pharma	We agree that enzalutamide plus ADT would be an appropriate comparator for apalutamide plus ADT in this population (subject to ongoing NICE appraisal).	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	Androgen deprivation therapy is the standard treatment currently used in the NHS. Enzalutamide is currently unlicensed in the UK for this indication and is scheduled for appraisal by NICE. As such it cannot currently be considered a standard or alternative treatment in the NHS and is therefore not a relevant comparator for this appraisal.	Comments noted. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals have been included "(subject to ongoing NICE appraisal)". No action required.
	NCRI-ACP-RCP-RCR	Yes Currently (UK) patients are treated with androgen deprivation (usually injectable LHRH analogue)	Comments noted. No action required.

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		MRC STAMPEDE study has recruited patients with N0M0 disease and is due to report results “soon.” Arm J included adding abiraterone and enzalutamide	
	Prostate Cancer UK	Enzalutamide is not currently used in the NHS in this indication, as the parenthesis explain Once radical treatment options have been exhausted or ruled out and the man has become castrate-resistant, there are no further treatment options for men until the prostate cancer metastasises elsewhere in the body. Patients are left in limbo, periodically receiving bone scans to determine whether the cancer has metastasised. Once the cancer progresses, treatment options for metastatic prostate cancer will be available to these patients.	Comments noted. No action required.
Outcomes	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	Janssen propose the following outcome measures to capture the most important health benefits of apalutamide: • Metastasis Free Survival • Overall Survival • Second Progression Free Survival • Progression Free Survival • Time to Symptomatic Progression	Comments noted. ‘Time to PSA progression’ has been added to the scope. The remaining measures are covered in the outcomes included in the scope.

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		• Time to Metastasis • Health-related quality of life measures • PSA response • Time to PSA progression	
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.
	Prostate Cancer UK	The key outcome measure will be metastases free survival. Given the early stage of this cancer, overall survival data has yet to mature and will take a long time to do so. Research finds metastases free survival to be a strong surrogate of overall survival in prostate cancer (http://ascopubs.org/doi/10.1200/JCO.2017.73.9987). Metastases free survival is particularly important at this stage of the disease. Non-metastatic disease is largely unsymptomatic and delaying progression will delay the point at which men will start suffering with the symptoms of advanced prostate cancer.	Comments noted. No action required.
Economic analysis	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	A cost-utility analysis incorporating a lifetime horizon is appropriate to reflect the differences in outcomes and costs between apalutamide and ADT. The cost-utility analyses will reflect the current NHS management of patients with non-metastatic castration-resistant prostate cancer and will also include	Comments noted. No action required.

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		current treatments received when the disease progresses to metastatic castration-resistant prostate cancer. NICE has made recommendations for treatment of metastatic castration-resistant prostate cancer therefore the cost-utility analyses will reflect this guidance when defining the prostate cancer treatment pathway.	
	NCRI-ACP-RCP-RCR	No comment	Comment noted. No action required.
	Prostate Cancer UK	Yes	Comment noted. No action required.
Equality and Diversity	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	There are no known equality issues.	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No changes suggested	Comment noted. No action required.
	Prostate Cancer UK	N/A	Comment noted. No action required.
Innovation	Astellas Pharma	No comment	Comment noted. No action required.

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	Bayer	There are currently no licensed treatments for this stage of prostate cancer but three treatments (apalutamide, enzalutamide and darolutamide) are likely to be licensed within the next two years.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
	Janssen-Cilag	There is an unmet need in the treatment of adult men with non-metastatic castration-resistant prostate cancer as there are currently no licensed medications available that have been demonstrated to impact survival. Current NHS clinical management involves ADT, however a subset of patients become resistant to ADT and are at a higher risk of developing metastases as indicated by rising prostate specific antigen (PSA) levels. Metastatic disease is a turning point in the prostate cancer pathway, associated with impactful symptoms and high mortality. There is therefore a need for innovative treatments that delay or prevent the progression to metastatic disease whilst minimising any adverse impact on patient's quality of life. Apalutamide is a once-daily, orally administered treatment with no routine monitoring requirements. It selectively blocks the receptor responsible for the growth of prostate cancer cells and thereby has an immediate, meaningful and durable impact on PSA levels. This impact results in a significant improvement in the time to develop metastases when compared to ADT alone (Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. The New England Journal Of Medicine. 2018).	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

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	NCRI-ACP-RCP-RCR	Yes Delay in progression/ metastasis and subsequent treatment for men with prostate cancer could be a step change delaying or avoiding treatment for metastatic disease. Published data on the phase 3 study are available (NEJM)	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
	Prostate Cancer UK	The technology is innovative because it delivers to an unmet need. The QALY calculation does not include the reduction in anxiety that men will experience from being able to take an active treatment rather than waiting for their cancer to progress to metastatic prostate cancer before further treatment options become available to them. Cryotherapy should not be considered as related NICE interventional procedures guidance since cryotherapy and HIFU are only available in clinical trial settings. Evidence for the efficacy of the other interventional procedures is in the hormone sensitive rather than castrate resistant setting and so will not be relevant here.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
Other considerations	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Prostate Cancer UK	The extent to which delays to cancer progression deliver an improved quality of life – comparing the quality of life among men with castrate-resistant localised and locally advanced prostate cancer to the quality of life experienced by men with castrate-resistant metastatic prostate cancer	Comments noted. No action required.

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Questions for consultation	Astellas Pharma	No comment	Comment noted. No action required.
	Bayer	No comments.	Comment noted. No action required.
	Janssen-Cilag	Have all relevant comparators for apalutamide been included in the scope? **Yes, androgen deprivation therapy is an appropriate comparator.** **Enzalutamide is currently unlicensed in the UK for this indication and is scheduled for appraisal by NICE. As such it cannot currently be considered a standard or alternative treatment in the NHS and is therefore not a relevant comparator for this appraisal.**	Comments noted. To ensure the timeliness of the scope in the event of any possible scenarios such as delays in the submission, the scope has been kept broad and comparators in relevant appraisals have been included "(subject to ongoing NICE appraisal)". No action required.
		Which treatments are considered to be established clinical practice in the NHS for non-metastatic, hormone-relapsed prostate cancer? **Androgen deprivation therapy**	Comment noted. No action required.
		Are radical prostatectomy or radical radiotherapy relevant comparators? **No, radical prostatectomy or radical radiotherapy are treatment options for localised prostate cancer. The indication under review is at**	Comment noted. No action required.

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		a later time in the non-metastatic pathway and refers to a population that already received treatment including radical therapy. Are the outcomes listed appropriate? **Janssen has provided more detail on outcomes in the comments above.** Are there any subgroups of people in whom apalutamide is expected to be more clinically effective and cost effective or other groups that should be examined separately? **There are no groups within the treatment population under consideration that should be considered separately.** Where do you consider apalutamide will fit into the existing NICE pathway, Prostate cancer? **Apalutamide is relevant after patients have had a biochemical recurrence following treatment for localised or locally advanced prostate cancer.** NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please, tell us if the proposed remit and scope:	Please see relevant section. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which apalutamide will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. **No comment** Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **No comment** Do you consider apalutamide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Yes, see innovation comments above.** Do you consider that the use of apalutamide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?	Comment noted. No action required. Please see relevant section. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		No Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **No comment** To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. **No** NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). **Janssen considers the STA process to be appropriate to appraise apalutamide.** NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. • Would it be appropriate to use the cost comparison methodology for this topic?	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		No, the efficacy of apalutamide differs to the standard of care (ADT) • Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? **No, the efficacy of apalutamide differs to the standard of care (ADT)** • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? **Yes** • Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? **No**	
	NCRI-ACP-RCP-RCR	To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly Yes: Currently patients may be managed by urology, oncology or primary care.	Comments noted. No action required.
	Prostate Cancer UK	**Which treatments are considered to be established clinical practice in the NHS for non-metastatic, hormone-relapsed prostate cancer?**	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Currently, men who are castrate resistant but with no visible metastases have no treatment options. They must wait for their cancer to metastasise, receiving periodic tests to diagnose metastasis, before treatment options become available to them. These men will have exhausted or ruled out radical treatment options including radical prostatectomy, radiotherapy and brachytherapy. These men and their carers will experience anxiety at the lack of treatment options, particularly if the man's PSA is rising rapidly. **Is radical prostatectomy a relevant comparator?** Unless radical treatment is ruled out, apalutamide should be taken following, not instead of, radical treatment including prostatectomy. As there is potential for prostate cancer to have disseminated, we do not believe that radical prostatectomy is a relevant comparator to apalutamide. **Are there any subgroups of people for whom apalutamide is expected to be more clinically effective and cost effective?** As the clinical trial for apalutamide (SPARTAN) and the licence will likely reflect, this treatment will be more effective in patients that the trial defines as having 'high risk' non-metastatic castrate-resistant prostate cancer. High risk is defined as a prostate-specific antigen doubling time of 10 months or less during continuous androgen-deprivation therapy. Further analysis of the data from the SPARTAN trial may find stratified patient groups are more or less likely to benefit from the treatment. Patients in the SPARTAN trial were stratified according to PSA doubling time (>6 months vs. <6 months), use of bone sparing agents, classification of local or	Comments noted. No action required. Comments noted. Subgroups have not been defined in the scope but the company can choose to submit evidence for specific subgroups. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		regional nodal disease (N0 vs. N1) at the time of trial entry, and previous prostate cancer treatment (radical treatment, Gondotropin or antiandrogen). **Where will apalutamide fit into the existing NICE pathway** This will fit into high-risk localised or locally advanced prostate cancer once men become castrate-resistant and after hormone therapy and /or radical prostatectomy or radical radiotherapy has been performed or considered. **Barriers to adoption** Administration of this treatment is simple, there should not be any barriers to adoption of this technology in practice.	Comments noted. No action required. Comments noted. No action required.
Additional comments on the draft scope	Astellas Pharma	Astellas Pharma Ltd considers it would not be appropriate to use the cost comparison methodology for this topic. Astellas Pharma Ltd considers a cost-utility approach more appropriate for this appraisal as this methodology allows for a better assessment of uncertainty regarding the expected costs and effects of the use of apalutamide in clinical practice.	Comments noted. No action required.
	Bayer	No further comments.	Comment noted. No action required.
	Janssen-Cilag	As noted in the background of the scope, patients with non-metastatic castration-resistant are monitored for evidence of disease metastases, at which point other treatments are considered. In recent years, NICE approved several treatments for metastatic castration-resistant disease (eg.,TA387, TA377, TA259). In order to model the disease pathway accurately over a lifetime horizon for the economic analysis, Janssen will compare the use of apalutamide versus	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		ADT in the non-metastatic castration-resistant setting followed by the NICE approved treatments for metastatic castration-resistant disease.	
	NCRI-ACP-RCP-RCR	Advances in imaging / other technology for improved staging (ie better diagnosis of men with metastatic disease not currently detected by current CT and nuclear medicine bone scans) are likely to be developed/ enter practice in the near future.	Comments noted. No action required.

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

Department of Health and Social Care
Ipsen Ltd