**APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION FOR ABIRATERONE FOR HIGH-RISK HORMONE-SENSITIVE METASTATIC PROSTATE CANCER**

**EXECUTIVE SUMMARY**

Janssen’s appeal against the Final Appraisal Determination for abiraterone for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) is based on the following grounds:

Ground 1(a) and (b)

* The Appraisal Committee has failed to consider whether and, if so, to what extent the change in health-related quality of life associated with use of abiraterone has been adequately captured in this appraisal;
* The Appraisal Committee’s conclusion that “*there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination*” does not: (a) provide adequate reasons for diverging from NHS England’s commissioning policy; (b) justify rejection of the criteria proposed by NHS England for determining access to abiraterone through the Blueteq management system; (c) provide reasons for deviating from its conclusions in the earlier appraisal of Radium-223; and (d) explain why it has adopted a different approach to that followed in the appraisal of lenalidomide;
* the Appraisal Committee has provided no reasons to explain its view that the benefits of abiraterone may be different in those patients who are unable to receive docetaxel;
* The conclusions of the Appraisal Committee in relation to the cost effectiveness of abiraterone in this appraisal are opaque;
* The fact that NICE disclosed its preferred ICERs to NHS England for the purposes of negotiation of a commercial agreement, but not to Janssen is unfair;
* The Appraisal Committee’s statement that “*the clinical experts involved in STAMPEDE confirmed that post-progression survival was shorter after abiraterone in combination than after ADT in this trial”* is based on unpublished data that have not been disclosed or confirmed;
* The Appraisal Committee’s focus on number of subsequent treatment options rather than outcomes relies on an irrelevant consideration
* The assertion by the Appraisal Committee that it is required to say whether abiraterone is “safe” in patients who cannot take docetaxel assumes the role of the regulatory authority

Ground 2

* The Appraisal Committee’s conclusion that “*there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination*” is unreasonable in the context of the available evidence;
* the Appraisal Committee’s conclusion that the benefits of abiraterone may be different in those patients who are unable to receive docetaxel is unreasonable in light of the evidence available

**INTRODUCTION**

Abiraterone (Zytiga) is indicated, in combination with prednisone or prednisolone, for the treatment of various prostate cancer indications. NICE has previously issued the following guidance for use of abiraterone:

* Abiraterone acetate with prednisone/prednisolone for the treatment of men with metastatic castrate-resistant prostate cancer (mCRPC), post chemotherapy (TA 259 issued in 2012)
* Abiraterone acetate with prednisone/prednisolone for the treatment of men with mCRPC, pre chemotherapy (TA 387 issued in 2016)

This appraisal concerns the use of abiraterone for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT).

Prostate cancer is an androgen-dependent malignancy which responds to treatment that decreases androgen levels. ADT is therefore the primary initial treatment strategy. ADT consists, in most cases, of a luteinising hormone-releasing hormone agonist or, less frequently, orchidectomy or bicalutamide monotherapy. These ADT therapies decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Accordingly, while most patients respond to ADT, the majority will develop progressive disease within 1-2 years.

Abiraterone is an inhibitor of the enzyme 17α-hydroxylase/C17,20-lyase (CYP17), required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. It is taken orally. The determination of high-risk prognosis for the purposes of this indication for treatment is defined as the presence of at least 2 of the following 3 risk factors:

(1) Gleason score (which measures the degree of abnormality of the tumour cells) of ≥8;

(2) presence of 3 or more lesions on bone scan;

(3) presence of measurable visceral (excluding lymph node disease) metastasis.

Abiraterone will lose patent protection in the UK in September 2022 and generic copies are already available in the USA and elsewhere. The launch of generic versions of abiraterone may therefore be expected in the UK from September 2022 onwards.

**PROCEDURAL HISTORY OF THE APPRAISAL**

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| **Date** | **Event** |
| 22 July 2016 | Referral to NICE |
| November 2017 | Abiraterone approved by the European Commission for the treatment of newly diagnosed mHSPC in adult men in combination with ADT. |
| 5 December 2017 | Final scope for appraisal |
| 6 February 2018 | Janssen submission to NICE |
| 10 May 2018 | First meeting of the Appraisal Committee |
| 6 June 2018 | Appraisal Consultation Document issued  “Abiraterone plus androgen deprivation therapy (ADT) is not recommended, within its marketing authorisation, for untreated high-risk hormone-sensitive metastatic prostate cancer in adults”. |
| 27 June 2018 | Janssen and other consultees and commentators submit responses to consultation on ACD. |
| 10 July 2018 | Second meeting of the Appraisal Committee |
| 16 July 2018 | Appraisal suspended for discussions regarding the price at which abiraterone will be made available to the NHS for this indication. |
| 16 August 2018 | Appraisal Committee provide list of preferred assumptions for the purposes of assessment of cost-effectiveness. |
| 10 July 2019 | Janssen provides submission addendum to NICE, providing new economic model and including preferred assumptions |
| 15 January 2020 | Third meeting of the Appraisal Committee  Appraisal paused for commercial discussions between Janssen and NHS England. |
| 10 June 2020 | Second Appraisal Consultation Document prepared following Second Appraisal Committee meeting but not published and not subject to consultation, provided to Janssen.  Recommendations unchanged from those in ACD |
| 19 June 2020 | Final Appraisal Determination issued  Recommendations unchanged from those in ACD |
| 10 July 2020 | Deadline for submission of appeal |

**METASTATIC PROSTATE CANCER: BACKGROUND INFORMATION**

The background information summarised in this document is provided to assist the Appeal Panel. It should not be viewed however as a substitute for the more detailed information provided by Janssen in its various submissions to NICE during the course of this appraisal.

Prostate cancer is the most common cancer in men in the UK. Approximately 48,500 men are diagnosed with the condition every year, of whom 18% present when their disease is already metastatic. About half of these patients are further classified as high-risk at diagnosis. The men with newly diagnosed high risk mHSPC are therefore a small group. These patients have a worse prognosis than patients who present when their disease is less advanced, with a typical life expectancy of less than three years. They experience a high clinical, psychological and economic burden of disease.

In addition to ADT, some patients with newly diagnosed high risk mHSPC are offered treatment with docetaxel, which improves survival compared with ADT alone. However, docetaxel is associated with toxicities, which mean that many patients are unable to receive such treatment and others refuse it, despite the likelihood of an earlier death. The National Prostate Cancer Audit 2020 has shown that only 27% of patients diagnosed with metastatic prostate cancer receive docetaxel in addition to ADT. These data align with statements from The Cancer Drugs Fund’s clinical lead, who noted “*around two-thirds of people presenting with hormone-sensitive metastatic prostate cancer in England have ADT alone*.” These data confirm that ADT alone is the most commonly established standard of care in England and the majority of patients diagnosed with high-risk mHSPC in England remain sub-optimally treated. There is, accordingly, a high clinical need for an alternative effective treatment for such patients.

**GROUNDS OF APPEAL**

1. **GROUND 1: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS a) FAILED TO ACT FAIRLY OR b) EXCEEDED ITS POWERS**
   1. **Ground 1(a).1: The Appraisal Committee has failed to consider whether and, if so, to what extent the change in health-related quality of life associated with use of abiraterone has been adequately captured in this appraisal**

Paragraph 6.3.3 of NICE’s Guide to the Methods of Technology Appraisal (“the Methods Guide”) states that, above a most plausible ICER of £20,000 per QALY gained, judgments about the acceptability of the technology as an effective use of NHS resources will specifically take account of certain factors including:

* “*The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.*
* *Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.*
* *The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.*
* *The technology meets the criteria for special consideration as a 'life-extending treatment at the end of life' …*
* *Aspects that relate to non-health objectives of the NHS…”*

In considering abiraterone in the context of this appraisal, the Appraisal Committee has focussed on the first of these factors and concluded that this is negative for abiraterone (its conclusions regarding uncertainty around the ICER) with the result that, at paragraph 3.13 of the FAD, the Committee concludes that abiraterone would need to have an ICER of less than £20,000 per QALY gained to be considered a cost-effective use of NHS resources. However, at no point in the FAD does the Committee consider the other factors listed in paragraph 6.3.3, including specifically whether its appraisal of abiraterone has adequately captured the change in HRQoL associated with such treatment or whether there are any aspects of the technology that relate to non-health objectives of the NHS.

(a) The capture of relevant benefits in the QALY calculation for abiraterone

The capture of HRQoL benefits is a highly relevant factor in this appraisal in circumstances where a significant proportion of eligible patients decline to receive treatment with docetaxel, the treatment preferred by Committee B. At paragraph 3.2, the FAD states:

“*The Cancer Drugs Fund’s clinical lead noted that around two-thirds of people presenting with hormone-sensitive metastatic prostate cancer in England have ADT alone. Of these some are not fit enough for docetaxel and many choose not to have it because of the adverse events associated with chemotherapy”* [emphasis added]*.*

However, the EQ-5D tool preferred by NICE for measuring quality of life (see e.g. paragraph 3.11 of the FAD) is a generic quality measure, rather than one specifically designed for prostate cancer. Use of the EQ-5D tool in STAMPEDE produced a utility decrement of -0.02 in patients who agreed to undergo docetaxel combination treatment with ADT, attributed to the first full-year of such treatment. This utility decrement is very small and appears inadequate to capture the full impact of docetaxel on quality of life, including patient anxiety in advance of treatment, significant immediate impact whilst receiving docetaxel or the prolonged time to recovery of quality of life. Moreover, such a utility decrement does not capture, on any view, the impact docetaxel would have on the “many” patients with mHSPC who prefer an earlier death rather than accepting treatment with docetaxel.

NHS England’s Commissioning Policy “Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer” recognises the toxicities associated with docetaxel and states:

“*However, the toxicity of docetaxel means some men (particularly those with poor performance status or comorbidities) may prefer other treatment options”.*

This is consistent with the evidence given to the Appraisal Committee and accepted in the FAD, that “many” patients accept the risk of an earlier death rather than receiving treatment with docetaxel. Such stark decisions, made by patients with a serious, life-threatening disease, cannot simply be dismissed as “patient choice”, as suggested at paragraph 3.2 of the FAD. The term “patient choice” suggests that the various treatments under consideration are valid options; however the fact that “many” patients decline to receive docetaxel in favour of ADT alone (i.e. where no treatment is offered instead of docetaxel) in circumstances where they can therefore expect an earlier death, provides powerful evidence indicating that, for many patients, docetaxel is not a valid option. These decisions to refuse treatment with docetaxel provide strong support for a conclusion, consistent with the results of the CHAARTED and STAMPEDE trials, that patients treated with docetaxel experience a material decrement in HRQoL and that this decrement has not been adequately captured in the assessment conducted by the Committee and relied upon for the purposes of the draft guidance in the FAD.

In circumstances where the actions of patients provide clear evidence of the negative effects of docetaxel, it is procedurally unfair and inconsistent with NICE’s processes for the Committee to omit to give any thought to the adequate capture of the relative benefits of abiraterone treatment in terms of HRQoL, despite the requirements of paragraph 6.3.3 of the Methods Guide. The benefits of abiraterone plus ADT relative to docetaxel plus ADT and ADT alone which may not have been captured could potentially include:

* 1. The value placed by a patient on maintaining his current quality of life, continuing to feel well and healthy for as long as possible and avoiding immediate detriment to quality of life attributed to toxicities of chemotherapy, which may outweigh the risk of earlier death associated with ADT alone (as demonstrated by the many quality of life benefits presented in addition to EQ-5D in Section B.2.6, Janssen’s Submission dated February 2018)
  2. The inability of the EQ-5D tool to capture anxiety experienced prior to and in anticipation of docetaxel treatment (as supported by the referenced patient experience study [Ito et al 2018] in Section B.1.3, Janssen’s Submission dated February 2018 and Section B.1.6, Janssen’s Re-Submission dated July 2019)

(b) Aspects of the technology that relate to non-health objectives of the NHS

Paragraph 6.3.3 of the Methods Guide provides that one of the factors which the Appraisal Committee is required to consider, in circumstances where most plausible ICER for a technology exceeds £20,000 per QALY gained, is whether there are aspects of the technology that relate to non-health objectives of the NHS. Such non-health objectives include, separately from costs comprised in the cost-effectiveness analysis, efficient service delivery and capacity constraints. In this context, the benefits of abiraterone relative to docetaxel which relate to non-health objectives of the NHS could potentially include:

1. The value to the NHS of an oral treatment taken by patients at home compared to an intravenous one administered in hospital (as discussed in Section B.2.12, Janssen’s Submission dated February 2018).
2. The value to the NHS of a treatment which does not cause immunosuppression.

While the use of oral treatments and avoidance of hospital admissions (both for administration and in order to deal with toxicities) are generally an objective of the NHS to address capacity issues, these issues are of even more importance in the current pandemic situation, with the necessity to avoid immunosuppressive treatments where possible in order to avoid exposing patients to unnecessary risk, and the need to ensure that patients can continue to receive treatment for prostate cancer, despite limitations on hospital services and the increased risks associated with hospital attendances. Accordingly, the availability of an oral treatment that may be administered at home may determine whether a patient can receive any treatment additional to ADT in the current pandemic and particularly in the event of a second wave of COVID-19.

In the absence of any or any sufficient reasons in the FAD, it must be assumed that no discussion regarding the adequate capture of the HRQoL benefits of abiraterone therapy or the non-health objectives of the NHS took place. However even if, despite the absence of any consideration in the FAD, the Committee did discuss such matters, the lack of any explanation of the reasons for the Committee’s position on these important issues represents an unacceptable lack of transparency. It is a fundamental aspect of a fair procedure that a person affected by a decision should understand why they have been unsuccessful and proper reasoning is a requirement of rigorous decision-making. The absence of proper or any reasons in this case has precluded appropriate participation by Janssen and other stakeholders in the appraisal process and would therefore represent a defect in the procedure.

* 1. **Ground 1(a).2: The Appraisal Committee’s conclusion that “*there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination*” does not: (a) provide adequate reasons for diverging from NHS England’s commissioning policy; (b) justify rejection of the criteria proposed by NHS England for determining access to abiraterone through the Blueteq management system; (c) provide reasons for deviating from its conclusions in the earlier appraisal of Radium-223; and (d) explained why it has adopted a different approach to that followed in the appraisal of lenalidomide**

While the Appraisal Committee has based its guidance for use of abiraterone in this appraisal on a comparison with docetaxel, as noted above, it is an accepted fact, stated by the Cancer Drugs Fund clinical lead that “*around two-thirds of people presenting with metastatic, hormone-sensitive prostate cancer in England have ADT alone*”.

At paragraph 3.2 of the FAD, the Committee refers to the unmet need for an alternative treatment option for people who cannot receive treatment with docetaxel. The Committee concludes *“there are no clear-cut clinical criteria to define who can have abiraterone in combination, but not docetaxel in combination”*. In making this determination however, the Committee has provided no reasons for diverging from the policy adopted by NHS England, the criteria proposed by NHS England for determining access to abiraterone and the Committee’s own conclusions in earlier appraisals.

(a) NHS England’s Commissioning Policy on docetaxel which determines the patients for whom docetaxel will be commissioned

NHS England’s Commissioning Policy on docetaxel (referenced at paragraph 3.2 of the FAD) refers to contraindications to use of docetaxel in this patient population as:

*“There are few absolute contra-indications for docetaxel therapy. However, an absolute contra-indication is severe prior hypersensitivity reaction to taxanes.*

*Other contra-indications would include, poor overall performance status (WHO performance status 3-4, caution for those with performance status 2), pre-existing significant peripheral neuropathy, poor bone marrow function due to extensive disease or other prior haematological problems, significant co-morbidity (e.g. cardio-vascular or respiratory disease) such that prostate cancer is not likely to be the life limiting illness for the patient”.*

In addition, the Commissioning Policy refers to discontinuation of treatment with docetaxel due to patient preference.

The Commissioning Policy therefore defines a group of patients with hormone naïve (or hormone sensitive) metastatic prostate cancer who, NHS England accepts, cannot receive docetaxel.

(b) NHS England proposed Blueteq criteria to define the patients unable to receive docetaxel

Blueteq is a system used by NHS England to ensure that access to certain medicines is limited to appropriate patients. The system operates by requiring prescribers to complete a questionnaire for relevant patients before funding of treatment is approved.

At the third meeting of the Appraisal Committee, NHS England proposed Blueteq criteria for abiraterone for patients with newly diagnosed, high risk, mHSPC. The questions to be answered by a prescriber prior to prescription of abiraterone were as follows:

*“I confirm that I have assessed this patient’s eligibility for receiving upfront docetaxel plus ADT and have concluded that the patient* ***cannot*** *or* ***should not*** *or has* ***chosen not*** *to be treated with docetaxel.*

*Please mark below which of these 3 clinical scenarios apply to this patient:*

* *the patient commenced docetaxel and has had to discontinue docetaxel within 2 cycles of its start on account of life-threatening toxicity (i.e.* ***the patient CANNOT receive docetaxel****)*
* *the patient has significant comorbidities which preclude treatment with docetaxel (i.e.* ***the patient SHOULD NOT be treated with docetaxel****) and this has been fully discussed with the patient. It is recommended that validated systems of scoring clinical frailty are used as part of the oncology assessment as to explaining the benefits and risks of chemotherapy and abiraterone*
* *the patient has been fully consented regarding the advantages and disadvantages of both upfront docetaxel chemotherapy and abiraterone and also that use of upfront abiraterone would result in there being no further possible treatment with any androgen receptor targeted agents when the patient’s disease progresses and that the patient may not be fit enough to receive docetaxel when the patient‘s disease progresses. After such informed consent, the patient has chosen to receive upfront abiraterone (i.e.* ***the patient has CHOSEN NOT to be treated with docetaxel****).”*

As such, in addition to the patients unable to receive docetaxel, the Blueteq criteria proposed by NHS England also included a group of patients who, after discussion with their treating doctors regarding the advantages and disadvantages of docetaxel therapy, has declined to receive such treatment.

(b) The issue of patients unable to take docetaxel was considered by Committee B during the appraisal of Radium 223.

NICE guidance on Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA 412) was prepared by Committee B (the same Appraisal Committee as that considering the current appraisal of abiraterone) and issued in September 2016. In that guidance, Committee B recommends use of Radium-223 including in patients where “*docetaxel is contraindicated or is not suitable for them”*.

Paragraph 4.2 of TA 412 refers to the consideration of the docetaxel ineligible population by Committee B:

*“The committee heard from clinical experts that there are people for whom*

*docetaxel is contraindicated or unsuitable, and who would typically have best*

*supportive care in clinical practice. The clinical experts stated that this group of people could be considered for treatment with radium-223. However, they emphasised that people in this group are difficult to define and that making such a treatment decision needed an assessment of multiple factors such as age, wellbeing and comorbidities. The committee accepted the views of the clinical experts that there is a clinically recognised group for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable. It concluded that, for this group of people, best supportive care is the most relevant comparator.”*

Accordingly, in the context of the appraisal of Radium-223, Committee B refers to potential difficulties defining patients ineligible for treatment with docetaxel and concludes that any such difficulties do not preclude the identification of this group of patients for the purposes of guidance.

In the current appraisal, Committee B referred at paragraph 3.2 of the Second ACD (prepared following the second meeting of the Appraisal Committee but never issued for consultation) to its conclusions in relation to Radium-223, stating:

“*The committee was aware that NICE recommends* [*radium-223*](https://www.nice.org.uk/guidance/ta412/) *as an option for treating hormone-relapsed prostate cancer with bone metastases in adults only if they already had docetaxel or if docetaxel is contraindicated or not suitable. However, this guidance notes that people for whom docetaxel is contraindicated or not suitable are difficult to define”*.

Accordingly, the Appraisal Committee has not only issued recommendation for use of another technology in a docetaxel - ineligible population in another appraisal, it has recognised the implications of this previous recommendations in the context of this appraisal but has, nevertheless failed to provide any explanation for adopting a different approach.

(c) The definition of patients unable to take an alternative treatment was also considered by Committee B during the appraisal of lenalidomide

NICE’s guidance on lenalidomide plus dexamethasone for previously untreated multiple myeloma (TA 587) which also followed an appraisal by Committee B, recommends use of lenalidomide subject to conditions, including that use is limited to patients for whom thalidomide is contraindicated or who cannot tolerate thalidomide.

Paragraph 3.2, TA 587 considers the patient population who are unable to take thalidomide and states:

“*The Cancer Drugs Fund clinical lead explained that it is unclear who cannot take thalidomide in clinical practice. The committee was aware that NICE's technology appraisal guidance for bortezomib and thalidomide for the first-line treatment of multiple myeloma did not define the people who cannot have thalidomide. The Cancer Drugs Fund clinical lead explained that this has led to a much wider group having bortezomib than those who cannot have thalidomide because of true contraindications or intolerance. Specifically, at least 50% of people with newly diagnosed myeloma who are not eligible for a stem cell transplant are currently having first-line bortezomib-based therapy, about 25% are having thalidomide-based therapy and about 25% are having cytotoxic chemotherapy. The clinical experts agreed that there are no standard criteria to define who cannot have thalidomide-based treatment in clinical practice, but these might include people who […..]*

*The committee agreed that it could not define this population any further because there are no strict criteria used in clinical practice to determine who can or cannot take thalidomide. However, it expected that clinicians would exercise their judgement when deciding whether someone can take thalidomide, taking into account the contraindications in the summary of product characteristics, the person's medical history and pre-existing conditions, and the effect of toxicity on overall treatment benefit. To help clinicians do this, it would be beneficial to have clear guidance from the commissioner, NHS England”.*

During the lenalidomide appraisal therefore, Committee B commented that it would be helpful to have guidance from NHS England to assist clinicians to define the relevant population of patients. Such guidance has, of course, been provided in the context of the current appraisal in relation to the patients who are unable to receive docetaxel.

In summary therefore, in a previous appraisal in metastatic prostate cancer, Committee B has considered the definition of the group of patients who are unable to receive treatment with docetaxel and has accepted that such a group can be adequately identified for the purposes of guidance. This approach has similarly been accepted and implemented by NHS England in its own Commissioning Policy on use of docetaxel in prostate cancer.

Committee B has taken a similar decision in other appraisals where the population of patients who are unable to receive an alternative treatment cannot be clearly defined, but where it is reasonable to rely on clinical judgment in accordance with the SmPC for the product in question and the medical condition and comorbidities present in the individual patient.

In the above circumstances and in the context of the NHS England Commissioning Policy, which defines which patients are unable to receive docetaxel, Committee B has provided no or no adequate explanation for its rejection of the NHS England criteria for docetaxel, and the Blueteq system incorporating the same criteria and proposed by NHS England for the purposes of determining access to abiraterone. Furthermore, it has provided no reasons for reaching the opposite conclusion in this appraisal to that it reached in the appraisal of Radium 223, in relation to the identification of the same group of patients or to the conclusion it reached in the appraisal of lenalidomide in relation to the identification of a similar group. The absence of adequate reasons to explain the Committee’s decision precludes understanding of the decision and fair participation by stakeholders in the appraisal process; it is inconsistent with rigorous decision-making. The general unfairness of this approach is materially increased where the decision conflicts with previous decisions on the same or very similar issues made by the same committee, which requires careful justification if they are not to appear arbitrary.

* 1. **Ground 1(a).3: the Appraisal Committee has provided no reasons to explain its view that the benefits of abiraterone may be different in those patients who are unable to receive docetaxel**

At paragraph 3.2 of the FAD, the Appraisal Committee refers to the group of patients who are unable to receive docetaxel and states:

“*The Committee was not presented with evidence of abiraterone’s effectiveness in people who cannot take docetaxel. Without this evidence it could not say whether abiraterone would be safe or effective in this group.*”

However, the mechanism of action of abiraterone is different from that of docetaxel and therefore it is not associated with the same toxicities.

In particular, clinical experts at the first Appraisal Committee meeting discussed the homogeneity of the treatment effect in STAMPEDE and, as noted at paragraph 3.4 of the ACD, “*two clinical experts, who were also investigators in STAMPEDE, explained that there was no subgroup in whom abiraterone were more or less effective*.” A further independent clinical expert statement submitted by the British Association of Urological Surgeons (BAUS) during consultation recognised “*there was no heterogeneity of effect when analysing the STAMPEDE data; administration of the active agent resulted in benefit*.”

The position in this appraisal is similar to that for lenalidomide in TA 587, where Committee B accepted that, while the pivotal clinical trial was not conducted in patients who were unable to receive thalidomide, the results could be generalised to use in that population as informed by clinical expert opinion, stating:

*“All patients enrolled in FIRST could, by definition, take thalidomide because the comparator arm of the trial was MPT, which is a thalidomide-based therapy. The committee queried whether the results would be relevant, given the company's focus on the population unable to take thalidomide. The clinical experts explained that being unable to take thalidomide would not be expected to change the rates of disease progression or death on lenalidomide seen in the trial. Therefore, they considered the results would be generalisable to the group who cannot have thalidomide. The committee was concerned that the main trial evidence did not reflect the relevant population in this appraisal, but accepted that the results for patients randomised to lenalidomide plus dexamethasone were unlikely to differ markedly in the group who cannot have thalidomide”.*

The position in the current appraisal is stronger than that for lenalidomide. As noted above, abiraterone has a different mechanism of action to docetaxel and there is no evidence suggesting a different effect in patients unable to receive docetaxel. At paragraph 3.2 of the FAD, the Committee notes:

“*The Cancer Drug’s Fund clinical lead explained that many factors besides a person’s performance status may affect whether they could have docetaxel.*”

The key clinical trials of abiraterone in newly diagnosed, high risk mHSPC did not exclude patients who were unable to receive docetaxel. All such evidence, confirmed by expert opinion, indicates that there is no difference in abiraterone treatment effect, depending on whether patients are or are not able to receive docetaxel.

In these circumstances, the Committee’s conclusion that, without data generated specifically in a group of patients who are unable to receive docetaxel, it is unable to say “*whether abiraterone would be safe or effective in this group”* must be explained and the basis for a different approach to that followed in the appraisal of lenalidomide adequately justified. Furthermore, in the context of the evidence of the Cancer Drug’s Fund clinical lead, the logical consequence of the Committee’s current position is that separate data would be required for each and every reason affecting whether a patient could receive docetaxel. Such a requirement would not only be unrealistic and, in Janssen’s view unnecessary, it would almost certainly be unethical. Accordingly, in the absence of proper reasoning for the Committee’s view that the currently available evidence does not address the situation of patients unable to receive docetaxel and its requirement for specific evidence in this population, the conclusions of the Committee lack transparency and are unfair.

* 1. **Ground 1(a).4: The conclusions of the Appraisal Committee in relation to the cost effectiveness of abiraterone in this appraisal are opaque**

At paragraph 3.14 of the FAD, the Appraisal Committee sets out its conclusions in relation to the cost-effectiveness of abiraterone stating:

“*The cost-effectiveness estimates without a commercial arrangement were considerably higher than the range normally considered a cost-effective use of NHS resources”*

and

“*Therefore the Committee concluded that it could not recommend abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer*”.

However, the FAD does not explain what conclusions were reached by the Committee in relation to cost-effectiveness including:

* what prices for abiraterone were considered by the Committee in the context of its assessment of cost-effectiveness (i.e. whether the Committee considered the list price for abiraterone, the discounted price generally available to the NHS in the UK and/or the discounted price proposed by Janssen for this appraisal and used as the basis for modelling);
* what the ICERs shared by NICE with NHS England were;
* what the preferred ICERs were and how far above the “*range normally considered a cost-effective use of NHS resources*” these fell;
  + the ICERs based on the list price for abiraterone were not confidential and could have been disclosed;
  + Janssen notes in particular, that at paragraph 1, the FAD states “*even accounting for the offered price for abiraterone, the cost-effectiveness estimates of abiraterone with prednisolone or prednisolone plus ADT compared with both ADT alone and docetaxel plus ADT are higher than the range normally considered a cost-effective use of NHS resources*”, but that these cost-effectiveness estimates have not been shared with Janssen;
* whether (in the context of the Committee’s observations regarding the definition of the group of patients who cannot receive docetaxel) the Committee reached any conclusion at all regarding the cost-effectiveness of abiraterone compared with ADT alone, despite agreeing that this was an appropriate comparison and in circumstances where two thirds of patients in England with newly diagnosed high risk mHSPC currently receive treatment with ADT alone.

In the above circumstances it is simply impossible for Janssen or any other stakeholder to understand why abiraterone has not been recommended, to assess the reliability of the Committee’s conclusions or to determine what it has to do in order to achieve a positive outcome.

For the avoidance of doubt, while the Appraisal Committee emphasises at paragraphs 1 and paragraph 3.14 of the FAD that Janssen has not agreed a commercial agreement with NHS England for the supply of abiraterone to the NHS for the purposes of this appraisal, this was a direct result of the conclusions of the Appraisal Committee. In other words, NHS England was prepared only to approve a commercial arrangement which would result in an ICER within a range that would be acceptable to the Appraisal Committee based on the position adopted at their previous meeting. The ICERs provided by NICE to NHS England for these purposes and based on % discounts from the list price for abiraterone, were not disclosed to Janssen.

This situation is patently unfair to patients and to all other stakeholders, including Janssen. Transparency is the cornerstone of a fair procedure and the lack of proper or any real explanation for the Committee’s conclusions in relation to the cost-effectiveness of abiraterone in relation to each of the comparators identified in the scope and apparently accepted by the Committee in the FAD, wholly fails to meet this requirement. The principles set out by the Court of Appeal in R (on the Application of Eisai Ltd) v National Institute for Health and Clinical Excellence (NICE) and Others [2008] EWCA Civ 438 are directly applicable.

* 1. **Ground 1(a).5 The fact that NICE disclosed its preferred ICERs to NHS England for the purposes of negotiation of a commercial agreement, but not to Janssen is unfair**

As indicated above, NICE disclosed its preferred ICERs for this appraisal to NHS England for the purpose of NHS England’s negotiation of a commercial agreement with Janssen. NICE did not however disclose the preferred ICERs to Janssen.

NICE has then noted that Janssen did not agree a commercial agreement with NHS England, even though NHS England will only approve a commercial agreement if this results in ICERs which fall within the range recommended by NICE. Janssen was therefore expected to propose commercial arrangements to NHS England based on ICERs it had not seen and which it had had no opportunity to consider and test. This procedure is not consistent with NICE’s written procedures or with standards of transparency and fairness set out by the Court of Appeal in Eisai, referenced above.

* 1. **Ground 1(a).6: the Committee’s statement that “*the clinical experts involved in STAMPEDE confirmed that post-progression survival was shorter after abiraterone in combination than after ADT in this trial*” is based on unpublished data that have not been disclosed or confirmed.**

At paragraph 3.7 of the FAD, the Appraisal Committee states “*the clinical experts involved in STAMPEDE confirmed that post-progression survival was shorter after abiraterone in combination than after ADT in this trial*”.

The clinical experts made this assertion at the first meeting of the Appraisal Committee in May 2018, while STAMPEDE was ongoing. While over two years have passed since that time and several papers reporting on the results of the STAMPEDE trial have been published, none of such published material has included the results referenced at paragraph 3.7 of the FAD in relation to post progression survival and such evidence has not been disclosed to consultees or, so far as Janssen is aware, to the ERG. Furthermore, there has been no further discussion regarding this issue at subsequent meetings of the Appraisal Committee or any request for substantiation of the comment by the clinical experts, in order to investigate the reliability of such findings and to ascertain whether they have been maintained now that the trial data are more mature.

The statement at paragraph 3.7 of the FAD is controversial. It is clearly unfair that such evidence should be repeated in the FAD in circumstances where it is based on unpublished data which have not been disclosed to NICE. While the assertion by the clinical experts over two years ago has been relied upon by the Appraisal Committee in reaching its conclusions regarding abiraterone, it is even unclear from the FAD whether the findings were statistically significant and therefore meaningful.

Reliance on a single, unsupported oral reference to unpublished data which have not been disclosed or verified, as a basis for decision making is lacking in transparency and inconsistent with a fair or rigorous procedure.

* 1. **Ground 1(a).7: The Appraisal Committee’s focus on number of subsequent treatment options rather than outcomes relies on an irrelevant consideration**

At paragraph 3.3 of the FAD, the Appraisal Committee refers to the number and type of subsequent treatments available to patients during hormone-relapsed disease and states:

*“The Committee understood that people who have abiraterone in combination for hormone-sensitive prostate cancer have fewer options for active follow-on treatments than people who start with something other than abiraterone in combination. This is because they cannot have abiraterone or enzalutamide later in the treatment pathway.*

And also

*“It also concluded that having abiraterone in combination at this position in the pathway limits the options for follow-on treatments for people who develop hormone-relapsed disease compared with people who have ADT alone or docetaxel in combination”.*

The Committee’s assessment suggests that the availability of fewer treatment options may result in worse outcomes for patients. However there is no evidence for this. The relevant considerations for the purpose of the assessment of effectiveness are the impact of the technology on progression free survival, overall survival and HRQoL. The number of treatment options is relevant only to the extent that it impacts one of these considerations.

The Committee’s own analysis suggests the same rates of overall survival with docetaxel in combination as with abiraterone in combination and superior overall survival with abiraterone in combination as compared with ADT. There is no suggestion that the number of treatment options has any bearing on survival, as opposed to the magnitude of effect from the treatments that are provided and the order in which they are given. In these circumstances, the Committee’s focus on the number of treatment options available to patients who receive abiraterone as compared with other treatments, in the circumstances considered in this appraisal is irrelevant and therefore unfair.

* 1. **Ground 1(b).8: the assertion by the Appraisal Committee that it is required to say whether abiraterone is “safe” in patients who cannot take docetaxel assumes the role of the regulatory authority**

At paragraph 3.2 of the FAD, the Appraisal Committee refers to use of abiraterone in patients who are unable to receive docetaxel and states that “*it could not say whether abiraterone would be safe and effective in this group*”.

The assessment of safety of a medicinal product is, together with its efficacy and quality, a matter to be determined by the licensing authority when considering an application for a marketing authorisation for such product in accordance with Directive 2001/83/EC (and, in the UK context, the Human Medicines Regulations 2012) and when deciding whether an authorisation should be maintained. Accordingly, it is the licensing authority who decides whether a medicinal product is safe for use in all patients within the licensed indication. In this case, the conclusions of the European Medicines Agency with respect to the safety of abiraterone, including in those patients who NHS England has concluded, in accordance with its Commissioning Policy, may not receive docetaxel, are set out in its SmPC.

In contrast, NICE is required to make recommendations based on the clinical and cost-effectiveness of health technologies referred for that purpose by the Secretary of State (see e.g. paragraph 1.3.2 of the Methods Guide). Those assessments must include “the broad balance between the benefits and costs of providing health services or social care in England” (paragraph 6.1.3 of the Methods Guide, reflecting section 233 of the Health and Social Care Act 2012). This may require consideration of adverse effects associated with use of a technology, to the extent that those adverse effects impact the benefits or costs associated with use of a technology. However there is no provision indicating that NICE may replicate the role of the regulator in determining whether a technology is acceptably “safe” or suggesting that NICE has any role in advising the NHS that technologies approved by the licensing authority are too toxic or are otherwise unsafe to be used by NHS patients.

In these circumstances, the Appraisal Committee’s assertion at paragraph 3.2 of the FAD that it requires evidence confirming the safety of abiraterone goes beyond the role of NICE and assumes the powers and responsibilities or the regulator.

1. **GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE**
   1. **Ground 2.1: The Appraisal Committee’s conclusion that “*there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination”* is unreasonable in the context of the available evidence**

It is Janssen’s primary case that the Appraisal Committee’s conclusion at paragraph 3.2 of the FAD that “*there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination”* fails to take into account relevant evidence and is inadequately reasoned contrary to standards of procedural fairness as set out at Ground 1(a).2 above. However, alternatively, the inconsistency between the conclusions of the Appraisal Committee at paragraph 3.2 of the FAD in this appraisal and (a) NHS England’s Policy on docetaxel; (b) the Blueteq criteria proposed by NHS England; (c) the conclusions of the same Committee in the appraisal of Radium 223; and (d) the approach of the Committee during the appraisal of lenalidomide are arbitrary and unreasonable. Janssen refers to the facts and matters set out under Ground 1(a).2 above.

* 1. **Ground 2.2: the Appraisal Committee’s conclusion that the benefits of abiraterone may be different in those patients who are unable to receive docetaxel is unreasonable in light of the evidence available**

As indicated under Ground 1(a).3 above, it is Janssen’s primary case that the Appraisal Committee is required to provide reasons for its conclusion that the benefits of abiraterone may be different in those patients who are unable to receive docetaxel, given the fact that its mechanism of action is different, that the available evidence from STAMPEDE supports a similar benefit in such patients, that this view is supported by expert opinion and that the approach suggested in this appraisal is different to that Committee B adopted in the appraisal of lenalidomide.

However, in the alternative, the Committee’s conclusions are unreasonable in light of such evidence. Janssen refers to the facts and matters set out under Ground 1(a).3 above.

1. **THE DETERMINATION OF THIS APPEAL**

Janssen requests an oral hearing for the determination of this appeal.

1. **REMEDY FOLLOWING APPEAL**

Janssen respectfully requests that the appraisal is returned to the Appraisal Committee for further consideration with the following directions:

* The Committee should reconsider its conclusion that use of abiraterone in patients with newly diagnosed, high risk, mHSPC requires an ICER of less than £20,00 per QALY gained in order to be cost effective, in circumstances where it is clear from the decisions made by patients to refuse treatment with docetaxel despite its life-extending effects, for whom ADT alone is the relevant comparator, and that the benefits of abiraterone in terms of effects on quality of life relative to docetaxel have not been adequately taken into account in this appraisal.
* The Committee should consider use of abiraterone in the group of patients unable to receive treatment with docetaxel as defined in NHS England’s Commissioning Policy and the Blueteq criteria proposed for abiraterone.
* The Committee should provide clarification of its decisions in relation to the cost-effectiveness of abiraterone.
* The references to
  + the relative duration of post-progression survival in patients treated with abiraterone and ADT in STAMPEDE should be removed from the draft guidance; and
  + the numbers of treatment options available to patients with newly diagnosed high risk mHSPC are irrelevant and should be disregarded;
* That it should not issue any finding on whether abiraterone is “safe” in patients unable to receive docetaxel