AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Abiraterone acetate for the treatment of non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer (OW20)

April 2024

One Wales Interim Decision

Abiraterone acetate for the treatment of non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer

Date of original advice: November 2022
Date of review: April 2024

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.

Using the agreed starting and stopping criteria, abiraterone in combination with prednisolone can be made available within NHS Wales for the treatment of non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer.

Abiraterone acetate should be prescribed on the basis of lowest acquisition cost.

The risks and benefits of the off-label use of abiraterone for this indication should be clearly stated and discussed with the patient to allow informed consent. Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 2 years or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for abiraterone acetate for the treatment of non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer

Starting criteria:
Patients with newly diagnosed, high-risk hormone-sensitive prostate cancer with either node positive (N1) disease or at least 2 of the following: tumour stage T3 or T4; a Gleason sum score of 8 to 10; a prostate-specific antigen (PSA) level of ≥ 40 ng/ml. Or relapsing, hormone-sensitive prostate cancer with high-risk features: previously treated with radical surgery or radiotherapy and hormone therapy for no longer than 12 months in duration with an interval of ≥ 12 months without treatment and either node positive disease (N1) or node negative disease (N0) with either a PSA concentration ≥ 4 ng/mL with a doubling time of < 6 months or a PSA concentration ≥ 20 ng/mL).
This advice excludes patients who have metastatic disease i.e. M1 disease in whom the cancer has spread to a different part of the body[1] and appropriate Health Technology assessment advice should be followed for this patient group. Patients for whom this decision does apply, should receive radical radiotherapy unless there is a contraindication. Patients will routinely receive androgen deprivation therapy (ADT) for up to 3 years.

The recommended treatment dose regimen for adult males is 1,000 mg (two 500 mg tablets) of abiraterone acetate taken as a single daily dose, in combination with 5 mg prednisolone daily. Treatment will start within 12 weeks of commencement of ADT and be continued for up to two years after radiotherapy (maximum treatment course of 2.5 years). The abiraterone acetate product available at the lowest acquisition cost should be prescribed.

Continuing and stopping criteria:
Monitoring is recommended in accordance with the Summary of Product Characteristics (SmPC)[3].
For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with abiraterone acetate should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline[3].
For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately. Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (1 tablet) once daily, in accordance with the SmPC[3].

Failure to respond to abiraterone acetate:
- biochemical failure, or
- radiological progression, or
- clinical progression

In the above situation, abiraterone should be stopped and alternative treatments should be instigated in accordance with NICE guidance or health technology assessment (HTA) advice.

Stopping criteria:

- Treatment failure/ disease progression
- Toxicity from treatment (that cannot or does not respond to temporary treatment interruption)
- Treatment has reached 2.5 years
- Patient request

Only one course of treatment may be issued in accordance with this advice. Requests for repeat courses or continuing treatment beyond 2.5 years should be explored through funding mechanisms such as the individual patient funding request process.

For patients who progress following the full treatment course, subsequent management including novel androgen receptor-targeting agents should be used in accordance with current HTA advice.

References:

(1) James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind, eds (2016). TNM Classification of Malignant Tumours, 8th Edition. Chichester, West Sussex, UK: Wiley-Blackwell. ISBN 978-1-4443-3241-4.

(2) James ND, de Bono JS, Spears MR et al. Abiraterone for prostate cancer not previously treated with hormone therapy. New England Journal of Medicine. 2017;377:338-351.

(3) Janssen-Cilag Ltd. ZYTIGA® 500 mg film-coated tablets. Summary of Product Characteristics. Sept 2022 Available at: https://www.medicines.org.uk/emc/product/2381. Accessed Oct 2022.

This is a summary of new evidence available and patient outcome data collected, to inform the review

NB. During the review process it was proposed that OWMAG consider amending the starting cristria to include high risk relapsing patients in line with the STAMPEDE trial inclusion criteria. **Please see Addendum for more information.**

Background:
Prostate cancer is the most common cancer in men in the UK. Survival depends on the type and grade of the cancer, as well its size, when it was diagnosed and whether it has spread. NICE guidance [NICE NG131] recommends treating high-risk, non-metastatic, hormone-sensitive prostate cancer with a combination of radiotherapy with at least 6 months of androgen deprivation therapy (ADT), and considering continuing the ADT for up to 3 years. The guidance recommends discussing the option of off-label docetaxel chemotherapy in combination with ADT with people newly diagnosed with high risk non-metastatic prostate cancer.

Clinicians in Wales said that treatment with an androgen receptor targeted agent (ARTA) is the preferred treatment choice for patients with newly diagnosed, high-risk non-metastatic prostate cancer. Clinical experts felt that, in their experience, abiraterone is better tolerated than off-label docetaxel. Abiraterone is therefore also suitable for patients who may be older or frail and would not be able to tolerate treatment with docetaxel.

Clinicians in Wales considered there was an unmet need, and a cohort of patients who could benefit from treatment. Therefore, abiraterone was considered suitable for the One Wales Medicines process, and was assessed for treating non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer. High risk is defined as per the STAMPEDE study; at least 2 of the following: tumour stage T3 or T4, a Gleason score of 8 to 10, and a prostate specific antigen (PSA) level of ≥ 40 nanograms/ml**.**

Current One Wales Decision: Recommended for use in combination with prednisolone in NHS Wales to treat non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer.

Licence status: Off-label use for this licensed medicine.
[CONFIDENTIAL INFORMATION REMOVED]

Guidelines: The National Cancer Medicines Advisory Group (NCMAG) for Scotland published updated guidance (NCMAG102) in January 2023, which supports the use of generic versions of abiraterone acetate to treat high-risk hormone-sensitive non-metastatic prostate cancer, in combination with prednisolone and androgen deprivation therapy. The NCMAG stated that the use of generic forms of abiraterone made this choice of treatment cost effective.
In March 2023 the Prostate Cancer Guidelines Panel issued a limited update of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. Given the benefits observed in the overall population in the STAMPEDE study, including patients with non-metastatic disease, for treatment of locally advanced disease the guidelines recommend offering

- Intensity modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image guided radiation therapy (IGRT) to the prostate in combination with long-term ADT and 2 years of abiraterone to patients with non-metastatic disease that has not spread to any lymph nodes and who have ≥ 2 high-risk factors (cT3-4, Gleason ≥ 8 or PSA ≥ 40 ng/mL);
- IMRT/VMAT plus IGRT to the prostate plus pelvis in combination with long-term ADT and 2 years of abiraterone to patients with non-metastatic disease involving nearby lymph nodes.

Licensed alternative medicines or Health Technology Assessment (HTA) advice for alternative medicines: No new medicines or HTA advice reported.

Enzalutamide (Extandi®) is in phase III studies in Europe (including sites in the UK) to treat non-metastatic, hormone-sensitive prostate cancer with high-risk biochemical recurrence. In August 2023, Pfizer and Astellas announced that the US Food and Drug Administration (FDA) granted Priority Review to a new drug application for this indication.

NICE guidance (GID-TA10802) is expected to be published in December 2023, for the use of olaparib with abiraterone to treat untreated, hormone-relapsed, metastatic prostate cancer. The appraisal is considering the clinical and cost-effectiveness of olaparib with abiraterone to treat hormone-relapsed metastatic prostate cancer in people who have not received prior chemotherapy or new hormonal agents at the hormone-relapsed metastatic stage. Expert opinion is that this advice would not affect the use of abiraterone in the hormone-sensitive non-metastatic setting; as a potentially curative treatment it would be chosen over olaparib with abiraterone later in the treatment pathway.

Effectiveness: A repeat literature search conducted by AWTTC did not find any new, relevant clinical studies.

Safety: No relevant safety analyses were identified in the repeat literature search.

Cost-effectiveness: No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact: Since the One Wales decision in November 2022, 69 patients at Velindre Cancer Centre (VCC) and [CONFIDENTIAL INFORMATION REMOVED] at South West Wales Cancer Centre (SWWCC) have been treated with abiraterone for non-metastatic hormone-sensitive prostate cancer (see patient outcome data below). SWWCC [CONFIDENTIAL INFORMATION REMOVED] it is expected that numbers will increase in this centre in the coming year. Figures have not been provided for uptake in North Wales; however, intelligence suggests that uptake has been low to date but is likely to also increase in the coming year. Based on extrapolation of the data available from VCC, the budget impact would appear similar to that estimated in November 2022.

Impact on health and social care services: moderate increase.

Patient outcome data: Since November 2022, 69 patients (aged 53–82 years;70% aged 65–79 years) at VCC have started treatment with abiraterone: 32 (46%)

patients were node positive; 14 (20%) patients had a PSA ≥ 40 ng/mL; 62 (90%) patients had stage T3–T4; and 39 (57%) had a Gleason score ≥ 8. Sixty patients (87%) had a positron emission tomography (PET) scan for prostate-specific membrane antigen (PSMA) before starting treatment. Patient outcomes reported to date show 100% overall survival and 100% progression-free survival. [CONFIDENTIAL INFORMATION REMOVED]

Evaluation of evidence

No significant new evidence has been published which challenges the original recommendation. Outcome data indicate lower uptake than predicted across Wales but this is expected to increase in 2024 and is in accordance with the budget impact estimates. With the exception of mucositis, grade 3 and 4 adverse events are in line with those reported in the Summary of Product Characteristics for abiraterone and prednisolone. Overall response to date is promising but it is too early to make any robust assessments.

Since the One Wales decision was published, NHS Scotland and European guidelines have been updated to support abiraterone use for non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer.

AWTTC recommends continuing access in NHS Wales to abiraterone to treat non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer.

Next review date: April 2026

References: a full reference list is available on request.

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk. Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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Addendum

After the initial review by OWMAG, clinicians in Wales agreed that aligning the starting criteria with the STAMPEDE inclusion criteria would be advisable. In the STAMPEDE trial 3% of non-metastatic patients had relapsing disease. In the initial Evidence Status Report (ESR) it was estimated that patient numbers in Wales would range between 120 and 263 annually. Velindre report treating 69 patients in the year following publication of One Wales advice, extrapolated to the whole of Wales this would equate to approximately 140 patients, therefore inclusion of relapsing patients at a rate of 3% (around 4 additional patients/annum) would not be expected to increase numbers beyond the upper estimate quoted in the original ESR. Results were not reported separately for the relapsing sub-group of patients for the STAMPEDE trial. AWTTC performed a literature search and no studies were found reporting results for relapsing patients. It was agreed by OWMAG that no additional clinical evidence was available on which to inform a re-assessment of the One Wales advice. It was also noted that the proposed amendment would not require a change to the current One Wales advice. Based on these findings, the amendment below was proposed by AWTTC and agreed by OWMAG as part of the review of the recommendation.

Current wording	**Proposed wording**
Patients with newly diagnosed non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer including pelvic node positive patients (N1). This advice excludes patients who have metastatic disease i.e. M1 disease in whom the cancer has spread to a different part of the body[1] and appropriate Health Technology assessment advice should be followed for this patient group. Patients for whom this decision does apply, should receive radical radiotherapy unless there is a contraindication. Patients will routinely receive androgen deprivation therapy (ADT) for up to 3 years. High risk is defined, as per STAMPEDE[2], as at least 2 of the following: *• tumour stage T3 or T4* *• a Gleason sum score of 8 to 10* *• a prostate-specific antigen (PSA) level of ≥ 40 ng/ml*	*Patients with newly diagnosed, high-risk hormone-sensitive prostate cancer with either node positive (N1) disease or at least 2 of the following: tumour stage T3 or T4; a Gleason sum score of 8 to 10; a prostate-specific antigen (PSA) level of ≥ 40 ng/ml. Or relapsing, hormone-sensitive prostate cancer with high-risk features: previously treated with radical surgery or radiotherapy and hormone therapy for no longer than 12 months in duration with an interval of ≥ 12 months without treatment and either node positive disease (N1) or node negative disease (N0) with either a PSA concentration ≥ 4 ng/mL with a doubling time of < 6 months or a PSA concentration ≥ 20 ng/mL).* *This advice excludes patients who have metastatic disease i.e. M1 disease in whom the cancer has spread to a different part of the body[1] and appropriate Health Technology assessment advice should be followed for this patient group. Patients for whom this decision does apply, should receive radical radiotherapy unless there is a contraindication. Patients will routinely receive androgen deprivation therapy (ADT) for up to 3 years*