# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# GUIDANCE EXECUTIVE (GE)

## Technology Appraisal Review Proposal paper

## Review of TA377; Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy, TA387; Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated and TA391; Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (review of TA255)

| | |
|---|---|
| **Original publication date:** | Various |
| **Review date** | January 2019 |
| **Existing recommendations:** | Enzalutamide and abiraterone are recommended, and cabazitaxel has an optimized recommendation<br>To see the complete existing recommendations and the original remit for TA377,TA387 and TA391 see Appendix A. |

### 1. Proposal

The guidance should be transferred to the 'static guidance list'.

### 2. Rationale

There is no current data to suggest the recommendations should change.

### 3. Summary of new evidence and implications for review

There are no new data to suggest that enzalutamide, abiraterone or cabazitaxel would be less clinically effective or cost effective than estimated at the time the 3 pieces of guidance were issued.

The treatment pathway for prostate cancer has changed. At the time of technology appraisals 377 and 387 the relevant comparators for decision making were best supportive care and in both appraisals the plausible cost effectiveness ratios compared with best supportive care were in a similar range. Since the publication of technology appraisals 377 and 387 enzalutamide and abiraterone have become established treatment options before docetaxel in NHS clinical practice. Although these technologies have a different mechanism of action there are no robust evidence from head to head trials to suggest that the clinical effectiveness would

differ sufficiently, or one would be more cost effective than the other to warrant a multiple technology appraisal being carried out.

The recommendations for cabazitaxel were optimised to reflect the population and treatment duration with cabazitaxel which the company provided evidence for in its submission. There have been no further trials of cabazitaxel taken for a longer maximum duration or in a wider population so this optimised recommendation does not need to be reviewed.

| **Has there been any change to the price of the technology(ies) since the guidance was published?** |
| --- |
| Enzalutamide has a patient access scheme. Abiraterone has a commercial access agreement. Cabazitaxel has a patient access scheme and a commercial access agreement. The Single Technology Appraisal for abiraterone for treating newly diagnosed metastatic hormone-naive prostate cancer (ID945) has been suspended while NICE are awaiting confirmation from the company of the price of abiraterone to the NHS for this indication. Once this price is confirmed the appraisal will re-start. This is not anticipated to decrease the likelihood of abiraterone being cost effective for the indication in TA387. |
| **Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?** |
| The EMA has extended the marketing authorisation for enzalutamide for the treatment of high- risk non-metastatic castration-resistant (hormone relapsed) prostate cancer. This indication is the subject of the ongoing NICE technology appraisal ID1359<br><br>The marketing authorisation for abiraterone has been extended to include its use in combination with androgen deprivation therapy for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer. This is the subject of the (currently suspended) NICE technology appraisal ID945.<br><br>These marketing authorisation extensions are unlikely to affect the existing guidance, but may affect the number of people who receive abiraterone or enzalutamide before chemotherapy because NHS England only commissions abiraterone or enzalutamide once in the treatment pathway (see 'Additional comments'). |
| **Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?** |
| Enzalutamide TA377<br><br>• Abiraterone was not a relevant comparator for decision making at the time of the appraisal because it was only available through the Cancer Drugs Fund and not embedded in the NHS. It would be a comparator now. There have been no head-to-head trials of enzalutamide compared with abiraterone.<br>• The average survival benefit on enzalutamide was estimated by extrapolating trial data, this estimate took into account the subsequent |

treatments people may have in the NHS, which differed from those in the trial. There are no data, such as real world data, to suggest the survival benefit estimated in the model were inappropriate.

Abiraterone TA387

- Enzalutamide was not a comparator at the time of the appraisal because it had not been licensed for this indication at that time. It would be a comparator now. There have been no head-to-head trials of enzalutamide compared with abiraterone.
- The average survival benefit on enzalutamide was estimated by extrapolating trial data, this estimate took into account the subsequent treatments people may have in the NHS, which differed from those in the trial. There are no data, such as real world data, to suggest the survival benefit estimated in the model were inappropriate.

Cabazitaxel TA391.

- This was an optimised recommendation (performance status, previous dose of docetaxel, treatment duration) reflecting a subgroup considered to be relevant from, and treatment duration in the regulatory trial (TROPIC). The committee considered the subgroup, dose of previous docetaxel and treatment duration of cabazitaxel to be generalizable to who would have cabazitaxel in clinical practice in the NHS. There is no new evidence assessing cabazitaxel in a broader population than in TROPIC.
- There was no comparative evidence with radium-223 (for the subgroup of people with symptomatic bone metastases and no known visceral metastases). There is no new evidence directly comparing cabazitaxel with radium-223 in this group.
- There were no direct data comparing cabazitaxel with abiraterone and with enzalutamide and an indirect comparison (network meta-analysis) was carried out. There were uncertainties around this indirect comparison because of differences between the trials in this network. There are no new head-to-head studies comparing cabazitaxel with enzalutamide or with abiraterone at this position in the treatment pathway.

**Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?**

*See Appendix C for a list of related NICE guidance.*

**Additional comments**

There is a NHS England treatment algorithm for prostate cancer in preparation. NHS England has stated to NICE that novel antiandrogens (abiraterone and enzalutamide) cannot be used in sequence and can only be used once within the treatment pathway.

Off-licence use of docetaxel in combination with androgen deprivation therapy is commissioned by NHS England.

The search strategies from the original ERG reports / NICE website documents were adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from October 2014 (TA377), September 2013 (TA387) and November 2010 (TA391) were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

## 4. Equality issues

In TA391 the recommendations take into account a person's performance status (fitness). The committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

**Contributors to this paper:**

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# Appendix A – Information from existing guidance

## 5. Original remit

TA377:

To appraise the clinical and cost effectiveness of enzalutamide within its licensed indication for treating metastatic, hormone-relapsed prostate cancer for people in whom chemotherapy is not yet clinically indicated.

TA387:

To appraise the clinical and cost effectiveness of abiraterone acetate in combination with prednisone or prednisolone within its licensed indication for the treatment of metastatic, castration-resistant prostate cancer in people who have not been previously treated with chemotherapy.

TA391:

To appraise the clinical and cost effectiveness of cabazitaxel within its licensed indication for the second line treatment of hormone refractory, metastatic prostate cancer that has progressed following or during docetaxel-based treatment.

## 6. Current guidance

TA377:

1.1 Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

- in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
- and only when the company provides it with the discount agreed in the patient access scheme.

TA387:

1.1 Abiraterone in combination with prednisone or prednisolone is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

- in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
- only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.

TA391:

1.1 Cabazitaxel in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people whose disease has progressed during or after docetaxel chemotherapy, only if:

- the person has an eastern cooperative oncology group (ECOG) performance status of 0 or 1
- the person has had 225 mg/m$^2$ or more of docetaxel
- treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first).

  In addition, cabazitaxel is recommended only if:

- the company provides cabazitaxel with the discount in the patient access scheme agreed with the Department of Health, and
- NHS trusts purchase cabazitaxel in accordance with the commercial access agreement between the company and NHS England, either:
  - in pre-prepared intravenous infusion bags, or
  - in vials, at a reduced price that includes a further discount reflecting the average cost of waste per patient (see section 2.3 for details).

1.2 When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

1.3 This guidance is not intended to affect the position of patients whose treatment with cabazitaxel was started within the NHS before this guidance was published and whose treatment with cabazitaxel is not recommended in this NICE guidance. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

## 7. Cost information from original guidance

TA377:

"The cost (list price) of enzalutamide is £2734.67 for a 112-capsule pack of 40 mg enzalutamide. The daily dose of enzalutamide is 160 mg and costs £97.67 per day."

TA387:

"The current list price of abiraterone is £2,930 for 120 tablets (excluding VAT)".

TA391:

"The list price of cabazitaxel is £3,696 per 60-mg vial (excluding VAT)".

## Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

| **Options** | **Consequence** | **Selected – 'Yes/No'** |
|---|---|---|
| A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appriasial process. | A review of the appraisal will be planned into the NICE's work programme. | No |
| The decision to review the guidance should be deferred to specific date or trial. | NICE will reconsider whether a review is necessary at the specified date. | No |
| A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process. | A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology. | No |
| A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process. | A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology. | No |
| The guidance should be incorporated into an on-going guideline. | The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the guideline is considered for review.<br><br>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal. | No |

## Appendix B

| Options | Consequence | Selected – 'Yes/No' |
|---|---|---|
| The guidance should be updated in an on-going guideline[1]. | Responsibility for the updating the technology appraisal passes to the NICE Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.<br>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation). | No |
| **The guidance should be transferred to the 'static guidance list'.** | The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review. | **Yes** |
| The guidance should be withdrawn | The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS.<br>The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved. | No |

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

## Appendix C – other relevant information Relevant Institute work

### Published

Prostate cancer: diagnosis and management (2014) NICE clinical guideline CG175 An update is in development and expected April 2019.

Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (2016) NICE technology appraisal guidance TA412

Degarelix for treating advanced hormone-dependent prostate cancer (2016) NICE technology appraisal guidance TA404

Enzalutamide for metastatic hormone‑relapsed prostate cancer previously treated with a docetaxel‑containing regimen (2014) NICE technology appraisal guidance TA316. *The NICE website says an update is in progress, January 2018.*

Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (2012) NICE technology appraisal guidance TA259. *The NICE website says an RPP is in progress, January 2018.*

Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (2006) NICE technology appraisal guidance TA101

### In progress

Apalutamide for treating localised hormone-relapsed prostate cancer. NICE technology appraisal guidance. Publication date to be confirmed.

Apalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer. NICE technology appraisal guidance. Publication date to be confirmed.

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer. NICE technology appraisal guidance. Publication date to be confirmed.

Prostate cancer (localised) - padeliporfin. NICE technology appraisal guidance. Publication expected November 2018.

Abiraterone for treating newly diagnosed high risk metastatic hormone-naïve prostate cancer. NICE technology appraisal guidance. Publication expected November 2018.

### Details of changes to the indications of the technology

| Indication and price considered in original appraisal | Proposed indication (for this appraisal) and current price |
|---|---|
| TA377: Enzalutamide is indicated for the treatment of 'adult men with | On the SPC the indication is given as follows: |

| Indication and price considered in original appraisal | Proposed indication (for this appraisal) and current price |
|---|---|
| metastatic castration‑resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated'.<br><br>"The cost (list price) of enzalutamide is £2734.67 for a 112‑capsule pack of 40 mg enzalutamide. The daily dose of enzalutamide is 160 mg and costs £97.67 per day." | • the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer<br>• the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated<br>• the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy<br><br>eBNF (last updated 2 Oct 18) gives the following indication:<br><br>"Metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after docetaxel therapy".<br><br>The list price in the above eBNF is the same. |
| TA387: (Abiraterone) "…is indicated for treating 'metastatic castration resistant [hormone-relapsed] prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated'. It is also indicated for treating 'metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen'."<br><br>"The current list price of abiraterone is £2,930 for 120 tablets (excluding VAT; British national formulary [BNF], accessed online November 2015)." | eBNF (last updated 2 Oct 18) gives the same indication as TA387.<br><br>It gives the NHS indicative price for fifty-six 500mg tablets as £2735.00<br><br>The SPC sets out the indication as follows:<br><br>• the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)<br>• the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated<br>• the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy |
| TA391: "Cabazitaxel has a UK marketing authorisation for use 'in combination with prednisone or prednisolone for the treatment of patients with hormone refractory | eBNF (last updated 2 Oct 18) gives the same indication as TA391.<br><br>It gives the same NHS indicative price as TA391. |

| Indication and price considered in original appraisal | Proposed indication (for this appraisal) and current price |
|---|---|
| metastatic prostate cancer previously treated with a docetaxel‑containing regimen'."<br><br>"The list price of cabazitaxel is £3,696 per 60‑mg vial (excluding VAT; British national formulary [BNF] edition 70)." | The SPC gives the same indication. |

### Registered and unpublished trials

| Trial name and registration number | Details |
|---|---|
| **Enzalutamide:** | |
| Asian Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral Enzalutamide in Chemotherapy Naïve Subjects With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy<br><br>NCT02294461 | Enrolment: 388 participants.<br><br>Active not recruiting. Estimated study completion date: March 2020.<br><br>Results available on the trial record |
| Prevail: A Multinational Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy And Safety Study Of Oral Mdv3100 In Chemotherapy-naïve Patients With Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy<br><br>NCT01212991 | Enrolment: 1735 participants.<br><br>Active not recruiting. Estimated study completion date: December 2018.<br><br>Results available on the trial record |

## Appendix D

| Trial name and registration number | Details |
|---|---|
| A Multicenter, Single-Arm, Open-Label, Post-Marketing Safety Study to Evaluate the Risk of Seizure Among Subjects With Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated With Enzalutamide Who Are at Potential Increased Risk of Seizure<br><br>UPWARD<br><br>NCT01977651 | Enrolment: 424 participants.<br><br>Active not recruiting. Estimated study completion date: November 2018. |
| A Randomized Phase IV Study Comparing Enzalutamide Versus Flutamide in CRPC Patients Who Have Failed Combined Androgen Blockade Therapy With Bicalutamide Plus ADT<br><br>NCT02918968 | Enrolment: 206 participants.<br><br>Active not recruiting. Estimated study completion date: March 2020. |
| Phase III Trial of Enzalutamide (NSC# 766085) Versus Enzalutamide, Abiraterone and Prednisone for Castration Resistant Metastatic Prostate Cancer<br><br>NCT01949337 | Enrolment: 1311 participants.<br><br>Active not recruiting. Estimated primary completion date: December 2019. |
| Effect of a reduced dose on cognitive side effects of enzalutamide in frail mCRPC patients<br><br>EudraCT Number: 2018-000779-33 | Enrolment: 50 participants<br><br>Phase IV, randomised, ongoing. |
| **Abiraterone:** | |
| A Pilot Study of Adaptive Abiraterone Therapy for Metastatic Castration Resistant Prostate Cancer<br><br>NCT02415621 | Enrolment: 40 participants.<br><br>Recruiting. Estimated study completion date: December 2020. |

# Appendix D

| Trial name and registration number | Details |
|---|---|
| A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer<br><br>NCT01591122 | Enrolment: 313 participants.<br><br>Active not recruiting. Estimated study completion date: December 2018. |
| A Phase 3b Multicenter, Open-label Abiraterone Acetate Long-term Safety Study<br><br>NCT01517802 | Enrolment: 36 participants.<br><br>Active not recruiting. Estimated study completion date: April 2021. |
| Toxicity of first-line abiraterone versus enzalutamide in men with metastatic castration-resistant prostate cancer: A randomized clinical trial<br><br>EudraCT Number: 2017-000099-27<br><br>HEAT | Enrolment: 170 participants.<br><br>Ongoing.<br><br>"The main objective of this project is to investigate if there is a group-difference in treatment related adverse effects between abiraterone and enzalutamide in regards to:<br><br>• Fatigue<br><br>• Metabolic profile<br><br>• Health related quality of life (HQoL)" |
| **Cabazitaxel:** | |
| Multicentre, Single Arm, Open Label, Non Controlled Phase IV Clinical Trial to Evaluate Safety of Cabazitaxel (Jevtana) in Combination With Oral Prednisone (or Prednisolone) for the Treatment of Patients With Metastatic Hormone Refractory Prostate Cancer Previously Treated With a Docetaxel-containing Regimen<br><br>NCT02074137 | Enrolment: 1200 participants.<br><br>Completed: March 2016. |

# Appendix D

| Trial name and registration number | Details |
|---|---|
| A Phase IV, Multicenter, National, Non-comparative, Open-label Study of Cabazitaxel, Combined With Prednisone and Prophylaxis of Neutropenia Complications in the Second-line Treatment of Patients With Metastatic Castration-resistant Prostate Cancer and After Failure of Docetaxel-based Chemotherapy. Descriptive Assessment of the Circulating Tumor Cells in This Context.<br><br>NCT01649635<br><br>PROSPECTA | Enrolment: 45 participants.<br><br>Completed: June 2016. |
| A Randomized, Open Label, Multicenter Study of Cabazitaxel Versus an Androgen Receptor (AR)-Targeted Agent (Abiraterone or Enzalutamide) in mCRPC Patients Previously Treated With Docetaxel and Who Rapidly Failed a Prior AR-targeted Agent (CARD)<br><br>NCT02485691 | Enrolment: 234 participants.<br><br>Recruiting. Estimated study completion date: August 2019. |
| A Randomized, Open Label, Phase IIB Trial of Optimal Sequencing of Treatment Options for Poor Risk Metastasized Castration Resistant Prostate Cancer Previously Treated With Docetaxel<br><br>NCT03295565<br><br>OSTRICh | The aim of this study is to identify the optimal second line treatment option for patients with a poor prognosis metastasized Castration Resistant Prostate Cancer (mCRPC) with respect to Clinical Benefit Rate (CBR) rate and quality of life.<br><br>The primary endpoint is CBR in mCRPC patients with poor prognostic features and previously treated with docetaxel, randomized between cabazitaxel (Arm A) and novel hormonal agents (abiraterone OR enzalutamide) as second-line therapy (Arm B).<br><br>Enrolment: 152 participants.<br><br>Recruiting. Estimated study completion date: May 2019. |

## Appendix D

| Trial name and registration number | Details |
|---|---|
| **Abiraterone and Enzalutamide:** | |
| Impact of New Generation Hormono-therapy on Cognitive Functions in Elderly Patients Treated for a Metastatic Prostate Cancer<br><br>NCT02907372 | Enrolment: 222 participants.<br><br>Recruiting. Estimated study completion date: November 2020.<br><br>"This study will assess the impact of the novel oral hormonal agents (**abiraterone acetate or enzalutamide**) among elderly metastatic prostate cancer patients. This study will assess the influence of treatments on patients' cognitive functions on a longitudinal basis and evaluate the quality of life and the adherence of patients who had or develop cognitive disorders." |