NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Apalutamide with androgen deprivation therapy for treating prostate cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using apalutamide in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using apalutamide in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 11 June 2021

Next appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Apalutamide plus androgen deprivation therapy (ADT) is not recommended, within its marketing authorisation, for treating prostate cancer in adults who have:

- hormone-relapsed non-metastatic disease at high risk of metastasising
- hormone-sensitive metastatic disease.

1.2 This recommendation is not intended to affect treatment with apalutamide 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

This appraisal considers apalutamide for:

- Non-metastatic prostate cancer that has stopped responding to hormone therapy (hormone relapsed) – this is usually treated with ADT alone or with darolutamide plus ADT.
- Hormone-sensitive metastatic prostate cancer – this is usually treated with docetaxel plus ADT if people can have docetaxel, or ADT alone if people cannot have docetaxel.

Clinical trial evidence suggests that, compared with placebo plus ADT, apalutamide plus ADT increases the time until the disease progresses and how long people live. But this evidence is uncertain because in the trials some people could switch from placebo plus ADT to apalutamide plus ADT. Also, some people could have treatments not available in the NHS.

Some of the assumptions in the economic modelling are also uncertain, including the time until the disease progresses and how long people live. The cost-effectiveness estimates are uncertain and higher than what NICE considers an acceptable use of

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NHS resources. Therefore, apalutamide plus ADT is not recommended for hormone-relapsed non-metastatic prostate cancer, or for hormone-sensitive metastatic prostate cancer.

2 Information about apalutamide

Marketing authorisation indication

2.1 Apalutamide (Erleada, Janssen) is indicated:

- 'in adult men for the treatment of non-metastatic castration-resistant prostate cancer in adults who are at high risk of developing metastatic disease
- in adult men for the treatment of metastatic hormone-sensitive prostate cancer in combination with androgen deprivation therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The price for apalutamide is £2,735 per pack of 112 tablets, each containing 60 mg of the active ingredient (excluding VAT; BNF online, March 2021). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Janssen, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

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Treatment pathway

Only 1 newer androgen receptor inhibitor would be used in the prostate cancer treatment pathway

3.1 People have a treatment until disease progression or until they can no longer tolerate it. NICE recommends the newer (second generation) androgen receptor inhibitors enzalutamide, abiraterone and darolutamide for treating either metastatic or hormone-relapsed non-metastatic prostate cancer at multiple positions in the treatment pathway:

- NICE's technology appraisal guidance on abiraterone for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen
- Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen
- Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated
- Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated and
- Darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer.

Apalutamide is also a second generation androgen receptor inhibitor. The Cancer Drugs Fund clinical lead explained that a person will have only one of these drugs in the NHS prostate cancer treatment pathway. The clinical experts confirmed that this is because of the similar way the drugs work, and probable resistance to drugs in the same group when used subsequently. For example, if prostate cancer metastasises on apalutamide, it would be expected to be resistant to subsequent treatment with enzalutamide or abiraterone. The Cancer Drugs Fund clinical lead confirmed that NHS England would not commission enzalutamide or abiraterone after apalutamide if it were recommended.

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The committee concluded that only 1 newer androgen receptor inhibitor would be used in the prostate cancer treatment pathway.

There is greater unmet need for hormone-sensitive metastatic prostate cancer than for hormone-resistant non-metastatic cancer

3.2 Until recently, treatment for hormone-relapsed non-metastatic prostate cancer involved continuing androgen deprivation therapy (ADT), even though the cancer may no longer respond to it. However, since NICE recommended darolutamide, there is no longer an unmet need for a new oral treatment at this stage in the pathway (see section **Error! Reference source not found.**). But another option would add choice and value for patients and their clinicians. Treatment for hormone-sensitive metastatic prostate cancer includes ADT or chemotherapy (docetaxel). People cannot progress from hormone-relapsed non-metastatic disease to hormone-sensitive metastatic disease, or vice versa. So taking apalutamide for 1 indication would not affect the other indication and people would not have to choose when to take apalutamide. A clinical expert explained that people do not need to have a corticosteroid with apalutamide, unlike with some of the other available treatments, so would likely have fewer adverse effects. The committee concluded that although people would value another treatment option at this stage in the pathway, there is greater unmet need for an oral treatment for hormone-sensitive metastatic disease.

Clinical management of hormone-relapsed non-metastatic disease

Treatment aims to delay metastasis

3.3 Once cancer stops responding to ADT it is hormone-relapsed. Apalutamide plus ADT is indicated for treating hormone-relapsed prostate cancer that is at high risk of metastasising. SPARTAN, the trial that informed apalutamide's marketing authorisation (see section 3.6), defined high risk as a blood prostate specific antigen level of 2 nanograms per millilitre or more that has doubled in 10 months. This is the same

indication appraised in NICE's technology appraisal guidance on enzalutamide and on darolutamide. But enzalutamide is not recommended for this population, and darolutamide was not routinely available in the NHS at the start of this appraisal. So darolutamide was not considered a relevant comparator for decision making. Treatment aims to delay metastatic disease, which is associated with reduced quality of life and survival. The patient experts explained that anxiety about cancer metastasising causes psychological distress, which adds to debilitating symptoms such as fatigue, pain, and urinary and bowel problems. The committee concluded that treating hormone-relapsed non-metastatic prostate cancer aims to delay metastasis.

Clinical management of hormone-sensitive metastatic disease

People would welcome the option of treatment with apalutamide plus ADT

3.4 The clinical experts explained that, in clinical practice, people with newly diagnosed hormone-sensitive metastatic prostate cancer have ADT alone or docetaxel plus the oral corticosteroid prednisolone plus ADT. This is in line with NICE's guideline on prostate cancer. Docetaxel is not licensed for hormone-sensitive metastatic prostate cancer, but NHS England commissions it for up to 6 cycles. It is administered as a 1-hour infusion every 3 weeks, with twice daily oral prednisolone 5 mg. People who have had docetaxel plus ADT for hormone-sensitive metastatic disease can have it again once their cancer metastasises. NHS England's interim guidance on treatment options during the COVID-19 pandemic allows use of enzalutamide plus ADT instead of docetaxel plus ADT, or abiraterone with prednisone or prednisolone plus ADT for people who are unable to tolerate enzalutamide. The patient experts explained that people who are diagnosed with metastatic disease may have no or few symptoms. They also explained that some people think that docetaxel worsens quality of life and so choose to have ADT alone, even though the long-term outcomes may be worse. Apalutamide plus ADT is generally better

tolerated than docetaxel plus ADT and is likely to be more effective than ADT alone (see sections 3.15 and 3.20). The committee concluded that people with hormone-sensitive metastatic prostate cancer would welcome the option of treatment with apalutamide plus ADT.

Scope of the appraisal

The committee consider the clinical and cost effectiveness of apalutamide plus ADT across its marketing authorisation

3.5 For hormone-sensitive metastatic prostate cancer, the company proposed apalutamide plus ADT as an alternative to ADT alone or docetaxel plus ADT. It also presented data for the group of people who have ADT alone. That is, people who are not well enough or who cannot tolerate docetaxel, or who choose not to have it because of the adverse events associated with chemotherapy. The Cancer Drugs Fund clinical lead noted that in NICE's technology appraisal on abiraterone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (in development) around two-thirds of people with hormone-sensitive metastatic prostate cancer in England have ADT alone. The committee recognised that there are 2 distinct populations who do not have docetaxel plus ADT:

- **People who cannot or should not have docetaxel:** The contraindications to docetaxel include severe prior hypersensitivity to taxanes. NHS England's commissioning policy indicates that contraindications include a poor overall performance status (World Health Organization [WHO] performance status 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. People over 70 years are disproportionately represented among people who cannot have docetaxel. Also, TITAN, the key clinical trial of apalutamide plus ADT for this indication (see section 3.14), included only people who were relatively well, with an Eastern Cooperative Oncology Group

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status performance status of 0 or 1. The committee was not presented with evidence of apalutamide plus ADT's effectiveness in people who cannot have docetaxel. The company suggested that because people who cannot have docetaxel represent most of the people with hormone-sensitive metastatic prostate cancer, the efficacy results for apalutamide plus ADT from TITAN were relevant for this population.

- **People who choose not to have docetaxel:** Most of these people want to avoid the adverse events associated with docetaxel. The company explained that this includes people with 'low-volume and low-risk' disease, who would have docetaxel at a later stage if they are well enough. The company claimed that this group is younger and has a better prognosis than people with hormone-sensitive metastatic prostate cancer who can have docetaxel. The company did not present evidence of apalutamide plus ADT's effectiveness in people with low-volume and low-risk disease.

The committee agreed that in NHS practice there are some people who cannot, should not or choose not to have docetaxel. NHS England's commissioning policy on docetaxel helps to identify these people. The committee concluded that it would first consider the clinical and cost effectiveness of apalutamide plus ADT within its full marketing authorisation. However, if it was not cost effective for the full population, then it would consider the people who can have docetaxel, and those who cannot, should not, or choose not to have docetaxel.

Clinical evidence for hormone-relapsed non-metastatic disease

The SPARTAN results are in line with planned analyses

3.6 SPARTAN was a phase 3, randomised, multicentre trial comparing apalutamide plus ADT (n=806) with placebo plus ADT (n=401) for hormone-relapsed non-metastatic prostate cancer. The committee considered that the people in SPARTAN reflected people in UK clinical practice reasonably well. The primary endpoint of SPARTAN was

metastases-free survival, that is, the time from randomisation to confirmed evidence of metastasis or death from any cause. Secondary outcomes included overall survival. Exploratory outcomes included time to progression-free survival on first subsequent treatment (PFS2) and health-related quality of life, measured using the EQ-5D questionnaire and the Functional Assessment of Cancer Therapy Prostate Module (FACT-P). PFS2 measures the time from disease progression to the next disease progression on the treatment that follows the trial treatment. The committee was aware that although PFS2 and EQ-5D were exploratory endpoints, the company used them in its cost-effectiveness modelling. The final analysis for metastases-free survival and interim analyses for overall survival and PFS2 were done in May 2017. At this time, most people's cancer had metastasised and the metastases-free survival endpoint had been met. In May 2017, the trial was unblinded and people who had placebo plus ADT could cross over to have apalutamide plus ADT if their cancer had not metastasised. The final analyses of overall survival and PFS2 were done in February 2020. After progression to metastatic disease, people could have abiraterone or enzalutamide as subsequent treatment, as well as other treatments (see section 3.1). The committee concluded that the results were in line with the trial's planned analyses.

In SPARTAN, apalutamide plus ADT is clinically effective compared with placebo plus ADT

3.7 In SPARTAN:

- median metastases-free survival on apalutamide plus ADT was 40.5 months and on placebo plus ADT it was 15.7 months (hazard ratio [HR] 0.30, 95% confidence interval [CI] 0.24 to 0.36)
- median overall survival on apalutamide plus ADT was 73.9 months and on placebo plus ADT it was 59.9 months (HR 0.78, 95% CI 0.64 to 0.96)

- median PFS2 on apalutamide plus ADT was 55.6 months and on placebo plus ADT it was 41.2 months (HR 0.57, 95% CI 0.47 to 0.68).
- mean change in EQ-5D-3L visual analogue score showed statistically significant improvements in the apalutamide plus ADT arm compared with the placebo plus ADT arm at cycles 21 (mean difference 3.03) and 25 (mean difference 3.28), $p<0.05$.

The committee concluded that apalutamide plus ADT extended metastases-free survival, overall survival, PFS2 and health-related quality of life when compared with placebo plus ADT and was clinically effective.

The company should explore methods to adjust for treatment switching other than the modified RPSFTM

3.8 There were 2 reasons to adjust the overall survival and PFS2 hazard ratios reported in SPARTAN for treatment switching because:

- people randomised to placebo plus ADT crossed over to apalutamide plus ADT
- people randomised to apalutamide went on to have abiraterone or enzalutamide.

The committee discussed both situations. In SPARTAN, 76 people (19.0%) randomised to placebo plus ADT crossed over to apalutamide plus ADT. The company explained that this could potentially underestimate the relative benefit of apalutamide plus ADT for overall survival and PFS2. This was because some people reached these endpoints only after the trial was unblinded (see section 3.6). However, the committee recognised that people could have abiraterone and enzalutamide as subsequent treatments when their disease had metastasised. This would mean that the trial endpoints may not need to be adjusted. The committee also recognised that, in the NHS, people can have only 1 newer androgen receptor inhibitor in the prostate

cancer treatment pathway (see section 3.1). Because more people randomised to apalutamide had a second newer androgen receptor inhibitor, the trial results may have overestimated apalutamide plus ADT's apparent effectiveness on PFS2 and overall survival. The number of people who had a second newer androgen receptor inhibitor is academic-in-confidence and cannot be reported here. The clinical expert explained that having a second newer androgen receptor inhibitor is unlikely to extend life, but might be associated with adverse effects. The committee appreciated that this was another reason to adjust for treatment switching. The company considered several different methods to adjust for treatment switching. These included the rank preserving structural failure time model (RPSFTM), iterative parameter estimation (IPE), inverse probability of censoring weights (IPCW) and 2-stage estimation. The company chose to use a 'modified' version of the RPSFTM (Diels et al. 2019) to adjust simultaneously for the effects of treatment switching. The company explained there were insufficient data to estimate the multiple parameters needed for the RPSFTM and IPE methods. It also stated that the IPCW method provided counterintuitive and clinically implausible results, and that the 2-stage method was not viable because of insufficient data and the need for a 'secondary baseline' before switching. The committee questioned whether it was necessary to adjust the results because of the likely minimal effect of multiple lines of newer treatments (see section 3.13). But it appreciated the company's attempt to explore this issue, and recognised that the modified RPSFTM appeared to be a reasonable first attempt to explore this uncertainty. However, it noted that the method used was less of a 'modified' RPSFTM, and more of a 2-stage method using aspects of all adjustment approaches, and propensity weighting. It also considered that the IPCW and 2-stage methods could have been appropriate, if appropriately specified. Given the concerns around how the company adjusted for treatment switching, the committee considered that using the IPCW or 2-stage

method might have been preferred. Whether or not the measures of effectiveness were adjusted, the committee appreciated that the costs of treatments not offered in the NHS would need removing from the economic analyses. The committee concluded that it would like to see:

- other methods explored in more detail or
- the uncertainties of the modified RPSFTM approach addressed, such as the costs of treatments not offered in the NHS and unadjusted PFS2 in the COU-AA-302 trial (see section 3.9).

Using the COU-AA-302 data to estimate the effect of a second newer androgen receptor inhibitor and adjust for survival causes uncertainty

3.9 Janssen manufactures abiraterone as well as apalutamide, so has access to individual patient data from trials of abiraterone in hormone-relapsed metastatic disease. To generate the modified RPSFTM, the company used data from another trial, COU-AA-302, to estimate and adjust for the survival benefit of a second newer androgen receptor inhibitor in SPARTAN. COU-AA-302 was a randomised trial later in the treatment pathway. It compared abiraterone plus prednisone with placebo plus prednisone in people with hormone-relapsed metastatic prostate cancer who had not had cytotoxic chemotherapy. The ERG explained it could not verify the results of the modified RPSFTM because the company had not provided the requested individual patient data. Although the ERG agreed with using the COU-AA-302 data and the SPARTAN data, it noted that the survival benefit of abiraterone may be underestimated. This was because people having placebo in the trial could cross over to have abiraterone at unblinding. To address the ERG's concern, the company estimated the survival benefits of abiraterone based on the COU-AA-302 trial's interim and final analysis data. Results showed that the final analysis data cut may be affected by crossover. But the effect should be minimal for the interim data cut because only 3 people (0.55% of the 542 originally randomised to the prednisone alone arm) had crossed over at this stage. The ERG considered that using the COU-AA-302 interim or final analysis

data had only a minimal effect on the adjusted hazard ratios for overall survival. It noted that the treatment in COU-AA-302 had a considerably bigger effect on PFS2 than on overall survival. Therefore adjusting for PFS2 crossover in COU-AA-302 would have a more pronounced effect on the adjusted hazard ratios and would likely increase the cost-effectiveness estimates. The committee concluded that using the COU-AA-302 data to estimate the effect of a second newer androgen receptor inhibitor and adjust for survival benefit caused uncertainty.

It may be unnecessary to adjust survival benefit for taking more than 1 newer androgen receptor inhibitor

3.10 The committee noted that COU-AA-302 included only people who had not had a newer androgen receptor inhibitor. So, using these data would 'over adjust' for overall survival of people having a second newer androgen receptor inhibitor in SPARTAN. This was because having a second newer androgen receptor inhibitor is unlikely to be as effective as having a first newer androgen receptor inhibitor. Given that more people in the apalutamide arm of SPARTAN had a second newer androgen receptor inhibitor, adjusting for a second newer androgen receptor inhibitor in this way could bias against apalutamide. The committee agreed that using COU-AA-302 data to estimate and adjust for the survival benefit of a second newer androgen receptor inhibitor caused uncertainty (see section 3.9). It noted that using an appropriately specified IPCW or 2-stage adjustment method applied only to SPARTAN may have avoided the potential bias associated with estimating the effect of a second newer androgen receptor inhibitor based on the COU-AA-302 trial. Also, the committee understood that the newer androgen receptor inhibitors could be used only once in the prostate cancer treatment pathway (see section 3.1). Because they are likely to lack effectiveness if they have already been used, it may be unnecessary to adjust the SPARTAN survival estimates for this type of treatment switching. The committee recalled the possibility of adverse events from multiple lines of newer androgen receptor inhibitors (see section 3.8). It agreed that it could be

reasonable to consider a scenario in which people who had a second newer androgen receptor inhibitor would have had improved survival than if they had followed NHS treatment pathways. The committee concluded that it may be unnecessary to adjust for the survival benefit of a second newer androgen receptor inhibitor. But given the uncertainty, it would have liked to have seen the cost-effectiveness estimates:

- with and without adjustment for the survival benefit of a second newer androgen receptor inhibitor
- with adjustment for the costs of treatment not offered in the NHS (see section 3.8).

How the company adjusts for crossover from placebo plus ADT to apalutamide plus ADT in SPARTAN may bias results

3.11 The committee considered whether the adjusted or the unadjusted hazard ratios were more appropriate for decision making. Adjusting for crossover from the placebo plus ADT arm to the apalutamide plus ADT arm meant that the company assumed that these people had no treatment after placebo plus ADT. But, in clinical practice, people would likely be offered a novel therapy including abiraterone plus ADT or enzalutamide plus ADT as their first subsequent treatment. However, the committee was aware that people can now have darolutamide plus ADT in the NHS. The committee considered that this part of the company's analysis could have biased against placebo plus ADT. It considered that an analysis that did not adjust survival estimates for crossover could be reasonable, if it is assumed that apalutamide has similar effectiveness to abiraterone, darolutamide and enzalutamide. In such a scenario, people who crossed over from the placebo plus ADT arm to the apalutamide plus ADT arm would be assumed instead to have abiraterone, enzalutamide, or darolutamide, and would incur the costs of these. The committee agreed that the company should explore this. The committee concluded that how the company adjusted for crossover from placebo plus ADT to apalutamide plus ADT in SPARTAN may bias results.

Adjusted and unadjusted hazard ratios for overall survival and PFS2 from SPARTAN should be taken into account

3.12 For hormone-relapsed non-metastatic disease, the company explained that the adjusted (0.77, 95% CI 0.64 to 0.94) and unadjusted hazard ratios (0.78, 95% CI 0.64 to 0.96) using the modified RPSFTM for overall survival were similar. The adjusted and unadjusted results for PFS2 were also similar. The committee questioned the face validity of the results, given that adjusting made almost no difference. It considered that this might be because the company had adjusted both arms of SPARTAN. The company explained that it considered the newer androgen receptor inhibitors the bigger driver of the adjustment results because the benefit of multiple lines of these treatments is so small. In their base cases, the company and the ERG used the adjusted hazard ratios for overall survival and PFS2 for treatment switching. The committee concluded that, although the difference was minor, it would take both adjusted and unadjusted hazard ratios for overall survival and PFS2 into account in its decision making. It also concluded that the results of the adjustment analyses may be biased (see sections 3.9 and 3.10).

SPARTAN is generalisable to NHS practice for people with hormone-relapsed non-metastatic disease

3.13 The ERG considered that people in SPARTAN reflected people in UK clinical practice with hormone-relapsed non-metastatic disease. People in SPARTAN could have multiple newer androgen receptor inhibitors, which they cannot have in the NHS (see section 3.6) because they are unlikely to be as effective as having a first newer androgen receptor inhibitor (see section 3.10). Although the impact on clinical effectiveness was likely to be minimal, the committee noted that people might have adverse events (see section 3.8). Also, people might miss out on the clinical benefit of other treatments that they could have had instead of additional lines of subsequent newer androgen receptor inhibitors. So, the committee was not clear on the effect of taking multiple newer androgen receptor

inhibitors on the direction of bias. However, the committee noted that SPARTAN was a large high-quality trial measuring relevant outcomes. It concluded that SPARTAN was generalisable to NHS practice for people with hormone-relapsed non-metastatic disease.

Clinical evidence for hormone-sensitive metastatic disease

The TITAN results are in line with planned analyses

3.14 TITAN was a phase 3, randomised, multicentre trial comparing apalutamide plus ADT (n=525) with placebo plus ADT (n=527) for hormone-sensitive metastatic prostate cancer. The committee considered that people in TITAN reflected people in UK clinical practice reasonably well. TITAN's co-primary endpoints were overall survival and radiographic progression-free survival, that is, the time from randomisation to confirmed evidence of radiographic progressive disease or death from any cause. Secondary outcomes included time to cytotoxic chemotherapy. Exploratory outcomes included progression-free survival on first subsequent treatment (PFS2; see section 3.6) and health-related quality of life. The committee was aware that although these were exploratory endpoints, the company used PFS2 and EQ-5D in its cost effectiveness modelling. Health-related quality of life was measured using the EQ-5D-5 level questionnaire, the FACT-P, the Brief Pain Inventory (BPI) and the Brief Pain Inventory Short Form (BPI-SF). The final analysis for radiographic progression-free survival and interim analyses for overall survival and PFS2 were done in November 2018. At this time, most people's cancer had progressed, and the radiographic progression-free survival endpoint had been met. In November 2018, the trial was unblinded and people who had placebo could cross over to have apalutamide if their cancer had not progressed. The final analyses of overall survival and PFS2 were done in September 2020. After disease progression, people could have abiraterone and enzalutamide as subsequent treatment options. The committee concluded that the results were in line with the trial's planned analyses.

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In TITAN, apalutamide plus ADT is clinically effective compared with placebo plus ADT

3.15 In TITAN:

- median radiographic progression-free survival on apalutamide plus ADT was not reached and on placebo plus ADT it was 22.1 months (HR 0.5, 95% CI 0.4 to 0.6)
- median overall survival on apalutamide plus ADT and on placebo plus ADT is academic-in-confidence and cannot be reported here
- median PFS2 on apalutamide plus ADT and on placebo plus ADT is academic in confidence and cannot be reported here.
- mean change in EQ-5D-5L visual analogue score showed no statistically significant differences between the apalutamide plus ADT and placebo plus ADT treatment arms for all treatment cycles. For example, mean change at cycle 21 on apalutamide plus ADT was 2.50 and on placebo plus ADT it was 2.04, with a difference of -0.46 (p=0.7678).

The company used the hazard ratio for the whole population (that is, people with hormone-sensitive metastatic prostate cancer) to show the effectiveness of apalutamide plus ADT for people who are not well enough to have docetaxel or who cannot tolerate it, or who choose not to have it. The committee understood that no evidence was available for this subgroup, and it considered whether any other subgroups could be used as a proxy. For example, the patient expert had explained that this subgroup is often older. The company confirmed that it did have a hazard ratio for a subgroup of older people for the endpoint of time to progression or death. But it explained that it did not use this because there were no statistically significant differences in the age interaction. The committee agreed that there would be a number of uncertainties in using age as a proxy, including confounding factors plus the usual problems of subgroup analysis with such small sample sizes. The

committee also appreciated that there were younger people who cannot or should not have docetaxel. It concluded that apalutamide plus ADT extended radiographic progression-free survival, overall survival and PFS2 when compared with placebo plus ADT and was clinically effective. However, there was no evidence available for a subgroup who cannot have docetaxel (see section 3.40).

Adjusted and unadjusted hazard ratios for overall survival and PFS2 from TITAN should be taken into account

3.16 The company adjusted for treatment switching in TITAN (as in SPARTAN, see section 3.8). In TITAN, a higher percentage of people randomised to placebo plus ADT than in SPARTAN crossed over to apalutamide plus ADT. The percentage is academic-in-confidence and cannot be reported here. The company explained that most crossover occurred between the interim and final data cuts (see section 3.14). The committee noted that the percentage was high. This meant that adjusting for crossover would likely influence the size of the reported relative efficacy effect between apalutamide plus ADT and placebo plus ADT. In its base case the company selected the unadjusted hazard ratios for overall survival and PFS2, which it considered the most conservative approach. The ERG considered it was more appropriate to adjust the hazard ratios for overall survival and PFS2. The committee was aware that, in clinical practice, people who had not had placebo plus ADT would not be offered abiraterone or enzalutamide, and agreed that both adjusted and unadjusted analyses should be considered (see section 3.11). The committee concluded that it would take both adjusted and unadjusted hazard ratios for overall survival and PFS2 into account in its decision making.

Other methods to adjust for treatment switching should be explored and uncertainties with the modified RPSFTM addressed

3.17 For people with hormone-sensitive metastatic disease, the company used the modified RPSFTM to adjust for treatment switching (as with

SPARTAN, see section 3.8). Treatment switching included crossing over to apalutamide and taking treatments that might alter life expectancy after progressing on either apalutamide plus ADT or ADT alone, which do not reflect NHS practice. The committee considered that the uncertainties were the same as with SPARTAN (see sections 3.8 and 3.9). It concluded that it would like to see other methods explored in more detail or the uncertainties of the modified RPSFTM approach addressed. For example, the costs of treatment not offered in the NHS and the unadjusted PFS2 results in COU-AA-302 (see section 3.9).

The company's indirect treatment comparison shows apalutamide plus ADT offers an advantage over docetaxel plus ADT for efficacy and is well tolerated

3.18 TITAN did not compare apalutamide plus ADT with docetaxel plus ADT. So the company did an indirect treatment comparison of apalutamide plus ADT with docetaxel plus ADT, for outcomes including overall survival, radiographic progression-free survival, PFS2, and safety. The network meta-analysis included TITAN and 3 randomised controlled trials linking docetaxel plus ADT to apalutamide plus ADT through the common comparator of placebo plus ADT (CHAARTED, GETUG-AFU15, STAMPEDE). The ERG was broadly satisfied with the company's approach. The results showed that apalutamide plus ADT offers a survival advantage over placebo plus ADT and over docetaxel plus ADT. The committee noted that although the hazard ratio was below 1, which indicates a benefit, the confidence interval included the possibility of no benefit. The results are academic-in-confidence and cannot be presented here. The committee concluded that the company's indirect treatment comparison showed apalutamide plus ADT offered an advantage over docetaxel plus ADT for efficacy and is well tolerated.

TITAN is generalisable to NHS clinical practice for people with metatastatic hormone-sensitive disease

3.19 In TITAN, people could have additional lines of subsequent newer androgen receptor inhibitors. This affected the treatment effect and caused uncertainty as to what people could have had instead, in the same way as in SPARTAN (see sections 3.13 and 3.13). So, the committee was unclear on the effect of taking multiple newer androgen receptor inhibitors on the direction of bias. However, the committee noted that TITAN was a large high-quality trial measuring relevant outcomes. It concluded that TITAN was generalisable to NHS clinical practice.

Adverse effects

Adverse effects with apalutamide are tolerable

3.20 The clinical experts explained that apalutamide plus ADT is well tolerated. Rash and hypothyroidism have been reported and are manageable. Treating hypothyroidism also treats fatigue, a symptom which otherwise might not be identified and treated. The committee concluded that adverse effects with apalutamide are tolerable.

Economic model

The model structure is appropriate for decision making

3.21 The company used the same model structure for hormone-relapsed non-metastatic prostate cancer and for hormone-sensitive metastatic prostate cancer. To estimate the cost effectiveness of apalutamide plus ADT compared with placebo plus ADT, the company used a partitioned survival model with health states for progression-free survival, progressed disease and death. After disease progression, people can go on to have up to 3 lines of subsequent therapy and have declining health-related quality of life. The company used PFS2 to inform the probability of moving between the first and second treatments for metastatic disease. It used mean health state durations to assign people to the remaining health states.

Within the progression-free survival health state, people could be on or off treatment as determined by trial data on time-to-treatment discontinuation. Efficacy data were informed by SPARTAN (metastases-free survival and overall survival) and TITAN (radiographic progression-free survival and overall survival). The committee concluded that the model structure was appropriate for decision making.

Modelling the SPARTAN and TITAN data

In SPARTAN, extrapolating metastases-free survival using a Weibull model is uncertain; a more flexible model is needed

3.22 Since the decision problem had a lifetime time horizon (32 years), the company sought data to estimate what would have happened had the SPARTAN trial lasted longer. The company did not identify any other studies that provided longer-term data for metastases-free survival to inform the extrapolations beyond the duration of SPARTAN. It therefore explored a range of curves to extrapolate metastases-free survival trial data from SPARTAN, including generalised gamma and Weibull. Most curves modelling metastases-free survival provided a good fit to the observed data, but the committee recognised that the observed data were limited. The company asked for clinical feedback, which suggested that the Weibull model was the most plausible for both apalutamide plus ADT and placebo plus ADT, although it could underestimate metastases-free survival at 10 years for apalutamide plus ADT. The clinical expert estimated that only 1% to 2% of people having placebo plus ADT would be metastases-free at 5 to 10 years. Therefore the Weibull model was a good fit to the observed data. In its base case, the company used the Weibull model to extrapolate metastases-free survival, and fitted the curves independently. The ERG also chose the Weibull to model metastases-free survival. However, clinical expert advice to the ERG suggested that none of the models adequately captured metastases-free survival. This was because most underestimated the proportion who remain metastases free on placebo plus ADT at 5 and 10 years. The

exception was the generalised gamma model, which had a clinically implausible long tail to the curve, and which may overestimate the proportion who remain metastases free on apalutamide plus ADT. The ERG explained that the model used had a large impact on the cost-effectiveness results. It suggested that more flexible models may be more appropriate. The committee was aware that metastases-free survival was not adjusted for treatment switching because this endpoint was reached before people could cross over between arms (see section 3.6). The committee concluded that, because of the uncertainty associated with the Weibull model, it would have liked to see a more flexible model fitted to extrapolate metastases-free survival beyond the trial duration.

In SPARTAN, extrapolating overall survival using a generalised gamma model is appropriate, but the treatment effect beyond the trial is uncertain

3.23 The company used a systematic review by Aly et al. (2018) to identify external clinical trial data that could inform survival projections for SPARTAN. It found 3 clinical trials with a similar population to SPARTAN. It referred to this as 'historical' data. But, it did not use this data to extrapolate overall survival because SPARTAN had longer follow up than the historical data studies. The company assessed if the proportional hazards assumption held for overall survival. The log-cumulative hazard plot for overall survival in both arms of SPARTAN showed that the curves were relatively parallel over time. The company stated that based on a statistical test (the Schoenfeld test), the proportional hazards assumption seemed to hold, because the resulting p-value was not significant (p=0.7321). Therefore, in its original base case, the company considered it appropriate to apply jointly fitted models. That is, rather than fitting survival models to each treatment independently, the company fitted 1 survival model to all data, and then generated treatment-specific survival curves by using the treatment group as a covariate. The company chose a Weibull distribution for extrapolating overall survival because of

its clinical plausibility. However, the ERG could not verify that proportional hazards would hold in the extrapolated part of the survival curves because of lack of evidence. It noted that the survival estimates from SPARTAN, on which the proportional hazards assumption was tested, were immature. Therefore, it considered that using models fitted to the treatment arms separately (independently) would be more appropriate. During technical engagement before the committee meeting, expert advice to the ERG was that both Weibull curves were likely to underestimate overall survival at 10 years, and possibly at 15 years. The ERG further noted that generalised gamma models have a good visual fit to the observed data, and better statistical fits (lower Akaike information criterion [AIC]/Bayesian information criterion [BIC] scores) compared with the Weibull models. After technical engagement, the company followed the expert's advice and, in their base cases, both the company and the ERG used the jointly fitted generalised gamma models. The committee was aware that the company had adjusted overall survival for treatment switching because of people who died; many did so after unblinding and the final analysis of SPARTAN (see section 3.6). The committee concluded that extrapolating overall survival using the generalised gamma model seemed appropriate, but the treatment effect beyond the observed trial period was uncertain.

In SPARTAN, extrapolating PFS2 using a Weibull model is appropriate, but estimates are based on immature data

3.24 The company, having assessed that the proportional hazards assumption held for PFS2, applied the Weibull models fitted jointly to both arms in its base case. This was based on the statistical fits (AIC/BIC scores) and clinical plausibility. The ERG also jointly fitted Weibull models in its base case, although it noted that the estimates were likely uncertain because data for PFS2 for apalutamide plus ADT in SPARTAN was relatively immature. The committee concluded that the company and ERG's approach to modelling PFS2 was broadly appropriate, but agreed that it was based on immature data.

In TITAN, extrapolating radiographic progression-free survival using a Weibull model is uncertain; a more flexible model is needed

3.25 The company assessed whether the proportional hazards assumption held for radiographic progression-free survival. Based on the log-cumulative hazard plot for radiographic progression-free survival, and a statistical test (the Schoenfeld test), it considered that the proportional hazards assumption may be violated. The company therefore decided to fit parametric curves to both arms independently. Based on clinical advice, it chose Weibull curves for its base case. The ERG also chose Weibull curves for its base case for both treatments. But it noted that radiographic progression-free survival data for apalutamide plus ADT was highly immature, which is a large driver of the cost-effectiveness results. The ERG also noted that the Weibull models have worse statistical fit (that is, higher AIC and BIC scores) than other models. The committee appreciated these measures reflected the model fit, but only to the observed data. Also, expert advice to the ERG suggested that the Weibull models are likely to underestimate the proportion of people who progressed in the ADT arm at 5, 10 and possibly 15 years. Therefore, the ERG suggested that more flexible models may be more appropriate. The committee concluded that, because of the uncertainty with the Weibull model, it would have liked to have seen a more flexible model fitted to extrapolate radiographic progression-free survival beyond the duration of TITAN.

The TITAN post-progression survival results lack face validity; a more flexible model for extrapolating overall survival is needed

3.26 The company collected historical data for ADT because overall survival estimates from TITAN were immature. The upper boundary of the confidence interval for median overall survival was not estimable because not enough events had occurred. The company did a systematic literature review and found 7 published trials with ADT arms which had longer follow up than TITAN. It pooled survival data for the ADT arms of these

studies and follow-up duration reached about 9 years. The ERG considered this a good attempt to collect longer follow-up data although it noted that only studies published after 2013 were included. The ERG could not verify the company's work because the company did not share its systematic review. The company assumed a common shape between the ADT arm, reflecting pooled data, and the placebo plus ADT arm in TITAN. Based on expert opinion, it chose the Weibull curves in its base case because these provided the most clinically plausible extrapolations. Expert advice to the ERG was that survival at 5, 10 and possibly 15 years in both treatment arms was higher in practice than estimated by the Weibull models. Despite this, the ERG chose the Weibull model for its base case because it gave the most conservative estimates. It suggested that more flexible models may be more appropriate. The committee was aware that people have a treatment until disease progression. It noted that the company's model showed that people with hormone-sensitive metastatic disease had longer post-disease progression survival if they had apalutamide plus ADT than either docetaxel or ADT plus placebo. Yet the committee was aware that people had fewer post-progression treatment options when they started apalutamide. The post-progression estimates are academic-in-confidence and cannot be reported here. The committee considered that this lacked face validity and biological plausibility. It concluded that, because of the uncertainty with the Weibull model, it would have liked to have seen a more flexible model fitted to extrapolate overall survival beyond the trial duration. The committee further concluded that it would like to see evidence justifying the difference in post-progression survival between treatment arms as well as scenarios exploring equal post-progression survival between apalutamide plus ADT and its comparators.

In TITAN, extrapolating PFS2 is uncertain because it is based on immature data

3.27 The company, having assessed that the proportional hazards assumption held for PFS2, applied a Weibull model fitted jointly to both arms in its

base case. This was based on clinical plausibility and consistency (which helps to avoid the issue of curves crossing) with the curves for radiographic progression-free survival (see section 3.25) and overall survival (see section 3.26). The ERG noted that both the Weibull and Gompertz models have the best statistical fits to the observed data. However, the Weibull model is likely to overestimate PFS2 at 10 and 15 years for the apalutamide plus ADT arm. Also, people seem to spend almost no time on the third-line treatment for metastatic disease. Therefore, the ERG considered that the Gompertz model was the only clinically relevant alternative although it is also likely to overestimate long-term survival in the apalutamide plus ADT arm. The ERG noted that, because the PFS2 estimates were immature in TITAN, extrapolating PFS2 assuming proportional hazards was likely to be highly uncertain. For radiographic progression-free survival and overall survival, the ERG suggested that more flexible approaches would be appropriate. The committee concluded that the true estimates of PFS2 after the end of the trial were uncertain because these were based on immature data.

Treatment effect waning has little effect on the cost-effectiveness results

3.28 The company considered that the relative benefits of apalutamide did not wane over time so did not apply any treatment effect waning in its base cases. It justified this, noting there was no evidence in SPARTAN or TITAN that the overall survival curves for both treatments converge over time. The ERG explored treatment effect waning but was unclear from the hazard plots if treatment benefit declined. Because no waning effect had been seen in clinical trials for another prostate cancer drug (abiraterone) with a longer follow up, the experts to the ERG did not expect to see treatment effect waning with apalutamide. However, a study in advanced prostate cancer (Antonarakis et al. 2016) suggested that resistance to newer androgen receptor inhibitors, such as enzalutamide and abiraterone, was likely to develop with time. The ERG noted that it was unclear if the study results were generalisable to hormone-relapsed non-metastatic disease. The ERG also noted that resistance to abiraterone or

enzalutamide does not necessarily imply that there would be a treatment waning effect. It considered that there was insufficient evidence to assess the best approach for duration of treatment benefits. The Cancer Drugs Fund clinical lead noted that, in clinical practice, most newer drugs for prostate cancer seem to lose at least some of their effectiveness over time. The committee was aware that both the company and the ERG had explored treatment waning in their original scenarios (that is, before technical engagement). The effect on the incremental cost-effectiveness ratio (ICER) was an increase of around £2,000 per quality-adjusted life year (QALY) gained when varying treatment effect waning from 100% to 0% for a duration of 5 years and 10 years. The committee concluded that treatment effect waning seemed to have a small impact on the cost-effectiveness results.

Treatment costs

The cost of apalutamide may be underestimated in the model

3.29 The committee was aware that apalutamide was being offered at a discount. It was also aware that duration of treatment determines cost. People would have apalutamide plus ADT until disease progression, or until they can no longer tolerate them or choose to stop taking them. The company explained that time-to-treatment discontinuation reflected the SPARTAN data cut of February 2020. Instead it chose to model time on treatment using metastases-free survival, calculated at an earlier data cut in May 2017. The company explained this was because several of the extrapolations for time-to-treatment discontinuation crossed the metastases-free survival curves towards the end of SPARTAN. The company and committee did not consider this would reflect practice because it contradicted apalutamide's summary of product characteristics, which states that people would stop treatment after progressing. Similarly, for TITAN the company said that it took time-to-treatment discontinuation and radiographic progression-free survival from TITAN data cuts that occurred at different times. The company explained that the costs used in

the model were informed by the minimum of either time-to-treatment discontinuation until progression, or metastasesfree survival curves. The company therefore capped the costs, which it noted might have slightly underestimated the cost of apalutamide in the model. The committee concluded that cost of apalutamide might have been underestimated in the model, and it would take this into account in its decision making.

Utility values

The ERG's utility values, unadjusted for line of treatment and difference in population, are appropriate

3.30 The company assumed that health-related quality of life declines over time as people in the model develop metastatic disease and move onto subsequent lines of therapy (see section 3.21). The utility value used for taking the first treatment for hormone-relapsed metastatic prostate cancer was from SPARTAN using the EQ-5D-3L. The utility values are considered confidential by the company so cannot be reported here. For second and third treatments for hormone-relapsed metastatic prostate cancer, the company used external data from NICE's technology appraisal guidance on abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). This was because a limited number of people completed the EQ-5D-3L questionnaire after developing metastases in SPARTAN. The company derived the utility values for second and third treatments from the first treatment by applying a 'relative decline ratio'. This was estimated by dividing the TA387 utility value for second-line treatment of hormone-relapsed metastatic disease by the TA387 utility value for first-line treatment of hormone-relapsed metastatic disease. This value was then multiplied by the utility value for the first hormone-relapsed metastatic disease treatment in the company's trials. This process was repeated to estimate the utility value for the third treatment for hormone-relapsed metastatic disease. The company adjusted the derived utility values to account for population differences between SPARTAN and TA387. This

was in line with the method described in the NICE Decision Support Unit's technical support document 12 on the use of health state utility values in decision models. The ERG had concerns with the company's adjusted utility values:

- They were much lower than those used in NICE's technology appraisal guidance on enzalutamide for treating metastatic hormone-refractory prostate cancer before chemotherapy is indicated (TA377) and enzalutamide for hormone-relapsed non-metastatic prostate cancer (TA580). The utility values were 0.658 and 0.612 in TA377 and 0.8 and 0.688 in TA580, for health states reflecting second- and third-line treatments of hormone-relapsed metastatic prostate cancer.
- It was unclear which line of treatment generated the utility values reported in TA387.
- By applying a 'relative decline ratio', the company assumed that the utility values would decrease by the same relative proportion between first-line and second-line treatments of hormone-relapsed metastatic prostate cancer (as in TA387). But, the committee considered that this assumption may not be appropriate given the different starting populations in this appraisal (hormone-relapsed non-metastatic disease or hormone-sensitive metastatic disease) and in TA387 (hormone-relapsed metastatic disease before chemotherapy is indicated).

In its base case, the ERG used the utility values from TA377 without adjusting them. The company used the same approach to derive utility values for second-line and third-line treatments of hormone-relapsed metastatic prostate cancer. The utility values are considered confidential by the company so cannot be reported here. The patient experts reiterated the effect of psychological distress (see section 3.3) and worry about a treatment's loss of efficacy. The clinical expert was aware that EQ-5D, measured in SPARTAN, included questions on anxiety and depression and agreed with the company's utility values. The committee agreed that this disease was associated with a

significant impact on quality of life. However, it was concerned with the lack of consistency with the utility values used in related technology appraisals. Also, the Cancer Drugs Fund clinical lead explained that the ERG's unadjusted utility values better fitted what had been seen in other disease areas with multiple lines of treatment. The committee therefore agreed that, on balance, the ERG's utility values had a higher face validity than the company's adjusted utility values. It concluded that the ERG's unadjusted utility values were most appropriate for decision making.

Modelling the adverse effects of docetaxel

The company and ERG's cost estimates are satisfactory

3.31 In the original model, the company assumed that the adverse effects of docetaxel occurred throughout the entire hormone-sensitive metastatic prostate cancer pre-progression health state. At technical engagement before the committee meeting, the ERG explained that this overestimated the costs of managing adverse effects, and it was more appropriate to apply those costs for the first 6 months. The company agreed that this overestimated the costs but suggested that after 6 months of treatment there would be additional costs associated with the adverse effects of ongoing ADT. Therefore, in its base case, the company applied the costs of managing adverse effects for docetaxel for 6 months and the costs of managing adverse effects for ADT alone thereafter. The ERG's base case reflected the company's assumption. The clinical experts explained that the adverse effects associated with docetaxel were likely to last for 6 to 12 months. The committee concluded that the company and ERG's cost estimates were satisfactory.

The committee is satisfied with the ERG's incidence rates for neutropenia and febrile neutropenia

3.32 The company's model included grade 3 to 4 neutropenia and febrile neutropenia, which are adverse effects associated with docetaxel. The

rates of these in the hormone-sensitive metastatic pre-progression phase were based on a real-world study on the use of docetaxel in the NHS (Patrikidou et al. 2017). These were 36.3% for neutropenia and 18.2% for febrile neutropenia per course of 6 cycles of docetaxel. The company suggested that these rates may be low compared with observational data. The ERG noted that the company's sources of observational data had methodological limitations including no information on patient numbers. In its base case the ERG used pooled data from 3 docetaxel trials (GETUG-AFU15, STAMPEDE and CHAARTED). It estimated combined rates of 10.6% for febrile neutropenia and 15.4% for neutropenia, at a constant rate over 6 months. STAMPEDE included only people from the UK and Switzerland, and therefore was more likely to represent NHS clinical practice. The committee concluded that it was satisfied with the ERG's pooled incidence rates for neutropenia and febrile neutropenia.

End of life

The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company did not make a case for end of life in its submission. The committee noted that the life expectancy of people who had ADT alone would normally be longer than 24 months.

The end of life criteria are not met for apalutamide in hormone-relapsed non-metastatic prostate cancer

3.33 In SPARTAN the median overall survival was 59.9 months (for placebo plus ADT) and the median improvement in life expectancy was 14 months. The committee concluded that the end of life criteria were not met for apalutamide in hormone-relapsed non-metastatic prostate cancer.

The end of life criteria are not met for apalutamide in hormone-sensitive metastatic prostate cancer

3.34 In TITAN the median overall survival for placebo plus ADT was not reached; the mean overall survival estimated in the company's base case

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was 4.6 years. The committee noted that the mean improvement in life expectancy was 6 months (compared with docetaxel plus ADT) and 17 months (compared with placebo plus ADT) in TITAN. It concluded that the end of life criteria were not met for apalutamide in hormone-resistant non-metastatic prostate cancer.

Cost-effectiveness estimates for apalutamide for hormone-relapsed non-metastatic disease

An acceptable ICER would be in the middle of the range normally considered cost effective

3.35 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee was aware that the unmet need had lessened because NICE has recommended darolutamide. The data are immature for overall survival and PFS2 and the appropriate extrapolation model for metastases-free survival was uncertain. So the committee agreed that an acceptable ICER would be in the middle of the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

Apalutamide is not cost effective for hormone-relapsed non-metastatic disease

3.36 Because of confidential commercial arrangements for apalutamide and other treatments in the pathway, the cost-effectiveness estimates cannot be reported here. The committee noted that the ERG's analyses better reflected the committee's preferred assumptions. These included:

- adjusting for treatment switching for overall survival and PFS2 (see section 3.11)
- using unadjusted utility values for second-line and third-line hormone-relapsed metastatic prostate cancer (see section 3.30).

- To offset uncertainty, the company increased its discount for apalutamide. Because the discount is confidential, the new ICERs were discussed at a private second committee meeting. The committee reviewed the deterministic ICERs and noted that these did not include its preferred assumptions, and it was not presented with the probabilistic ICERs or with analyses that reflected the uncertainty. It considered that the ICER that most closely reflected its preferred assumptions is higher than what would be considered a cost-effective use of NHS resources. Also, if its preferred assumptions were included, it would likely increase the ICER. Therefore, apalutamide could not be recommended as a cost-effective use of NHS resources for treating hormone-relapsed non-metastatic prostate cancer.

For hormone-relapsed non-metastatic disease the uncertainties should be explored

3.37 The ERG's base case best reflected the committee's preferred assumptions, but several uncertainties should be explored, including:

- other adjustment methods and analyses for treatment switching, such as IPCW or 2-stage methods, or addressing the uncertainties of the modified RPSFTM approach (see section 3.8)
- cost-effectiveness estimates with and without adjustment for survival benefit of a second newer androgen receptor inhibitor, with the removal of the costs of treatments not offered in the NHS (see sections 3.8 and 3.10), but accounting for the fact that people who crossed over from placebo plus ADT to apalutamide plus ADT may have instead had abiraterone, enzalutamide, or darolutamide
- justification of the difference in post-progression survival between treatments and scenarios including equal post-progression survival between apalutamide plus ADT and its comparators (see section 3.26)

- a more flexible method to extrapolate metastases-free survival (see section 3.22).

Cost-effectiveness estimates for apalutamide for hormone-sensitive metastatic disease

An acceptable ICER would be below the middle of the range normally considered cost effective

3.38 The data are immature for overall survival and PFS2 and there was uncertainty about the appropriate extrapolation model for radiographic progression-free survival, overall survival and PFS2. So the committee agreed that an acceptable ICER would be below the middle of the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

Apalutamide is not cost effective for hormone-sensitive metastatic disease

3.39 Because of confidential commercial arrangements for apalutamide and subsequent treatments, the cost-effectiveness estimates cannot be reported here. The committee was satisfied with some of the ERG's preferred assumptions. These included:

- adjusting for treatment switching for overall survival and PFS2 (see section 3.16)
- using unadjusted utility values for second-line and third-line metastatic disease (see section 3.30)
- using pooled incidence rates for neutropenia (15.4%) and febrile neutropenia (10.6%; see section 3.32)
- incremental cost-effectiveness analyses including docetaxel plus ADT, apalutamide plus ADT, and ADT alone.

To offset uncertainty, the company increased its confidential discount for apalutamide after the committee's first meeting. Because the

discount is confidential, the new estimates of cost effectiveness were discussed at a private second committee meeting. Based on incremental deterministic ICERs, the committee agreed that the cost-effectiveness estimates for docetaxel plus ADT were below the range normally considered a cost-effective use of NHS resources, whereas the cost-effectiveness estimates for apalutamide plus ADT were above £30,000 per QALY gained. Therefore apalutamide could not be recommended as a cost-effective use of NHS resources for treating hormone-sensitive metastatic prostate cancer.

Apalutamide is not cost effective for hormone-sensitive metastatic disease in a subgroup of people who cannot have docetaxel

3.40 The committee went on to consider the population who cannot or should not have docetaxel. It recalled that TITAN excluded people with poor performance scores, but did include older people. The committee was aware of data from consultees and from NHS England documenting the association between older age and decreasing use of docetaxel for hormone-sensitive disease. It was also aware of subgroup analyses from TITAN which showed a hazard ratio for progression or death of 0.65 for people over 75 years compared with hazard ratios of 0.57 and 0.74 for younger age groups. The company tested all subgroups for interaction and found none. The committee recognised that data might not be available for all of the inputs to this model, but that a modelled scenario for this group should be presented nonetheless. The committee considered that it should include:

- a population with a baseline survival curve reflecting an older more unwell population
- a measure of effect that recognises uncertainty, including the possibility that apalutamide is less effective for this population than for the population in TITAN
- utility values reflecting an older more unwell population and

- a model in which people do not go on to get docetaxel or cabazitaxel when their disease becomes hormone relapsed.

In its response discussed at the private committee meeting, the company attempted to model a group who cannot or should not have docetaxel, by:

- using a poorer baseline prognosis by proportionally reducing progression-free survival, PFS2 and overall survival (to explore worsening of baseline survival)
- using the ERG's preferred assumptions for treatment effectiveness (to explore reducing apalutamide's treatment effect)
- reducing utility values for all lines of treatment by 10% (to explore utility values reflecting the older more unwell population)
  removing subsequent chemotherapy (to explore a model in which people do not go on to get docetaxel or cabazitaxel when their disease becomes hormone relapsed).

The committee appreciated the company's attempt to explore this issue. But it remained concerned that the effectiveness of apalutamide for the older and more unwell population was the same as for the younger and less unwell population. The committee considered that because it had not been presented with any evidence, it was unsure whether apalutamide was equally effective in both populations. Also, it considered that it would be unlikely to make age-based recommendations. The committee wished to see analyses that took into account this uncertainty. It agreed that the probabilistic ICERs were more likely than the deterministic ICERs to capture the uncertainty associated with these analyses, and were likely to be higher. However, the company had not presented these. Also, the company had not fully implemented the committee's preferred assumptions outlined in section 3.38, which was a further source of uncertainty. The company did not present evidence or analyses for people with low-volume and

low-risk disease, who the company noted were less likely to have docetaxel plus ADT (see section 3.5). The committee considered that the ICER that most closely reflected its preferred assumptions is above what it would consider a cost-effective use of NHS resources. Also, if its preferred assumptions were included and the uncertainties outlined above taken into account, it would likely increase the ICER. Taking all this into account, apalutamide could not be recommended as a cost-effective use of NHS resources for treating hormone-sensitive metastatic prostate cancer in a subgroup of people who cannot have docetaxel.

For hormone-sensitive metastatic disease the uncertainties should be explored

3.41 The ERG's base case best reflected the committee's preferred assumptions, but several uncertainties should be explored including:

- other adjustment methods and analysis for treatment switching, such as IPCW or 2-stage methods, or addressing the uncertainties of the modified RPSFTM approach (see sections 3.8 and 3.17)
- cost-effectiveness estimates with and without adjustment for survival benefit of a second newer androgen receptor inhibitor, with the removal of the costs of treatments not offered in the NHS (see sections 3.8, 3.10 and 3.17), but accounting for the fact that people who crossed over from placebo plus ADT to apalutamide plus ADT may have instead had abiraterone, enzalutamide, or darolutamide
- justification of the difference in post-progression survival between treatments and scenarios including equal post-progression survival between apalutamide plus ADT and its comparators (see section 3.26)
- more flexible methods for extrapolating radiographic progression-free survival, overall survival and PFS2 (see sections 3.25 to 3.27).

Innovation

Apalutamide is not innovative for hormone-relapsed non-metastatic prostate cancer

3.42 Darolutamide, a new androgen receptor inhibitor that was not available when this appraisal started is now an option with ADT for treating hormone-relapsed non-metastatic prostate cancer in the NHS. The recommended dose of darolutamide is twice daily, and the recommended dose of apalutamide is once daily (as 4 tablets). The committee considered this an advantage, but concluded that this was not sufficient to consider apalutamide plus ADT a step-change in treatment and therefore innovative.

Apalutamide may be innovative for hormone-sensitive metastatic prostate cancer

3.43 The company considered apalutamide plus ADT to be innovative because it is an oral treatment, and requires less monitoring than docetaxel plus ADT. The committee agreed that apalutamide plus ADT would fulfil an unmet need, particularly for people who cannot or should not take docetaxel. The committee was aware that there are other androgen receptor inhibitors with marketing authorisations for this indication, notably enzalutamide and abiraterone, but none are currently recommended by NICE. It concluded that there was a possible case for innovation but it would depend on the outcome of ongoing apraisals.

Equality issues

The recommendations apply to all people with prostate cancer

3.44 The committee noted that, as in previous NICE technology appraisals of prostate cancer treatments, its recommendations should apply to all people with prostate cancer. It further noted that a person can have a prostate but not identify as a man. Gender reassignment is a protected characteristic under the Equality Act 2010. The committee also noted that,

in clinical practice, older people are less likely to have docetaxel than younger people. It was aware that although docetaxel is more likely to be contraindicated or unsuitable for older people, age alone will not determine whether a person could or should have docetaxel in clinical practice. The committee was also 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. The committee concluded that, by considering the cost effectiveness for people who could not or should not have docetaxel (see sections 3.15 and 3.40), it took into account older people in its recommendations.

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. NICE welcomes comment on this proposed date. 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
May 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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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), a technical adviser and a project manager.

Aminata Thiam
Technical lead

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Technical adviser

Shonagh D'Sylva
Project manager

ISBN: [to be added at publication]

Issue date: May 2021