National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer ID1605

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Astellas Pharma Ltd	The wording reflects the issues	Thank you for your comment. No action required.
	Janssen-Cilag Ltd	No comment	No action required.
Timing Issues	Astellas Pharma Ltd	Men with metastatic prostate cancer require effective alternative treatment options that offer different risk-benefit profiles. Specifically, these men need options with demonstrable clinical benefit for improving progression free survival, overall survival and maintaining QoL. Increasingly evidence suggests treating men earlier in their disease whilst they remain sensitive to hormonal therapy achieves better clinical outcomes than treating them later in the disease once the cancer loses response to hormonal therapies such as ADT. We therefore believe this appraisal should occur and guidance be published as close to marketing authorisation as possible.	Thank you for your comment. No action required.
	Janssen-Cilag Ltd	No comment	No action required.

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Additional comments on the draft remit	Astellas Pharma Ltd	Astellas believe that timing of the appraisal decision and subsequent publication on the NICE website may face delays if the United Kingdom leaves the European Union on 31 October [redacted] [The marked text is commercial sensitive information as it relates to the operational of Astellas Pharma Ltd. In addition, information about the regulatory process provides an indication for when marketing authorisation and therefore market launch is anticipated]. We would like to enter the appraisal process with a joint commitment to achieve timely decisions, but with a collaborative and solutions based approach to any challenges that exiting the EU may create.	Thank you for your comment. No action required.
	Janssen-Cilag Ltd	No further comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Astellas Pharma Ltd	We believe the description 'metastatic, hormone-sensitive prostate cancer' in the draft scope is currently intended to include patients with recurrent, metastatic, hormone-sensitive prostate cancer, as well as newly diagnosed metastatic, hormone-sensitive prostate cancer [i.e. we assume the description includes patients who have had an initial diagnosis of non-metastatic prostate cancer e.g. receiving radical treatment with curative intent	Thank you for your comment. The background section has been amended to reflect this:

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		such as surgery or radiotherapy, but in whom disease has subsequently returned with a diagnosis of metastatic, hormone sensitive prostate cancer (mHSPC)]. These patients will also be metastatic hormone sensitive prostate cancer patients and Astellas has included both newly diagnoses (de-novo) and recurrent patients in the two key phase III studies ARCHES and ENZAMET that provide the main evidence to support our regulatory and HTA submissions. We would suggest the following wording: **The description 'metastatic, hormone-sensitive prostate cancer' refers to a population that includes people with metastatic prostate cancer who are newly diagnosed and are hormone naïve or are continuing to respond to androgen deprivation therapy, as well as patients who have received a prior diagnosis of non-metastatic prostate cancer whose cancer has now metastasised, but is still sensitive to ADT.**	The description 'metastatic, hormone-sensitive prostate cancer' refers to a population that includes people with metastatic prostate cancer who are hormone naïve or are continuing to respond to androgen deprivation therapy.
	Janssen-Cilag Ltd	No comment	No action required.
The technology/ intervention	Astellas Pharma Ltd	Enzalutamide is currently being studied in two trials for metastatic hormone sensitive prostate cancer these trials. These are known as ARCHES (ClinicalTrials.gov Identifier: NCT02677896) which aims to evaluate the efficacy and safety of enzalutamide plus androgen deprivation therapy (ADT) and ENZAMET (ClinicalTrials.gov Identifier: NCT02446405) which aims to determine the effectiveness of enzalutamide versus a conventional NSAA, when combined with a LHRHA or surgical castration, as first line androgen deprivation therapy (ADT)	Thank you for your comment. No action required.
	Janssen-Cilag Ltd	No comment	No action required.

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Population	Astellas Pharma Ltd	Astellas agrees that the proposed population – "People with metastatic hormone-sensitive prostate cancer", is appropriate.	Thank you for your comment. No action required.
	Janssen-Cilag Ltd	No comment	No action required.
Comparators	Astellas Pharma Ltd	Astellas recommends rephrasing this comparator in line with NICE guideline [NG131] – Prostate cancer: diagnosis and management, May 2019. That is: "Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide". Comparator Abiraterone: Astellas do not believe abiraterone is an appropriate comparator for the following reasons. i) Abiraterone is only licensed for the treatment of a sub-population (newly-diagnosed high risk) mHSPC, not all patients with mHSPC. Reference: https://www.medicines.org.uk/emc/product/2381 . Accessed 29/07/19 Therefore, it should not be considered as a comparator for the full population. ii) Abiraterone is not an appropriate comparator because it does not meet a requirement of comparitors that it may be considered a good use of NHS resources. The STA for abiraterone in mHSPC had the 1st appraisal committee meeting on 10 May 2018 [ID945]. The appraisal was then suspended on 16 July 2018 until the manufacturer confirmed the price the drug will be made available to the NHS for this indication. The lack of confirmed price for the indication is noted as the ongoing reason for the appraisal suspension on 09 April 2019. Astellas believe with no movement	Thank you for your comment. The comparator section has been updated to reflect your comments: • Androgen deprivation therapy alone (including orchidectomy, luteinising hormone-releasing hormone agonist therapy) or monotherapy with bicalutamide It is acknowledged that abiraterone is currently going through the NICE technology appraisal process for this indication. However, to ensure the timeliness of the scope in the event

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		on this matter for over 12 months since the initial suspension, being receiving a positive NICE guidance before our submission is unlikely. When considering the additional time required for a FAD and Guidance, along with a 90 day implementation period together, mean abiraterone will not be considered routine clinical practice between now and our final submission in early November 2018. iii) Abiraterone cannot be classified as “established practice” having only received EC license extension in November 2017, and lacking national funding approval since then. Astellas consider that with no positive STA NICE Guidance, and not being part of NICE treatment pathways for prostate cancer e.g. NG131, abiraterone cannot be considered as “embedded in clinical practice”.	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 evaluation)”. As the marketing authorisation for abiraterone specifies newly diagnosed high-risk disease, it has been clarified in the scope that the comparator would be relevant for this subgroup only.
	Janssen-Cilag Ltd	Abiraterone with prednisone or prednisolone and androgen deprivation therapy should only be considered a relevant comparator, • if it receives a positive NICE recommendation for reimbursement by the time of the enzalutamide submission, AND • only in the specific subgroup of newly diagnosed, high risk mHSPC patients in line with the marketing authorisation for abiraterone.	Thank you for your comment. The scope has been amended to reflect that abiraterone would only be a comparator for people with newly diagnosed high risk disease, subject to ongoing NICE appraisal.

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Outcomes	Astellas Pharma Ltd	Yes	Thank you for your comment. No action required.
	Janssen-Cilag Ltd	The following is an important outcome, which should be included if captured. • **Second progression free survival (PFS2)**	Thank you for your comment. The scope includes progression free survival which could include second progression free survival if appropriate. No action required.
Economic analysis	Astellas Pharma Ltd	No further comment	Thank you for your response. No action required.
	Janssen-Cilag Ltd	No comment	Thank you for your response. No action required.
Equality	Astellas Pharma Ltd	There are no equality issues based on the proposed remit and scope.	Thank you for your response. No action required.
	Janssen-Cilag Ltd	No comment	Thank you for your response. No action required.
Other considerations	Astellas Pharma Ltd	The Scoping document identifies 2 further sub-groups that will be considered. See comments specific to each point and a statement on our overall position on the use of sub-groups:	Thank you for your comment. NICE considers the

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		• Evidence of the efficacy and safety of enzalutamide in mHSPC patients that comes from ARCHES and ENZAMET show efficacy in all mHSPC patients regardless of disease risk level (high/low), disease volume (high/low) or time since diagnosis (newly diagnosed/recurrent). Astellas consider that enzalutamide should be assessed in the context of all mHSPC patients. • "Newly diagnosed" – Astellas does not believe this is a relevant sub-group. There is inconsistent use of "newly diagnosed" for randomisation across all mHSPC trials, and this sub-population would be most relevant to abiraterone which is specifically licensed for this population. Astellas have provided clear rationale why abiraterone is not an appropriate comparator. These reasons mean it is likely to prevent meaningful conclusions on this sub-group and does not need specific consideration. • "People with high risk prostate cancer" – Astellas have the same concerns as with "newly diagnosed". This term is not consistently applied across trials and may not be aligned with how treatment decisions are made in clinical practice. Indeed in ARCHES and ENZAMETS Astellas used volume as a stratification factor not risk. We therefore do not believe this is a population which requires specific consideration.	subgroups 'newly diagnosed' and 'high-risk metastatic prostate cancer' to be appropriate subgroups if evidence allows. Limitations of the subgroup analyses will be taken into account in the committee's decision making. No action required.
	Janssen-Cilag Ltd	No comment	Thank you for your response. No action required.

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Innovation	Astellas Pharma Ltd	Enzalutamide plus ADT has been shown to increase survival compared to ADT and bicalutamide , and is therefore an innovative therapy. As noted by the CDF clinical lead in the ACD for NICE appraisal [ID945], 50% of potential chemotherapy patients are “not fit enough [for] chemotherapy and have ADT alone”. The patients who are not receiving chemotherapy have no effective funded alternatives to ADT alone. Enzalutamide can provide this as an oral once-daily medicine. If NICE still consider abiraterone a relevant comparator, Astellas considers the introduction of a once-daily, oral medication, combined with anti-androgen therapy innovative, compared to abiraterone, which must be combined with steroids, and combined, require a complex dosing regimen. E.g. Abiraterone “should be taken at least one hour before or at least two hours after eating” (abi SPC), however steroids should be taken “The tablets should be taken with or after food.”	Thank you for your comment. The committee will consider the potential innovative nature of enzalutamide in its deliberations. No action required.
	Janssen-Cilag Ltd	No comment	Thank you for your response. No action required.
Questions for consultation	Astellas Pharma Ltd	*“Have all relevant comparators been included in the scope? Which treatments are considered to be established clinical practice in the NHS for prostate cancer?”* Astellas believe abiraterone is not an appropriate comparator because it is not recommended by NICE (appraisal suspended), and is not part of routine clinical practice for mHSPC, nor will it be by the time of our submission in early November. *“Are the subgroups suggested in ‘other considerations appropriate? Are there any other subgroups of people in whom enzalutamide is expected to be more*	Thank you for your comment. The scope has been amended to reflect that abiraterone would only be a comparator for people with newly diagnosed high risk disease, subject to ongoing NICE appraisal. Abiraterone has been included in the scope to

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		clinically effective and cost effective or other groups that should be examined separately?." Astellas consider no sub-groups should be included. *"Where do you consider enzalutamide will fit into the existing NICE pathway, prostate cancer?"* Astellas anticipate enzalutamide in combination with ADT will be added as a treatment alternative to the treatment options listed for metastatic prostate cancer patients in NG131. This is based on the enzalutamide data from ARCHES and ENZAMET, Astellas anticipate that enzalutamide will be an alternative to ADT in all patients and to docetaxel in newly-diagnosed patients. Based on the CDF clinical leads statement in the ACD for abiraterone "50% of all mHSPC pts currently receive chemotherapy". We anticipate clinicians will use enzalutamide as an alternative to chemotherapy in newly diagnosed mHSPC based on factors such as patient fitness, convenience and proximity to treating hospital along with patient preference. Astellas also anticipate enzalutamide use will be used as an alternative to ADT or bicalutamide monotherapy in patients who are not deemed eligible for chemotherapy, or through patient choice to decline chemotherapy. Enzalutamide fits this place in treatment as it is where the relevant therapeutic goal is to improve OS whilst maintaining the patients current QoL. We do not anticipate use in combination with chemotherapy or as a maintenance therapy post-chemotherapy in mHSPC. *"Do you consider that enzalutamide can result in any substantial health related benefits that are unlikely to be included in the QALY calculation"*	ensure the timeliness of the appraisal in the event of any possible scenarios such as delays in the submission. Thank you for your comment. No action required. Thank you for your comment. No action required.

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		Astellas believe the once daily oral administration, with no food-effect and without the need for additional routine clinical monitoring means that patients or their carers who have life-styles suited to convenient oral administration will be better served, especially in comparison to intra-venous infusions required with chemotherapy. Astellas also believe that patients who have significant journey times to the treating hospital will benefit from the option of enzalutamide, because it would require less frequent hospital and other clinical appointments compared to chemotherapy. *"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"* Astellas anticipate the introduction of this technology could have two pathway impact. Astellas anticipate there may be fewer patients requiring chemotherapy which is delivered in specific *i.v.* chemotherapy clinics In addition, Astellas understand from discussions across the NHS with HCPs and service budget holders, that current prostate cancer services are struggling to meet current capacity challenges. If approved for use mHSPC patients would not add to the footfallor capacity challenges of uro-oncology prostate clinics, as these patients would not require additional clinical monitoring to comply with the license for enzalutamide and these patients are already being seen regularly to receive their ADT or ADT plus chemotherapy, and currently have disease assessment and clinical follow-up. Monitoring of response to therapy would not be more frequent due to the introduction of enzalutamide .	Thank you for your comment. The committee will take into account the impact on patients and carers in its decision making. No action required. Thank you for your comment. No action required.

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		Given that enzalutamide has been shown to increase survival, patients who are prescribed enzalutamide will be alive longer, and will still attend prostate cancer clinics for this extended period of life, which may lead to a small incremental clinical capacity over time.	
	Janssen-Cilag Ltd	No comment	Thank you for your response. No action required.
Additional comments on the draft scope	Astellas Pharma Ltd	-	-
	Janssen-Cilag Ltd	No further comments	Thank you for your response. No action required.