NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer

1 Recommendations

1.1 Abiraterone with prednisone or prednisolone plus androgen deprivation therapy (ADT) is not recommended, within its marketing authorisation, for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer in adults.

1.2 This recommendation is not intended to affect treatment with abiraterone with prednisone or prednisolone plus ADT that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Treatment for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer in the NHS in England includes ADT alone, docetaxel plus ADT and, as of July 2021, enzalutamide plus ADT.

Clinical trial results show that, compared with ADT alone, a combination of abiraterone plus ADT and either prednisone or prednisolone increases the time until the disease progresses and how long people live. Results also show that, compared with docetaxel plus ADT, abiraterone plus ADT increases the time until the disease

progresses, but not how long people live. Docetaxel plus ADT cannot be used by or is unsuitable for some people but there is no clinical evidence for abiraterone plus ADT compared with ADT alone for this group.

There is a proposed commercial arrangement that would make abiraterone available to the NHS at a discount. Even accounting for this, the cost-effectiveness estimates of either abiraterone in combination compared with ADT alone or with docetaxel plus ADT for the whole population are higher than what NICE considers cost effective. There are no appropriate cost-effectiveness estimates for when docetaxel cannot be used or is unsuitable. Therefore, abiraterone is not recommended for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer.

2 Information about abiraterone

Marketing authorisation

2.1 Abiraterone (Zytiga; Janssen) with prednisone or prednisolone has a UK marketing authorisation for treating 'newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)'. In LATITUDE, a key trial in this appraisal, high-risk prognosis was defined as having at least 2 of the following 3 risk factors: a Gleason score of 8 or more; 3 or more lesions on bone scan; and measurable visceral metastasis (excluding lymph node disease).

Dosage in the marketing authorisation

2.2 The dosage is available in the summary of product characteristics.

Price

2.3 The cost of abiraterone is £2,735 for a pack of 56 x 500 mg tablets (excluding VAT; BNF online, accessed June 2021). The company has a commercial arrangement that makes abiraterone available to the NHS with a confidential discount when it is used later in the disease pathway for treating hormone-relapsed metastatic prostate cancer before

chemotherapy is indicated, or for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen. Had abiraterone been recommended, it would have been available to the NHS with a discount for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer.

3 Committee discussion

The appraisal committee considered evidence submitted by Janssen and a review of this submission by the evidence review group (ERG). It also considered the decision of the appeal panel. See the committee papers for full details of the evidence.

This appraisal consultation document reflects discussions had during the fifth committee meeting after 4 committee meetings and an appeal. The first public consultation on this topic occurred after the first committee meeting in May 2018. NICE suspended the appraisal to allow price negotiations between the company and NHS England after the second meeting in July 2018. The third meeting was held in January 2020 without an agreement having been reached. Then, after further negotiations in which the company and NHS England did not reach an agreement, NICE issued a final appraisal determination in June 2020. An appeal followed in September 2020. NICE's guidance executive decided, on the basis of the appeal panel's decision, that the appraisal committee should address any upheld appeal points. It also decided to allow some of the appellants (the British Uro-oncology Group (BUG), Prostate Cancer UK and Tackle Prostate Cancer) to submit data because they considered they had not been given the opportunity to do so for previous committee meetings. To address the appeal points, a fourth committee meeting was held in December 2020, after which there was a further public consultation and fifth committee meeting.

Clinical management

Androgen deprivation therapy with or without docetaxel are the first-line treatment options for hormone-sensitive metastatic prostate cancer

3.1 The clinical experts explained in the first committee meeting in May 2018 that, in clinical practice, people with newly diagnosed hormone-sensitive metastatic prostate cancer have androgen deprivation therapy (ADT) alone or docetaxel plus ADT plus the oral corticosteroid prednisolone (from now on, 'docetaxel in combination'). NICE's guideline for prostate cancer recommends ADT in the form of continuous luteinising hormone-releasing hormone agonists, bilateral orchidectomy (removal of the testicles) or bicalutamide with ADT. The guideline also recommends docetaxel. Docetaxel is now licensed for hormone-sensitive metastatic prostate cancer, and NHS England commissions it for up to 6 cycles at this point in the treatment pathway. Docetaxel is administered intravenously with oral prednisolone 5 mg twice daily for 3 weeks. The clinical experts explained that orchidectomy and bicalutamide are rarely used in the NHS. The committee was aware that NICEs technology appraisals on enzalutamide plus ADT for treating hormone-sensitive metastatic prostate cancer and on apalutamide plus ADT for hormone-sensitive metastatic prostate cancer started during this appraisal, and enzalutamide plus ADT was recommended. Because the final guidance for enzalutamide plus ADT was not published by the time of the fifth committee meeting, it did not become a comparator in this appraisal. The committee agreed that ADT includes luteinising hormone-releasing hormone agonists. It concluded that ADT alone and docetaxel in combination were appropriate comparators to abiraterone plus ADT plus 5 mg of the oral corticosteroid prednisone (from now on, 'abiraterone in combination').

It may be appropriate to consider the comparator for abiraterone in combination separately when docetaxel is contraindicated or unsuitable

3.2 The committee recognised its obligation to appraise technologies across their marketing authorisations. This meant that, if abiraterone in combination was not cost-effective across its marketing authorisation, the committee could consider a narrower population if there was a case for this. Although the company's original submission was for the full population covered in the marketing authorisation, it noted at the time that there was a group of people for whom docetaxel was clinically unsuitable or who chose not to have docetaxel. The company proposed abiraterone in combination as an alternative treatment to ADT alone for this group, which it termed 'chemotherapy ineligible' in its submission for the third committee meeting. The Cancer Drugs Fund's clinical lead noted in the third meeting that, at that time (January 2020), up to two-thirds of people presenting with hormone-sensitive metastatic prostate cancer in England had ADT alone. The committee noted that this included both people for whom docetaxel is contraindicated or unsuitable (the terminology agreed by the company, experts and committee in the fourth meeting) and people who choose not to have docetaxel. A patient expert explained that there is an unmet need for an alternative treatment option to ADT alone for this group. The committee recognised that most people who choose to have ADT alone rather than docetaxel in combination may wish to avoid the adverse events associated with docetaxel. The committee considered that this unmet need was in part addressed by NICE recommending enzalutamide plus ADT at this point in the pathway, which occurred during the course of this appraisal. The committee agreed that patient choice was important but that, for people who could have docetaxel, the comparators should be docetaxel in combination and ADT alone. If clinically and cost effective, abiraterone would be recommended as an option for the populations who can and cannot have docetaxel (from now, referred to as the 'whole population'). The committee agreed that it would be appropriate to define a group of people for whom docetaxel is

unsuitable. It also agreed that the clinical and cost-effectiveness of abiraterone in combination in this group should be considered if it was not cost-effective for the whole population.

Identifying who cannot or should not have docetaxel involves assessing a person's risks and may include people who cannot take abiraterone

3.3 In its fourth meeting, the committee set out to understand more clearly how experts define people for whom docetaxel is contraindicated or unsuitable. The clinical and patient experts had previously explained that, although there are contraindications for docetaxel, defining the group for whom it is unsuitable is complicated. The committee had been aware that NHS England's commissioning policy indicates that someone may not be fit enough for docetaxel if they have a poor overall performance status (World Health Organization [WHO] performance 3 to 4), pre-existing peripheral neuropathy, poor bone marrow function or a life-limiting illness. The policy also states that docetaxel should be used with caution in people with a WHO performance status of 2 and that there are few absolute contraindications for docetaxel therapy. The Cancer Drugs Fund's clinical lead explained that many factors besides a person's performance status may affect whether they could have docetaxel. One of these is patient choice after hearing the risks and benefits of each available treatment. In the fourth meeting, the clinical experts explained that, while creating an exhaustive list of criteria for this group is unfeasible, developing a framework would be possible. The clinical lead for the Cancer Drugs Fund explained that a clinician assesses a person's suitability for having docetaxel based on contraindications, fitness, comorbidities and preference. An oncologist would identify and discuss with a patient the individual risks and benefits associated with any treatment option before starting treatment. People for whom docetaxel is contraindicated or unsuitable would include:

- people who have contraindications to docetaxel as listed in the summary of product characteristics for docetaxel and NHS England's

clinical commissioning policy statement for docetaxel in combination with ADT

- people with poor performance status (WHO or Eastern Cooperative Oncology Group [ECOG] performance status 3 or 4, and possibly status 2 because docetaxel is used with caution in this group), which is a measure of fitness
- people with significant comorbidity (for example, cardiovascular, respiratory or liver disease) such that prostate cancer is not likely to be the only life-limiting illness
- people with peripheral sensory neuropathy or poor bone marrow function
- people with poor cognition or social support leading to a decreased ability to understand treatment options or make a decision.

Prescribing clinicians should assess the individual risks and potential benefits of having docetaxel. This should include the advantages and disadvantages of all treatment options, including fewer later treatments for people who would choose to start with abiraterone (see section 3.4). The clinical experts explained that some people who would not be fit enough for treatment with docetaxel would also not be fit enough for abiraterone, and would be offered ADT alone. It concluded that identifying people in whom docetaxel was contraindicated or unsuitable would be based on a clinical framework considering individual patient risk, and may include people who cannot take abiraterone.

The first treatment for hormone-sensitive prostate cancer affects the type and number of later treatments for hormone-refractory disease

3.4 The clinical experts explained that people who have docetaxel as first-line treatment in the hormone-sensitive setting can have docetaxel again for up to an additional 10 cycles in the hormone-relapsed setting. This is because the benefit of docetaxel is not exhausted when used for only 6 cycles. The Cancer Drugs Fund's clinical lead explained that

abiraterone and enzalutamide are commissioned by NHS England only once in the treatment pathway. This is because there is no evidence of substantial clinical benefit for enzalutamide after abiraterone or for abiraterone after enzalutamide. The committee understood that people who have abiraterone in combination for hormone-sensitive prostate cancer have fewer options for active follow-on treatments (when the disease becomes hormone- refractory) than people who start with ADT alone, or docetaxel in combination. This is because people who started with abiraterone cannot have abiraterone or enzalutamide later in the treatment pathway. The committee noted that the sequence of follow-on treatments when disease becomes hormone refractory may vary from person to person, but that ADT would be continued alongside subsequent therapies. It considered that possible follow-on treatments include:

- after ADT alone:
  - abiraterone or enzalutamide (before or after docetaxel)
  - docetaxel (unless docetaxel is contraindicated or unsuitable)
  - other active treatments such as cabazitaxel or radium-223
- after docetaxel in combination:
  - abiraterone or enzalutamide (before or after docetaxel)
  - docetaxel again
  - other active treatments such as cabazitaxel or radium-223
- after abiraterone in combination:
  - docetaxel (unless docetaxel is contraindicated or unsuitable)
  - other active treatments such as cabazitaxel or radium-223.

The committee concluded that the first-choice treatment for hormone-sensitive metastatic prostate cancer affects the follow-on treatments a person may have. 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 had ADT alone or docetaxel in combination.

Clinical evidence

LATITUDE and STAMPEDE are both relevant for assessing the clinical effectiveness of abiraterone in combination in the whole population

3.5 Two randomised controlled trials have investigated the clinical effectiveness of abiraterone in combination in hormone-sensitive metastatic disease:

- LATITUDE was a multinational double-blind trial including 1,199 people with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer. High-risk was defined as at least 2 of a Gleason score of 8 or more (that is, cancer which is aggressive or likely to spread); 3 or more lesions on a bone scan; or visceral metastasis (excluding lymph nodes). People were randomised to either abiraterone plus ADT plus a corticosteroid (5 mg prednisone once daily) or ADT alone. The co-primary end point of the trial was progression-free and overall survival.
- STAMPEDE was a UK multi-arm non-blinded adaptive trial that included some people with newly diagnosed hormone-sensitive metastatic, node-positive or high-risk localised disease (with at least 2 of: a tumour stage of 3 or 4; a Gleason score of 8 to 10, and prostate-specific antigen levels of 40 ng/ml or more); or prostate cancer previously treated with radical surgery or radiotherapy and now relapsing with high-risk features. Randomised trial arms included, but were not limited to, abiraterone plus ADT plus a corticosteroid (5 mg prednisolone once daily), ADT alone, and docetaxel plus ADT plus a corticosteroid (10 mg prednisolone once daily). The primary end point was overall survival. Data were available for 502 people with metastatic prostate cancer in the ADT alone arm, 500 in the abiraterone-in-combination arm and 115 in the docetaxel in combination arm. A comparison between abiraterone in combination and ADT alone was prespecified in the trial protocol. A comparison between abiraterone and docetaxel was done post hoc with 115 people in the docetaxel in combination arm and 227 people in the abiraterone-in-combination

arm.

The company considered that LATITUDE evaluated the clinical effectiveness of abiraterone in combination in the population in the marketing authorisation. STAMPEDE included people with locally advanced disease and metastatic disease and provided analyses for metastatic prostate cancer for both relevant comparators: ADT alone and docetaxel in combination. During the course of the appraisal, the STAMPEDE investigators published 2 analyses aligned to the licensed population (that is, the subgroup of people with high-risk metastatic disease). These were for abiraterone in combination compared with ADT alone (Hoyle et al. 2018) and docetaxel in combination compared with ADT alone (Clarke et al. 2019). The committee concluded that both LATITUDE and STAMPEDE were relevant for assessing the clinical effectiveness for abiraterone in combination in the whole population for whom it is licensed.

To compare abiraterone in combination with docetaxel in combination, estimates from STAMPEDE are preferred

3.6 To compare abiraterone in combination with docetaxel in combination, the company was concerned that results from the subgroup of people with metastatic disease in STAMPEDE did not reflect the population included in the licence for abiraterone for the proposed indication (see section 3.5). The company further stated that STAMPEDE was not statistically powered to detect a difference in survival in this post-hoc analysis. The company instead developed a network meta-analysis which, as well as including the direct data from STAMPEDE, included several other trials. The company argued that additional trials contributed information to the estimated treatment effect of abiraterone compared with docetaxel. The trials included in the network were:

- abiraterone in combination compared with docetaxel in combination: data from the STAMPEDE broad metastatic subgroup

- abiraterone in combination compared with ADT alone: data from LATITUDE (licensed population) and STAMPEDE (subgroup matching the licensed population)
- docetaxel in combination compared with ADT alone: data from STAMPEDE (subgroup matching the licensed population), CHAARTED and GETUG-AFU 15 (subgroups with 'high-volume' disease, which the company considered similar to the licensed population).

The committee noted that the company had not requested data from STAMPEDE directly comparing abiraterone in combination with docetaxel in combination for the subgroup matching the licensed population. It considered that the trials in the network may have differed in ways that could have influenced the effect estimate. The committee acknowledged that both direct and indirect evidence contributes to the total body of evidence. However, given the difference in results between the direct and indirect comparisons (see section 3.8), it concluded that the results from the direct comparison, being randomised, were less likely to be biased.

Abiraterone in combination extends survival compared with ADT alone in the whole population

3.7 Abiraterone in combination improved both progression-free and overall survival compared with ADT alone in LATITUDE and in people with high-risk metastatic disease in STAMPEDE. The size of the relative improvement for abiraterone plus ADT compared with ADT alone was similar in the 2 trials. In LATITUDE, median progression-free survival was 14.8 months with ADT alone and 33.0 months with abiraterone in combination (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.39 to 0.55). Based on the planned final analysis of overall survival, the median overall survival with ADT alone was 36.5 months compared with 53.3 months with abiraterone in combination (HR 0.66, 95% CI 0.56 to 0.78). In STAMPEDE, at a median follow up of 3.3 years, the

hazard ratio for progression-free survival in the high-risk metastatic subgroup was 0.46 (95% CI 0.36 to 0.59), and for overall survival was 0.54 (95% CI 0.41 to 0.70). Data from STAMPEDE shared after the appeal showed that the hazard ratio for overall survival was maintained after 8 years of follow up (HR 0.54, 95% CI 0.43 to 0.69). The committee noted that the survival benefit reported in LATITUDE was larger than that seen in clinical trials using abiraterone in hormone-relapsed disease, in which median overall survival was extended by 4.4 months compared with ADT alone. However, it acknowledged that its remit was to appraise abiraterone in the proposed indication and not to identify the best order and sequence of treatments. The committee concluded that abiraterone in combination improved both progression-free and overall survival compared with ADT alone. However, it noted that there was uncertainty about the magnitude of the long-term survival gain with abiraterone in combination. This was because of potential differences in the proportion of people who had life-extending treatments after disease progression on ADT in LATITUDE and STAMPEDE compared with clinical practice (see section 3.9).

Compared with docetaxel in combination, abiraterone in combination may improve progression-free survival, but not overall survival

3.8 In people with metastatic disease in STAMPEDE, abiraterone in combination improved progression-free survival compared with docetaxel in combination (HR 0.69, 95% CI 0.50 to 0.95). However, for overall survival, the hazard ratio favoured docetaxel (HR 1.13, 95% CI 0.77 to 1.66). In the company's updated base case, rather than use the results reflecting a direct comparison from STAMPEDE, it used the results of the indirect network meta-analysis that included data from LATITUDE, CHAARTED, GETUG-AFU 15 and STAMPEDE. This showed similar results to the direct comparison for progression-free survival. However, the point estimate for overall survival favoured abiraterone, but the credible interval included 1, that is, the possibility of no difference in

benefit of 1 treatment over the other. The company considered these values to be academic in confidence so they cannot be reported here. Considering the direct and indirect comparisons, the committee concluded that abiraterone in combination improves progression-free survival, but not overall survival compared with docetaxel in combination.

Neither STAMPEDE nor LATITUDE likely capture all the overall survival benefit of follow-on treatments used in current NHS clinical practice

3.9 The committee recognised that life-extending treatments offered when the disease is no longer hormone sensitive (that is, is hormone-relapsed) affects life-expectancy. Follow-on treatments in the unblinded UK STAMPEDE trial were expected to reflect what people would have in NHS clinical practice, for example, not getting abiraterone twice. This was because the choice of next treatment depended on knowing the first treatment. In STAMPEDE, people were aware of their treatment but, in the blinded LATITUDE trial, people were not. The committee noted that the trials differed from UK clinical practice in 2 ways:

- In LATITUDE, after abiraterone, 10% of the intention-to-treat (ITT) population had enzalutamide, and 5% had abiraterone again. In STAMPEDE 3% of the ITT population had enzalutamide after abiraterone, and 1% had abiraterone again.
- After ADT alone, fewer people in both STAMPEDE and in LATITUDE had follow-on treatment for hormone-relapsed disease with abiraterone or enzalutamide than would occur in NHS clinical practice. Of people who had treatments for hormone-relapsed disease, 40% had enzalutamide or abiraterone in LATITUDE, and 55% had enzalutamide or abiraterone in STAMPEDE. This was lower than the 80% modelled by the company, which was based on an estimate of UK market shares for these treatments (see section 3.18).

The committee concluded that differences between the subsequent treatments used in STAMPEDE and current UK market shares are

likely to be related to abiraterone and enzalutamide becoming increasingly available over time. It recognised that the trials may have overestimated the relative clinical effectiveness of abiraterone if fewer people in the ADT arms of the trials had benefitted from follow-on treatments for hormone-relapsed prostate cancer than do in NHS clinical practice. The committee concluded that the estimates of survival from STAMPEDE were likely more relevant to clinical practice in the NHS than those from LATITUDE because they better reflected the options available on the NHS after a patient needed a next treatment.

No data are available on the effectiveness of abiraterone compared with ADT in people for whom docetaxel is contraindicated or unsuitable

3.10 No evidence was presented for abiraterone's relative effectiveness compared with ADT alone, specifically for the group for whom docetaxel is contraindicated or unsuitable. LATITUDE and STAMPEDE, the key clinical trials of abiraterone in this indication (see section 3.5), only included people with adequate haematological function, and an ECOG or WHO performance status of 0, 1 or 2 (meaning they were reasonably fit). Also, they could not have any condition that would interfere with them taking part in the trial. As part of the initial protocol, all people recruited to STAMPEDE had to be able to have docetaxel because it was 1 of the arms in the trial. A clinical expert explained that, in 2013, that arm closed but the trial continued to recruit to the ADT alone and abiraterone-in-combination arms (among others). This meant people recruited to the trial from this point could have included people for whom docetaxel was contraindicated or unsuitable. They noted that James et al. (2017) presented an analysis showing that the hazard ratio for overall survival for abiraterone in combination compared with ADT was 0.69 (95% CI 0.53 to 0.90) between November 2011 and January 2013. This was when the docetaxel arm of the trial was open. After the docetaxel arm closed, the hazard ratio for data collected between April 2013 and January 2014

was 0.59 (95% CI 0.44 to 0.78). The ERG highlighted, and the committee agreed, that this did not provide the evidence specifically for the group for whom docetaxel was contraindicated or unsuitable. This was because the 2013 to 2014 data would also have included people who could have docetaxel. The committee heard during its fourth meeting that STAMPEDE enrolled people who could take abiraterone but could not have docetaxel. However, in response to the consultation after the committee's fourth meeting, the company and consultees commented that data specific to this subgroup could not be separated from the metastatic, high-risk cohort in STAMPEDE. This was because the trial did not collect data on all the baseline characteristics specified in the suggested clinical framework describing people who cannot or should not have docetaxel (see section 3.3). The committee was aware that many of these characteristics were similar to the STAMPEDE exclusion criteria. It noted that stakeholders had explored several further data sources for people who are 'chemotherapy ineligible' but identified none that would resolve the uncertainty about clinical and cost-effectiveness in this population. The company agreed that it was reasonable for the committee to request data specific to people who cannot or should not have docetaxel. However, the company did not consider it ethical to conduct a new clinical trial specifically in this group because trials have already shown that abiraterone is superior to ADT alone in the whole population. Acknowledging the uncertainties in the existing data, the company preferred to use the treatment effect from the whole population to represent the group for whom docetaxel is contraindicated or unsuitable. The committee concluded that assessing data specific to the relevant population was preferred, but acknowledged that this evidence was not available. It therefore considered the treatment effect from the LATITUDE whole population for people who cannot or should not have docetaxel in its decision making, while acknowledging this uncertainty.

Abiraterone in combination may be less effective in people who are unlikely to be able to have docetaxel, but data are limited and uncertain

3.11 No data were presented specifically for the group of people who cannot have docetaxel (see section 3.10). So, the committee discussed the uncertainties associated with applying the treatment effect of abiraterone in combination for the whole trial population to people who cannot or should not have docetaxel. It did this by looking at the treatment effect in people whose baseline characteristics meant they were unlikely to be able to have docetaxel. It was aware that older people (see section 3.24) and people with poorer levels of performance status would be less likely to have docetaxel. It noted the available evidence from LATITUDE and STAMPEDE on subgroups based on age and performance status. For the comparison of abiraterone in combination with ADT alone from STAMPEDE, the committee noted effect modification by age. For overall survival, abiraterone was not as effective in people 70 years and over (HR 0.94, 95% CI 0.69 to 1.29) compared with people under 70 years (HR 0.51, 95% CI 0.40 to 0.65; test for interaction p value 0.003) (James et al. 2017). The company argued that these results were not representative of the population covered by the licence for the proposed indication. This was because they included people with non-metastatic prostate cancer, who are generally younger and have earlier stage disease. The committee noted a similar pattern in LATITUDE, in which the hazard ratio for overall survival for abiraterone in combination compared with ADT alone was: 0.65 (95% CI 0.50 to 0.84) for people under 65 years; 0.68 (95% CI 0.55 to 0.83) for people 65 years and over and 0.86 (95% CI 0·62 to 1·21) for people 75 years and over (Fizazi et al. 2019). In response to the second consultation, the company stated that the test for interaction based on age was non-significant, suggesting that it was possible that age had no effect on treatment response. However, it also acknowledged in the fifth committee meeting that the test may be underpowered to detect a difference. The committee also noted a hazard ratio of 0.64 (95% CI 0.50 to 0.75) in people with an ECOG status of

0 or 1, and a hazard ratio of 1.42 (95% CI 0.65 to 3.08) for those with an ECOG status of 2 in LATITUDE (Fizazi et al. 2019). It recognised that age alone would not determine whether a person could have docetaxel, but that age was associated with decreased docetaxel use based on data provided by BUG. It also heard that people with a poor performance status may not get abiraterone. The committee agreed that abiraterone appears less effective among people with characteristics shared by people who cannot or should not have docetaxel based on subgroup data. However, it noted that subgroup data should be interpreted with caution when based on data from a small group of people (40 out of 1,159 people in LATITUDE had a performance status of 2). The committee recalled that the subgroups did not specifically reflect the population for whom docetaxel is contraindicated or unsuitable. Overall, the committee concluded it was not possible to determine the size of the effectiveness for people for whom docetaxel is contraindicated or unsuitable. It therefore chose to look at its preferred effect measures from existing data (the treatment effect seen in the whole LATITUDE population; see section 3.10), acknowledging the uncertainty.

The baseline risks from which to estimate the absolute effectiveness of abiraterone in people who cannot have docetaxel are not presented

3.12 Both the relative benefits of treatment with abiraterone compared with ADT alone, and the baseline risks of progression and dying, may differ between populations who can and cannot have docetaxel. The committee recognised that many of the risk factors for not having docetaxel (for example, age and poor performance status) are also risk factors for dying. It concluded that any modelling should take this into account (see section 3.15).

Overall survival estimates from LATITUDE include follow-on treatments not used in people who cannot or should not have docetaxel

3.13 The company considered that the results of LATITUDE could be generalised to people who cannot or should not have docetaxel in its

modelling (see section 3.15). The clinical experts explained that, with some exceptions, people with hormone-sensitive disease for whom docetaxel is contraindicated or unsuitable would not have docetaxel after their cancer progressed to being hormone relapsed. People in LATITUDE and STAMPEDE could go on to have docetaxel after abiraterone in combination or ADT alone. This did not reflect the treatment pathway for people who cannot have docetaxel, and yet was reflected in the trial results. The evidence of clinical effectiveness from LATITUDE does not reflect the treatment pathway for people for whom docetaxel is contraindicated or unsuitable. The committee therefore again agreed that it had not been presented with data on the effectiveness of abiraterone in combination compared with ADT in people for whom docetaxel is contraindicated or unsuitable. It concluded that estimates of overall survival from LATITUDE included the effect of taking docetaxel when indicated for hormone-relapsed metastatic disease, which would not apply to people who cannot or should not have docetaxel.

Company's economic model

A partitioned survival model is appropriate

3.14 The company provided 2 models. In its original submission, it provided a multistate Markov model. The committee deemed that this did not provide plausible estimates of post-progression or overall survival and did not generate valid estimates of cost effectiveness. In its submission for the third committee meeting, the company provided a partitioned survival model. Both models were split into 2 phases:

- A **hormone-sensitive** phase, in which the company used LATITUDE to model probabilities of progressing and dying while on abiraterone in combination or ADT alone: For abiraterone in combination compared with docetaxel in combination, the company applied hazard ratios from its revised network meta-analysis (including STAMPEDE) to data from LATITUDE.

- A **hormone-relapsed** phase: In the Markov model, the company based the time spent in the hormone-relapsed phase on the survival curves from NICE's technology appraisal guidance on abiraterone for treating metastatic hormone-relapsed prostate cancer before docetaxel is indicated. However, this approach did not produce valid estimates of overall survival for docetaxel. For example, modelled overall survival was much longer with abiraterone in combination than with docetaxel in combination, even when using the hazard ratio for overall survival that suggested a survival benefit for docetaxel (1.13 from the STAMPEDE direct comparison). The partitioned survival model extrapolated progression-free and overall survival from LATITUDE, with the time spent in the hormone-relapsed phase being the difference between these 2 survival curves.

  The committee concluded in its third and fourth meetings that, because the company's Markov model did not give plausible estimates of post-progression and overall survival, it would consider the company's partitioned survival model.

There is no modelling reflecting the treatment pathway, costs and benefits for people for whom docetaxel is contraindicated or unsuitable

3.15 For the third committee discussion, the company provided estimates of the cost-effectiveness of abiraterone in combination compared with ADT alone for a population it referred to as 'chemotherapy ineligible' (see section 3.2). The committee noted that the company based these estimates on data for the whole population. The committee recognised that the clinical data used in the model may not be generalisable to the 'chemotherapy ineligible' group. It also recognised that the modelled treatment pathway did not reflect the treatments people for whom docetaxel is contraindicated or unsuitable would have. Specifically:

- It is uncertain whether abiraterone is as effective for people for whom docetaxel is contraindicated or unsuitable as it is for people able to have docetaxel (see section 3.11).
- People in the modelled abiraterone-in-combination arm or the ADT arm went on to have docetaxel once their prostate cancer was hormone relapsed (see section 3.13).
- People for whom docetaxel is contraindicated or unsuitable compared with people who can have docetaxel may:
  - have differing rates of adverse effects that would influence health-related quality of life
  - have a higher baseline risk of dying
  - have a different risk of dying over time.

The committee concluded that the company had not provided it with modelling that reflected the treatment pathway, costs, survival and quality of life for people for whom docetaxel is contraindicated or unsuitable.

In the full population, Weibull and log-logistic distributions are plausible for extrapolating progression-free and overall survival respectively

3.16 The committee agreed with the company that the hazards of progression and death for abiraterone in combination compared with ADT alone from LATITUDE were not proportional. It concluded that it was appropriate to fit curves to each arm separately. During the committee's third meeting, the company presented results for both progression-free and overall survival. It used the log-logistic distribution for each modelled treatment arm (which the company considered plausible but optimistic) and the Weibull distribution (which it considered plausible but pessimistic). The committee considered that the Weibull curves were plausible for progression-free survival. It noted that results from STAMPEDE for abiraterone in combination compared with ADT (submitted by BUG after the appeal for the fourth meeting) represented an 8-year follow up. These suggested an ongoing benefit with abiraterone in combination compared with ADT alone (HR 0.54, 95% CI 0.43 to 0.69). The results supported using the log-

logistic distribution to extrapolate overall survival from LATITUDE. At the third meeting, the ERG highlighted that a consequence of the model was that the company assumed the treatment effect to be maintained over the long term. However, in clinical practice, it may wane and the ERG provided scenarios to adjust for this at that time. The committee noted that the longer-term data from STAMPEDE could be used to determine the validity of these adjustments. It concluded that the progression-free survival extrapolation using the Weibull distribution was broadly appropriate for the overall population. However, it did not see evidence of extrapolating outcomes in people for whom docetaxel is contraindicated or unsuitable. The committee recognised that these people, being on average older, may have a different pattern of mortality. It further concluded that the predicted overall survival based on extrapolations using the log-logistic distribution was plausible for the overall trial population. The committee would have preferred to see further extrapolations exploring alternative time points for equalising the hazard using 2 plausible curves: 1 for the whole population, and another for people for whom docetaxel is contraindicated or unsuitable.

Utility values in the model

The utility estimates should be taken from the same source as the data on effectiveness

3.17 The company considered separately the effects on quality of life of adverse effects and of being on treatment. The sources of these data are in table 1.

Table 1 Company's sources of data for modelled utility values

Treatment	Quality of life relating to treatment	Quality of life relating to adverse events
Androgen deprivation therapy (ADT) alone	Based on EQ-5D data from LATITUDE	Published utility values for adverse effects and skeletal-related events

Abiraterone plus ADT plus 5 mg of the oral corticosteroid prednisone	Based on EQ-5D data from LATITUDE: the company modelled a further utility increase for being on abiraterone compared with androgen deprivation therapy alone	Published utility values for adverse effects and skeletal-related events
Docetaxel plus ADT plus the oral corticosteroid prednisolone	Based on a preference study commissioned by the company: the company modelled a further utility decrement for being on docetaxel	Published utility values for adverse effects and skeletal-related events

The company used different approaches to estimate the effect on quality of life of having abiraterone in combination or ADT alone than it did to estimate the effect with docetaxel in combination. It sourced utility values for being on abiraterone in combination from EQ-5D results from LATITUDE, and for being on docetaxel in combination from a separate preference study of the general public that it had carried out. The NICE methods guide states that EQ-5D is the preferred measure of health-related quality of life. The committee noted that STAMPEDE collected EQ-5D data for a UK population randomised to abiraterone in combination, to docetaxel in combination and to ADT alone. In response to the first consultation and in the third committee meeting, the company confirmed that it did not request or have access to these data. The ERG carried out a scenario using the disutility estimate for docetaxel from the economic evaluation of docetaxel in combination in NICE's guideline for prostate cancer. The ERG derived the disutility value from EQ-5D data collected in STAMPEDE (whole population and metastatic subgroup). The company stated that the ERG's and company's scenarios were consistent, irrespective of the disutility source used. The committee considered that the effectiveness data from the metastatic subgroup from STAMPEDE were generalisable to the higher-risk population under appraisal (see section 3.5). However, it considered that it was plausible that the level of risk affects quality of life. It concluded that it was preferable to use EQ-5D data from the subgroup of people from

STAMPEDE with high-risk hormone-sensitive metastatic prostate cancer to assess quality of life. It further noted that comparable data were available for abiraterone in combination, docetaxel in combination and ADT alone. The committee then went on to consider evidence submitted by BUG after the appeal. This showed the results of a quality-of-life study from STAMPEDE using data relevant to people with metastatic disease but not limited to high-risk disease. The data used a different measure of quality of life to EQ-5D. Results supported an improved quality of life for abiraterone in combination compared with docetaxel in combination. However, the difference was clinically meaningful according to predefined criteria only for the first 6 months after starting treatment. The committee considered that the findings supported the company's modelling that showed a worse quality of life with docetaxel in combination compared with abiraterone in combination. It also agreed that the ERG's estimate was likely to be broadly appropriate. The committee concluded that, in the absence of STAMPEDE trial data from the company, the company's and ERG's approaches were broadly consistent with each other and acceptable for decision making.

Costs used in the company's model

The company's model includes costs of follow-on treatments for metastatic hormone-relapsed disease, but not the full benefits

3.18 In response to the committee's second meeting, the company revised the treatment pathways in the hormone-relapsed state to reflect NHS market shares of treatments for hormone-relapsed disease. It based its estimates of market shares on the opinion of 4 clinicians, which the committee concluded may not reflect the actual market shares in UK clinical practice. The company assumed that:

- About 80% of people had abiraterone or enzalutamide after ADT alone or docetaxel in combination.
- People who had docetaxel in combination could have docetaxel again.

- People in each modelled treatment arm could have 3 treatments once their prostate cancer was hormone relapsed. Fewer people in the abiraterone arm had an active treatment as their third treatment for hormone-relapsed prostate cancer than in the comparator arms.

  The committee noted that there was a mismatch between the modelling of treatments for hormone-relapsed prostate cancer and the proportions of people who had these treatments in LATITUDE and STAMPEDE (see section 3.9). The committee recognised that the company's model therefore accounted for the high costs of some of these treatments, but potentially not all of the life-extending benefits. So, the benefits may not have been fully captured in the trials. The committee concluded that it had not been presented with a validated estimate of treatments offered in the NHS. It further concluded that accounting for the costs, but not the benefits, of life-extending treatment could have biased the cost-effectiveness results. This would mean that the incremental cost-effectiveness ratio (ICER) for abiraterone in combination compared with its comparators may be higher than that estimated by the model.

Cost-effectiveness results

The company's base case for the whole population covered by abiraterone's licence does not reflect the preferred assumptions

3.19 The committee agreed that its preferred approach to modelling would reflect the company's base case with the following assumptions:

- incremental probabilistic, rather than pairwise deterministic, analyses comparing abiraterone in combination with the relevant comparators (that is, ADT alone and docetaxel in combination)
- progression-free survival extrapolated using the Weibull distribution and overall survival extrapolated using the log-logistic distribution

- the same rates of overall survival for abiraterone in combination and docetaxel in combination (that is, assume an overall survival HR of 1.00).

The committee concluded that the following scenarios were useful:

- using the hazard ratio of 1.13 for overall survival for abiraterone in combination compared with docetaxel in combination from the direct comparison of the metastatic subgroup from STAMPEDE
- using the hazard ratio for overall survival for abiraterone in combination compared with docetaxel in combination from the company's indirect comparison (the hazard ratio is academic in confidence)
- assuming equal hazards of progression and overall survival at various time points to account for potential treatment waning.

The results of the cost-effectiveness analyses should be made transparent

3.20 The prices of abiraterone made by Janssen and technologies made by company's other than Janssen are confidential. This meant that estimates of the ICERs could not be presented in the final appraisal determination that followed the committee's third meeting. In this meeting, NICE asked the committee to consider abiraterone at list price for this indication (and abiraterone at a discount for its other indications). This was because the company and NHS had not agreed a discounted price. The final appraisal determination stated that the cost-effectiveness estimates without a commercial arrangement were considerably higher than the range normally considered a cost-effective use of NHS resources. The company appealed, and the appeal panel concluded that this was not transparent. At the time of the fourth committee meeting, the company agreed a confidential discounted price for abiraterone but noted it did not wish NICE to publish a narrow range of ICERs. This was because the cost-effectiveness estimates using list prices had been published previously

and the company stated that this would allow back calculation of its discount for abiraterone. The committee addressed this appeal point (see section 3.21) by stating a figure above which the ICER lies. It supported transparency in reporting cost effectiveness, and agreed that this did not fully address the appeal panel's suggestion. However, the company acknowledged in the fifth meeting that it had not agreed to a range of cost-effectiveness estimates being available for publication for the reasons stated above. So, the committee could not provide a more accurate representation of the ICER. The committee concluded that it strongly supported being more transparent in reporting estimates of cost effectiveness when possible without compromising confidential commercial arrangements.

Abiraterone is not a cost-effective use of NHS resources for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer

3.21 The committee noted its duty to appraise technologies across their marketing authorisation. At the confidential discount chosen by the company, the company's base case with the appraisal committee's preferred modelling assumptions was:

- Over £100,000 per quality-adjusted life year (QALY) gained when compared with docetaxel in combination
- Over £30,000 per QALY gained compared with ADT alone.

The committee concluded that, for the whole population, the ICERs were above the range considered a good use of NHS resources. It reflected this decision in the appraisal consultation document that followed its fourth meeting. For the committee's fifth meeting, the company presented no new inputs, assumptions or price in its modelling. The committee then considered whether abiraterone in combination might be a clinically effective and cost-effective treatment option for people for whom docetaxel was contraindicated or unsuitable, and for whom the relevant comparator would therefore be

ADT alone. It agreed that the modelled comparison with ADT as presented by the company was not a valid estimate for people for whom docetaxel is contraindicated or unsuitable (see sections 3.10 to 3.13 and 3.15). Despite this, in the absence of any data specific to this group, the committee considered estimates from the whole LATITUDE population, while acknowledging the uncertainty in its decision-making. It also noted that the ERG had presented scenarios which attempted to model the group in whom docetaxel was contraindicated or unsuitable. It did this by removing chemotherapy as a follow-on treatment, along with any associated survival benefit. The committee noted that in the company's own base case and in all ERG scenarios comparing abiraterone in combination with ADT alone, the ICERs were above £30,000 per QALY gained. It concluded that cost-effectiveness results in the population who cannot or should not have docetaxel were highly uncertain. However, even when considering the company's own modelling for this group compared with ADT alone, the ICERs were above the range considered a good use of NHS resources. The committee also agreed that there was considerable uncertainty around the cost effectiveness of abiraterone in people for whom docetaxel is contraindicated or unsuitable, which should be taken into account in decision making.

Abiraterone may be associated with benefits unaccounted for in the modelling

3.22 The committee recognised that there was an unmet need for another treatment option to ADT in people for whom docetaxel is contraindicated or unsuitable. However, it agreed that this need was lessened by enzalutamide plus ADT having been recommended for this indication. It noted that the benefits of abiraterone being an oral treatment that could be taken at home were not captured in the model. It also acknowledged the increasing need for oral treatments during the COVID-19 pandemic.

The committee concluded that abiraterone may be associated with benefits unaccounted for in the modelling.

Equality issues

The recommendations apply to all people with prostate cancer and do not discriminate on the basis of age

3.23 The committee noted that, as in previous NICE technology appraisals of technologies for treating prostate cancer, its recommendations should apply to anyone with a prostate. It also noted that, in clinical practice, older people are less likely to have docetaxel than younger people based on NHS data from appellants presented at the fourth committee meeting. The clinical experts explained that, although docetaxel is more likely to be contraindicated or unsuitable for older people, age itself will not determine whether a person could or should have docetaxel in clinical practice. The committee was aware that making recommendations by age to reflect people who cannot or should not have docetaxel could discriminate against younger people for whom docetaxel is contraindicated or unsuitable. It noted the appeal panel's conclusions that: 'the current reasoning around the failure to define this subgroup does not address the fact that the subgroup will tend to comprise older men'. It also noted that the appeal panel: 'wishes to be clear that although equality legislation requires this subgroup to be more fully considered it does not necessarily follow that in this case, after appropriate consideration, special provision will need to be made for them'. The committee concluded that its recommendations should apply to all people with prostate cancer and not discriminate on the basis of age.

The points upheld in appeal are addressed

3.24 The committee noted that 22 points were discussed in the appeal, 16 of which were dismissed by the appeal panel and 6 of which were upheld. The upheld points related to transparency (see section 3.20), equality issues (see section 3.23) and defining a population for whom docetaxel is

contraindicated or unsuitable (see section 3.3). The appeal panel stated that the committee should:

- consider whether it is possible to define a group of people for whom docetaxel is contraindicated or unsuitable (see section 3.3)
- consider whether there is evidence available for the clinical and cost-effectiveness of abiraterone in this group (see sections 3.10 to 3.12 and 3.15)
- if it concludes that approaches taken in other settings (notably NICE's technology appraisal on radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases) are unsuitable in this appraisal, give clear reasons for this.

Similar to the appraisal for radium-223 dichloride, section 3.3 in this appraisal defines a group for whom docetaxel is contraindicated or unsuitable. The committee noted that, for the radium-223 appraisal, clinical trial data were available for people not eligible to have docetaxel, who declined docetaxel, or for whom docetaxel was unavailable. However, no such data were presented in this appraisal for abiraterone in combination (see sections 3.10 to 3.12). The committee concluded that, having defined a framework for identifying people for whom docetaxel is contraindicated or unsuitable (see section 3.3), it had used a consistent approach to radium-223 in this appraisal. It also noted that radium-223 is used in a different position in the treatment pathway to abiraterone in combination (see section 3.3). It further concluded that it had addressed all the points upheld in the appeal.

4 Review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. The guidance executive will decide whether the technology

should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
June 2021

5 Appraisal committee members

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), technical advisers and a project manager.

Jessica Cronshaw, Mary Hughes and Emma Douch
Technical leads

Ross Dent, Jasdeep Hayre and Lorna Dunning
Technical advisers

Jeremy Powell
Project manager

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