AWTTC
All Wales Therapeutics & Toxicology Centre
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Evidence Status Report: Abiraterone acetate (ZYTIGA®), enzalutamide (Xtandi®) and apalutamide (Erleada®▼) for the treatment of high-risk locally advanced, and metastatic, hormone-sensitive prostate cancer during the COVID-19 pandemic

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Background
Standard of care for newly diagnosed metastatic hormone-sensitive (hormone-naïve, hormone dependent) prostate cancer (mHSPC) is docetaxel which is licensed in combination with androgen deprivation therapy (ADT) delivered by intravenous infusion in a hospital setting. Docetaxel may also be considered as an off-label option for a cohort of patients with high-risk locally advanced prostate cancer commencing long-term ADT with no significant co-morbidities.

A cohort of patients was identified due to the ongoing COVID-19 pandemic, as clinicians indicated that there was a need for access to alternative, oral preparations with less immunosuppression to treat either continuing patients or new patients with HSPC. Switching from intravenous treatments, such as docetaxel, to oral alternatives, such as oral androgen receptor targeted agents, is broadly supported by National Institute for Health and Care Excellence (NICE) guidance, "COVID-19 rapid guideline: delivery of systemic anticancer treatments". Clinicians in Wales considered there to be an unmet need and based on these factors these medicines were deemed suitable for a One Wales Interim Commissioning decision during the COVID-19 pandemic. In April 2020, the following One Wales decision was issued: using the agreed starting and stopping criteria, abiraterone acetate (ZYTIGA®), apalutamide (Erleada®) and enzalutamide (Xtandi®) can be made available within NHS Wales for the treatment of high-risk locally advanced and metastatic, hormone-sensitive prostate cancer during the COVID-19 pandemic.

At the three month review in August 2020, IPCG members indicated that they wished to review the current treatment options based on new information and the IPCG Chair agreed to a full reassessment of the evidence.

Efficacy/Clinical Effectiveness
Results from a randomised control trial (RCT) showed that abiraterone acetate plus prednisone with ADT improves overall survival (OS) in high-risk mHSPC by approximately 17 months compared to ADT alone. In a multi-arm RCT OS for metastatic or non-metastatic HSPC was significantly higher in the abiraterone acetate group compared to the ADT alone arm.

Two RCTs provide evidence for the use of enzalutamide with ADT in mHSPC. For one study progression free survival at time of reporting favoured enzalutamide over ADT alone (not reached versus 19 months respectively). OS data were immature. In the other trial a 47% reduction in risk of death was reported for patients treated with enzalutamide plus ADT and no planned early docetaxel compared with ADT alone.

Evidence for the efficacy of apalutamide was provided by one RCT, all patients had mHSPC. Results reported a 52% lower risk of radiographic progression free survival or death in the apalutamide group compared with placebo. Results showed that apalutamide statistically significantly increased OS compared with placebo. At 24 months, OS was 82% in the apalutamide group compared with 74% in the placebo group.

Safety
The most commonly reported grade 3 or 4 adverse event for abiraterone acetate, enzalutamide and apalutamide was hypertension. Abiraterone acetate is also associated with an elevation of liver enzymes.

Patient factors

- Due to the associated risk of elevated liver enzymes (indicating hepatotoxicity) for those patients receiving abiraterone acetate, it is recommended that regular monitoring of liver function is undertaken at baseline, every two weeks for the first three months of treatment, and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly.
- Due to the potential for significant drug interactions, a medication review is recommended by the manufacturers before commencing apalutamide or enzalutamide.

Cost effectiveness

The manufacturer of abiraterone provided a copy of the cost-effectiveness model submitted to the Scottish Medicines Consortium (SMC) as part of their health technology assessment of abiraterone acetate for the treatment of newly diagnosed, high-risk mHSPC. When the commercial arrangement for abiraterone during COVID-19 for the treatment of newly diagnosed, mHSPC and the Patient Access Schemes (PAS) discounts for the other medicines in later line treatment are included, the incremental cost-effectiveness ratio (ICER) for abiraterone acetate compared with ADT alone, [Confidential data removed]. The committee papers published by NICE for the assessment of abiraterone acetate for the treatment of newly diagnosed high risk metastatic hormone-naïve prostate cancer (ID945) were also reviewed. When compared with ADT alone, the company base case ICER estimates were below £20,000 per quality adjusted life year (QALY) gained but in updated analyses, the estimated ICER was likely to exceed £30,000 per QALY gained based on the NICE committee's preferences. It should be noted that the decision for abiraterone is currently under appeal. Additionally, based on differences in the population under consideration (patients may be fit for chemotherapy but are not receiving treatment due to COVID-19) and the agreed commercial arrangements in Wales, drawing comparisons is subject to significant uncertainties.

Budget impact

At the three month review in August 2020, patient numbers reported by clinicians estimated that 111 patients have received one of these medicines for the indications under consideration over a period of four months since the original One Wales decision was issued (50% abiraterone acetate, 25% apalutamide, 25% enzalutamide). Since the original document there has been an update to the commercial arrangements for the three medicines. Information from the service on usage has been used to estimate the market share of each medicine. As a result the budget impact has been recalculated to better reflect the situation in Wales. If we assume that the market share remains the same and that 200 patients start treatment during a 12 month period, the estimated cost over 12 months is [Confidential data removed] using the confidential commercial arrangement price for the three medicines.

Commercial agreement

Commercial agreements are available in NHS Wales for abiraterone acetate, enzalutamide and apalutamide offering treatments at a reduced price during the COVID-19 pandemic.

Impact on health and social care services

There are limited treatment options available for patients with high-risk locally advanced and metastatic prostate cancer where docetaxel is unsuitable due to COVID-19. The move to oral based therapies will reduce hospital contact time and is anticipated to reduce the burden of care for this patient cohort.

Innovation and/or advantages

Clinicians in Wales have reported using all three agents and consider there to be a clinical need to retain availability of more than one agent due to variance in patient tolerability and drug interactions. Specifically they feel it is important to have an alternative to enzalutamide for patients with potential drug-drug interactions or for men who tolerate enzalutamide poorly, or have other contraindications. However they are minded of the opportunity to rationalise the treatment pathway to make better use of available NHS resources.

BACKGROUND

Target group

Patients with newly diagnosed high-risk locally advanced and metastatic, hormone-sensitive prostate cancer during the COVID-19 pandemic. In line with the STAMPEDE trial, high-risk is defined as T3/T4 staging or Gleason score 8 to 10 or prostate specific- antigen (PSA) > 40 nanogram/mL. Abiraterone acetate, apalutamide or enzalutamide treatment may be given to patients eligible to start treatment with docetaxel, or patients who have received less than five cycles of docetaxel before stopping due to the COVID-19 pandemic. Refer to the One Wales recommendation and agreed start/stop criteria for further information[1].

Technology

Abiraterone acetate (ZYTIGA®) is changed in the body to abiraterone which stops the body producing testosterone[2]. Abiraterone does this by blocking an enzyme found in the testes and elsewhere in the body. This slows down the growth of the prostate cancer which needs a supply of testosterone to grow and survive[3].

Both enzalutamide (Xtandi®) and apalutamide (Erleada®) work similarly. They block the action of the male hormone testosterone and other male hormones known as androgens by blocking the receptors to which these hormones attach[4,5]. This slows down the growth of the prostate cancer which needs these hormones to grow and survive[6,7].

Licence status

Apalutamide (Erleada®) is licensed for the treatment of mHSPC in combination with ADT[4]. It is not licensed to treat high-risk locally advanced HSPC (off-label use)[4].

Abiraterone acetate (ZYTIGA®) is licensed in combination with prednisolone for the treatment of newly diagnosed high-risk mHSPC in adult men in combination with ADT[2]. It is not licensed to treat low-risk metastatic and high-risk locally advanced HSPC (off-label use)[2].

Enzalutamide (Xtandi®) is not licensed for the treatment of newly diagnosed high-risk locally advanced and metastatic HSPC (off-label use)[5]. Licensing for the treatment of mHSPC is filed for approval in the EU[8].

Dosing

Abiraterone acetate: The recommended dose is 1,000 mg (two 500 mg tablets) as a single daily dose in combination with 5 mg prednisolone daily[2].
Enzalutamide: Based on current dosing for castrate-resistant prostate cancer (CRPC), the recommended dose is 160 mg (four 40 mg film-coated tablets or two 80 mg film-coated tablets) as a single daily dose[5].
Apalutamide: The recommended dose is 240 mg (four 60 mg tablets) as a single daily dose[4].

Each of the three medicines are given in combination with ADT.

Clinical background

Most prostate cancers are acinar adenocarcinomas (95%); they arise from gland cells that line the prostate gland, are mostly slow growing and are unlikely to spread[9,10]. A small number of prostate cancers are aggressive, invade local tissues and metastasise to remote sites[10]. Localised prostate cancer usually develops in the outer area of the prostate and is usually asymptomatic[9]. There are three risk groups for localised prostate cancer: low, medium (intermediate) and high risk (includes locally advanced prostate cancer) (Table 1). Locally advanced prostate cancer spreads beyond the capsule of the prostate and is often also asymptomatic when diagnosed[9]. Metastatic prostate cancer usually presents as bone metastases causing pain and fractures[10].

Table 1. Risk stratification for men with localised prostate cancer[9]

Risk of progression	PSA level	Gleason score	Clinical stage
Low risk	< 10 nanogram/mL	and ≤ 6	and T1-T2a
Intermediate risk	10-20 nanogram/mL	or 7	or T2b
High risk	> 20 nanogram/mL	or 8-10	or T2c
PSA: prostate specific antigen			

Prostate cancer is the most common cancer in men in the UK, and the second most common cause of cancer death in men in the UK[11]. The 10-year survival rate for men diagnosed with prostate cancer in England is 77.6%, the five-year survival rate is 86.6%. Prostate cancer survival has tripled in the past 40 years in the UK, possibly as a result of greater disease awareness and increased PSA testing[11]. In 2017, around 40% of all prostate cancers were diagnosed at stage III or IV in Wales[12]. Survival for prostate cancer is related to the stage at diagnosis. The five-year relative survival rate ranges from more than 100% (accounting for background mortality patients have better survival rate than general population) for patients diagnosed at stage I to 49% for those diagnosed at stage IV[11].

The risk factors for prostate cancer are not clearly understood although ethnicity, family history, and obesity or being overweight have been identified[10]. Age is the most significant factor. Prostate cancer is uncommon in men under the age of 50 years and increases with age[10].

Incidence/prevalence

According to the National Prostate Cancer Audit, between April 2017 and March 2018, there were 2,239 new cases of prostate cancer diagnosed in Wales[13]. Taking in to account missing data on disease status, 15% (282/1,893) had metastatic disease and 34% (722/2,151) had high risk locally advanced disease. Based on English data (Welsh data missing), 27% (range 0–39%) of patients with metastatic disease received docetaxel plus ADT as a first line therapy. The figures for docetaxel usage in patients with high risk locally advanced disease were not provided. Around a third (27%) of English centres would consider docetaxel's use in this group. Overall, 59% of diagnoses had a performance score of 0 and 38% had a score of 1–2; 84% of all patients were aged 80 or younger. Based on the metastatic group, if only those patients aged 80 years or younger with a performance score of 0 received treatment, this would equate to 140 patients in Wales eligible for treatment with docetaxel[13].

Current treatment options

For the treatment of newly diagnosed mHSPC, NICE guideline recommends docetaxel chemotherapy for patients without significant comorbidities[14]. Docetaxel should be started within 12 weeks of starting ADT, for six 3-weekly cycles at a dose of 75 mg/m^2, with or without prednisolone. Other recommendations for this patient group include bilateral orchidectomy as an alternative to continuous luteinising hormone-releasing hormone agonist therapy. Bicalutamide may be offered as an alternative to ADT to retain sexual function but is associated with lower overall survival[14].

During the COVID-19 pandemic, enzalutamide in combination with ADT is recommended in England for the treatment of newly diagnosed metastatic disease instead of docetaxel to reduce toxicity and potential for admission; abiraterone acetate is recommended for patients who are intolerant of enzalutamide[15]. In Scotland, abiraterone acetate in combination with ADT is recommended for the treatment of newly diagnosed low-risk mHSPC during the COVID-19 pandemic[16]. Abiraterone acetate is already available in Scotland for high risk mHSPC following a recommendation by the Scottish Medicines Consortium (SMC) in January 2020[17].

Updated guidelines for mHSPC from the European Association of Urology recommend ADT combined with abiraterone acetate plus prednisolone as an alternative to docetaxel plus ADT[18]. Choice of treatment is determined by patient preference, agent-specific side effects and cost[18].

For newly diagnosed high-risk locally advanced HSPC, NICE guideline recommends radical treatment[14]. Radical prostatectomy or radical radiotherapy in combination with ADT are recommended treatment options, ADT may be given for up to three years. Off-label docetaxel may be offered for patients who are newly diagnosed, starting long-term ADT and have no significant comorbidities. High-risk disease is defined in the NICE guideline as: T3/T4 staging, or Gleason score of 8 to 10, or PSA greater than 40 nanogram/mL[14].

Guidance and related advice

- NHS England interim treatment options during the COIVD-19 pandemic (last updated 23 September 2020)[15].
- Scottish Government Health Department guidance. Coronavirus (COVID-19): Interim cancer treatment options for the delivery of systematic anticancer treatment during COVID-19 (June 2020)[16].
- NICE Clinical Guidelines (NG131) Prostate cancer: diagnosis and management (May 2019)[14].
- European Association of Urology (EAU). Updated guidelines on prostate cancer (2018)[18].
- European Society for Medical Oncology (ESMO). eUpdate. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up (2017)[19].
- NICE guidance in development: Abiraterone acetate for treating newly diagnosed high risk metastatic hormone-naïve prostate cancer [ID945]. The decision was not recommended in June 2020 and is currently under appeal. Expected publication date TBC[20].
- NICE guidance in development: Apalutamide for treating prostate cancer [ID1534]. Expected publication date May 2021[21].
- NICE guidance in development: Enzalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer [ID1605]. Expected publication date TBC[22].

- SMC advice: Abiraterone acetate with prednisone or prednisolone for the treatment of newly diagnosed high-risk metastatic hormone sensitive prostate cancer in combination with androgen deprivation therapy [SMC2215]. Published 13 January 2020[17].

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Literature searches were conducted by AWTTC for abiraterone acetate, enzalutamide and apalutamide on 1-2 April 2020. A systematic review and meta-analyses relevant to all three medicines compared the efficacy of combination treatments in mHSPC. There were two relevant randomised controlled trials (RCTs) which investigated the use of abiraterone acetate for the treatment of HSPC. Two RCTs investigated the use of enzalutamide for the treatment of mHSPC and one RCT investigated the use of apalutamide for the treatment of mHSPC; this RCT had associated health related quality of life (HRQoL) data published separately. A follow-up search for all three medicines was conducted on 14 September 2020 and identified two additional systematic reviews and meta-analyses relevant to all three medicines. These studies are briefly described below. High volume disease is defined throughout the studies (generally) as four or more bone metastases on bone scan, including one or more outside the vertebral bodies or pelvis, and/or visceral metastases. Low volume disease is defined as disease pattern not meeting the criteria of high volume disease.

Efficacy

Abiraterone acetate

LATITUDE is a double-blind, placebo-controlled, phase III study in patients with newly diagnosed high-risk mHSPC[23,24]. High-risk was defined as at least two of the following factors: a Gleason score of 8 or more; at least three bone lesions; and the presence of measurable visceral metastasis[23,24]. Patients were randomly assigned to the abiraterone acetate plus low dose prednisone plus ADT group (n = 597) or ADT alone (placebo) group (n = 602)[23]. At the planned interim analysis after a median of 30.4 months and 406 deaths, the median overall survival (OS) and radiographic progression-free survival (rPFS) were significantly longer in the abiraterone acetate group compared to the placebo group (Table 2). The overall relative risk of death was 38% lower in the abiraterone acetate group compared to placebo (HR 0.62; 95% CI: 0.51 to 0.76; $p < 0.001$)[23].

Following the interim analysis the Independent Data Monitoring Committee recommended that the study was un-blinded and crossover allowed for patients in the placebo group to receive abiraterone acetate[24]. The final OS analysis following the open-label extension was done after a median of 51.8 months and 618 deaths. At the time of the analysis 72 patients had crossed over from placebo to the abiraterone acetate group. This confounded the analysis and the authors' state the power could have been negatively affected. These final analysis results continue to show significant improvement in OS for patients treated with abiraterone acetate plus ADT versus those treated with ADT alone (Table 2)[24].

Based on post hoc analysis, patients with high volume disease had significantly longer OS and rPFS rates with abiraterone acetate (n = 487) when compared to placebo (n = 468; Table 2)[24]. Fewer patients had low volume disease in the study and median OS was not reached for either group rPFS was also significantly longer for low volume disease in the abiraterone acetate group[24]. Patient reported outcomes consistently showed a clinical benefit for the abiraterone acetate group in the progression of pain, prostate cancer symptoms, fatigue, functional decline and overall HRQoL[25].

Table 2. Outcomes from LATITUDE[23,24]

	Abiraterone acetate	ADT alone	Hazard ratio (95% CI) P value
Overall population (interim analysis)			
Overall survival (months)	NR	34.7	0.62 (0.51 – 0.76) < 0.001
Radiographic progression free survival (months)	33	14.8	0.47 (0.39 – 0.55) < 0.001*
Overall population (final analysis)			
Overall survival (months)	53.3	36.5	0.66 (0.56 – 0.78) < 0.0001
High volume disease subgroup (post hoc analysis)			
Overall survival (months)	49.7	33.3	0.62 (0.52 – 0.74) < 0.0001
Radiographic progression free survival (months)	33.1	14.7	0.46 (0.39 – 0.54) < 0.0001
Low volume disease subgroup (post hoc analysis)			
Overall survival (months)	NR	NR	
Radiographic progression free survival (months)	49.8	22.4	0.59 (0.40 – 0.85) = 0.0048

*considered to be final analysis for this outcome, ADT: androgen deprivation therapy; CI: confidence interval; NR not reached

STAMPEDE is a multistage, multi-arm, open-label RCT which includes stages comparing abiraterone acetate plus prednisolone and docetaxel plus prednisolone each to standard of care (ADT or ADT and radiotherapy)[26-28]. Eligible patients had newly diagnosed metastatic, node positive, or high-risk (at least two of the following: stage T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥ 40 nanogram/mL) locally advanced disease or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features. In the abiraterone acetate comparison, patients who received abiraterone acetate plus prednisolone plus ADT (n = 960) had significantly higher rates of OS (median 40 months follow-up) and failure-free survival (three-year) to those who received ADT alone (n = 957) (Table 3)[26]. Due to evidence of non-proportional hazards, the restricted mean failure free time was presented: 43.9 months and 30.0 months in the first 54 months following randomisation in the abiraterone acetate and ADT alone groups, respectively. A difference of 13.9 months (95% CI: 12.3 to 15.4); the effect was noted across all patient subgroups[26].

Abiraterone acetate was associated with better outcomes for OS and failure free survival over ADT alone in both metastatic and non-metastatic subgroups (Table 3). It is unclear what proportion of non-metastatic patients included in the STAMPEDE trial were considered to have high-risk locally advanced HSPC[26]. The benefit for OS in the non-metastatic group is uncertain as confidence intervals cross 1.0. No statistically significant differences were demonstrated between metastatic and non-metastatic subgroups in OS (p = 0.37) or failure free survival (p = 0.08)[26].

The clinical evidence for the off-label use of abiraterone acetate for the treatment of low-risk metastatic prostate cancer comes from post hoc analysis of this patient subgroup in the STAMPEDE trial[29]. Staging scans for the metastatic patients were evaluated and stratified to low- (n = 428) and high-risk (n = 473) according to the LATITUDE study criteria[23,29]. Analyses were also applied to the same population stratified by volume. For high- and low-risk patients, OS, failure-free survival and three-year survival was improved in the abiraterone acetate group over the ADT alone group (Table 3). There was no significant difference in treatment effect between the high- and low-risk groups (p = 0.39) although the number needed to treat to prevent one death after three years in the low-risk group was four times more than the high risk (20 versus 5). Subgroup analyses showed no significant differences

in OS, failure-free survival, skeletal-related events, PFS and prostate cancer-specific related death in patients with high or low volume disease when treated with abiraterone acetate; however the study was not powered to make these comparisons[29].

Table 3. Outcomes from STAMPEDE[26,29]

	Abiraterone acetate	ADT alone	Hazard ratio (95% CI) P value
Overall population			
Overall survival, number of deaths (%)	184 (19%)	262 (27%)	0.63 (0.52 – 0.76) < 0.001
Failure free survival, number of events (%)	248 (26%)	535 (56%)	0.29 (0.25 – 0.34) < 0.001
Three year survival	83%	76%	0.63 (0.52 –0.76) < 0.001
Metastatic subgroup			
Overall survival, number of deaths (%)	150 (30%)	218 (43%)	0.61 (0.49 – 0.75)
Failure free survival, number of events (%)	210 (42%)	393 (78%)	0.31 (0.26 – 0.37)
Non-metastatic subgroup			
Overall survival, number of deaths (%)	34 (7%)	44 (10%)	0.75 (0.48 – 1.18)
Failure free survival, number of events (%)	38 (8%)	142 (31%)	0.21 (0.15 – 0.31)
High-risk metastatic subgroup (LATITUDE criteria)			
Overall survival, number of events (%)	94 (39%)	142 (61%)	0.54 (0.41 – 0.70)
Failure free survival, number of events (%)	135 (56%)	202 (87%)	0.31 (0.25 – 0.39)
Absolute three year survival	65%	45%	-
Low-risk metastatic subgroup (LATITUDE criteria)			
Overall survival, number of events (%)	41 (20%)	53 (24)%	0.66 (0.44 – 0.98)
Failure free survival, number of events (%)	56 (27%)	152 (69%)	0.24 (0.17 – 0.33)
Absolute three year survival	83%	78%	-
ADT: androgen deprivation therapy; CI: confidence interval			

Six published network meta-analyses (NMA) explored the treatment of HSPC, all included data from the LATITUDE and STAMPEDE studies[30-35]. Abiraterone acetate was found to be at least as effective as docetaxel in three studies that showed significant improvements in OS and failure free survival when comparing both agents with ADT alone[31-33]. One study showed that abiraterone acetate is as least as effective as docetaxel in reducing the risk of death in mHSPC, while it is associated with a reduced risk of disease progression and an improved quality of life compared with docetaxel[30]. Only one of the NMAs reported results for non-metastatic HSPC patients, in this subgroup treatment with abiraterone acetate or docetaxel plus ADT showed a benefit for failure free survival over ADT alone (HR 0.49; 95% CI: 0.41 to 0.58)[31]. Significant benefit for OS was not demonstrated (HR 0.85; 95% CI: 0.62 to 1.16), as confidence intervals crossed 1.0, however, OS data were immature at time of the NMA[31]. A fifth NMA performed a number of subgroup analyses finding abiraterone acetate (and new anti-androgens) was associated with improved OS in patients with higher Gleason score but this was not the case for patients with low Gleason score[35]. The sixth NMA found that, while no treatment was superior to docetaxel for OS, abiraterone acetate did show lower overall mortality rates than docetaxel (HR 0.89; 95% CI: 0.76 to 1.05)

and significantly lower disease progression rates than docetaxel plus ADT (HR 0.71; 95% CI: 0.59 to 0.86)[34].

Enzalutamide

ARCHES was a double-blind, phase III multinational study conducted to evaluate the efficacy and safety of enzalutamide in mHSPC[36]. A total of 1,150 patients were given ADT and randomly assigned 1:1 to 160 mg per day enzalutamide (n = 574) or placebo (n = 576). Randomisation was stratified by disease volume and prior docetaxel chemotherapy for prostate cancer: 727 (63.2%) had high-volume disease and 205 (17.9%) received prior docetaxel chemotherapy[36].

After a median follow-up of 14.4 months, radiographic PFS was not reached for enzalutamide versus 19 months for placebo[36]. Enzalutamide plus ADT reduced the risk of radiographic disease progression or death by 61% (HR 0.39; 95% CI: 0.30 to 0.50; $p < 0.001$). This treatment effect was consistent across all pre-specified subgroups, including disease volume and prior docetaxel chemotherapy. Data for OS are immature, with 84 deaths (enzalutamide, n = 39; placebo, n = 45). Patients are still being followed-up for this secondary endpoint and a final OS analysis will be performed when 342 deaths have occurred. Mean baseline quality of life (QoL), as measured using the Functional Assessment of Cancer Therapy–Prostate (FACT-P), was high for both groups. Enzalutamide did not affect time to deterioration in QoL or pain progression (Brief Pain Inventory–Short Form: BPI-SF) compared to placebo[36].

ENZAMET is an open label phase III multinational study examining the clinical benefit of enzalutamide in mHSPC[37]. Median follow-up was 34 months. Eligible patients (n = 1,125) from 83 sites were randomised 1:1 to receive enzalutamide (160 mg daily) plus ADT or ADT alone (standard-care group). Ten subgroups were pre-specified for analysis including planned early docetaxel use and volume of disease. Early, concurrent use of docetaxel was permitted in both randomised arms after it was approved in this setting and was planned in 45% of all patients (61% of patients with high volume disease and 27% of patients with low volume disease). As subgroup analysis by volume was not split by docetaxel use, these results have not been included in this report. OS, clinical- and PSA-PFS benefited from enzalutamide over standard-care in the overall population and in those who did not receive docetaxel. No significant differences in OS or PFS for high volume and low volume disease were found when testing the effect of docetaxel use. However, for OS, the confidence intervals crossed one in those patients who received concomitant docetaxel for both high and low volume disease. These results are exploratory as the study was neither designed nor powered to analyse these subsets of patients[37].

Table 4. ENZAMET outcomes[37]

	Enzalutamide	Standard care	Hazard ratio (95% CI) P value
Overall population			
Overall survival, number of deaths (%)	102 (18%)	143 (25%)	0.67 (0.52 – 0.86) = 0.002
Clinical progression free survival, number of events (%)	167 (30%)	320 (57%)	0.40 (0.33 – 0.49) < 0.001
PSA progression free survival, earliest event; number of events (%)	174 (31%)	333 (59%)	0.39 (0.33 – 0.47) < 0.001
No planed early docetaxel			
Overall survival, number of deaths (%)	50 (16%)	88 (28%)	0.53 (0.37 – 0.75)
Clinical progression free survival, number of events (%)	76 (25%)	174 (56%)	0.34 (0.26 – 0.44)
Planned early docetaxel			
Overall survival, number of deaths (%)	52 (20%)	55 (22%)	0.90 (0.62 – 1.31)
Clinical progression free survival, number of events (%)	91 (36%)	146 (59%)	0.48 (0.37 – 0.62)
Low volume disease (no docetaxel)			
Overall survival, number of deaths (%)	15 (8%)	36 (18%)	-
Clinical progression free survival, number of events (%)	30 (16%)	85 (44%)	-
High volume disease (no docetaxel)			
Overall survival, number of deaths (%)	35 (31%)	52 (44%)	-
Clinical progression free survival, number of events (%)	46 (40%)	89 (75%)	-
CI: confidence interval; NR: not reported; PSA: prostate specific antigen			

Two published NMAs explored the treatment of HSPC and included enzalutamide[34,38]. The aim of the first NMA was to characterise the comparative efficacy of combination approaches with mHSPC[38]. Included trials used either docetaxel, abiraterone acetate, enzalutamide, or apalutamide in combination with ADT. The comparator was ADT alone. Due to the ARCHES data being immature, only data from the ENZAMET study were included and this was restricted to those patients without planned early docetaxel. All four interventions demonstrated significantly improved OS compared to ADT alone. No intervention was clearly superior but enzalutamide plus ADT had the absolute lowest HR compared with ADT alone (HR, 0.53; 95% CI: 0.37 to 0.75). For low volume disease, only enzalutamide demonstrated significantly improved survival compared with ADT (HR 0.38; 95% CI: 0.20 to 0.68). For high volume disease, all four interventions demonstrated superior OS to ADT alone. With regard to PFS, abiraterone acetate and enzalutamide were similar to each other and preferred over apalutamide and docetaxel[38]. The second NMA found that, while no treatment was superior to docetaxel for OS, enzalutamide did show lower overall mortality rates than docetaxel plus ADT (HR 0.90; 95% CI: 0.69 to 1.19) and significantly lower disease progression rates than docetaxel plus ADT (HR 0.61; 95% CI: 0.49 to 0.75). There was no statistically significant difference when comparing abiraterone acetate, apalutamide and enzalutamide to each other with regards to disease progression[34].

Apalutamide

TITAN is an ongoing, double-blind, placebo-controlled multinational phase III study that is due to complete in July 2021[39,40]. TITAN investigated the effect of apalutamide among patients with metastatic, castration-sensitive prostate cancer who were also receiving ADT. Previous treatment included docetaxel use in 10.7% of patients. Patients were randomly assigned in a 1:1 ratio to receive apalutamide (240 mg; n = 525) or matched placebo (n = 527) administered orally once daily, in addition to continuous ADT. The primary endpoints were radiographic PFS and OS. Median follow-up at the first interim analysis cut-off date was 22.7 months[39].

At 24 months, both radiographic PFS and OS significantly benefited from apalutamide over placebo (Table 4)[39]. There was a 52% lower risk of radiographic PFS or death in the apalutamide group and apalutamide was favoured across all subgroups analysed including Gleason score at diagnosis, previous docetaxel use and disease volume. Although a benefit for OS was seen with high volume disease and Gleason stage of ≤ 7, the confidence intervals for low volume disease and Gleason stage > 7 crossed 1 and therefore are less certain[39].

Table 5. TITAN outcomes[39]

	Apalutamide	Placebo	Hazard ratio (95% CI) P value
Overall population			
Patients with overall survival at 24 months (percentage)	82%	74%	0.67 (0.51 – 0.89) = 0.005
Overall survival, number of events (%)	83 (16%)	117 (22%)	0.68 (0.51 – 0.90)
Patients with radiographic progression free survival at 24 months (percentage)	68%	47.5%	0.48 (0. 39 – 0.60) < 0.001
Radiographic progression free survival, number of events (%)	134 (26%)	231 (44%)	0.49 (0.40 – 0.61)
No previous docetaxel			
Overall survival, number of events (%)	72 (15%)	108 (23%)	0.63 (0.47 – 0.85)
Radiographic progression free survival, number of events (%)	124 (27%)	212 (45%)	0.49 (0.39 – 0.62)
Previous docetaxel			
Overall survival, number of events (%)	11 (19%)	9 (16%)	1.27 (0.52 – 3.09)
Radiographic progression free survival, number of events (%)	10 (17%)	19 (35%)	0.47 (0.22 – 1.01)
Low volume disease			
Overall survival, number of events (%)	14 (7%)	20 (10%)	0.67 (0.34 – 1.32)
Radiographic progression free survival, number of events (%)	25 (13%)	58 (30%)	0.36 (0.22 – 0.57)
High volume disease			
Overall survival, number of events (%)	69 (21%)	97 (29%)	0.68 (0.50 – 0.92)
Radiographic progression free survival, number of events (%)	109 (34%)	173 (52%)	0.53 (0.41 – 0.67)
CI: confidence interval			

An associated publication presented results of TITAN's pre-specified analyses of patient-reported outcomes including pain, fatigue, prostate cancer symptoms and overall HRQoL[41]. These were respectively measured using the BPI-SF, the Brief Fatigue Inventory

(BFI), FACT-P and the EuroQoL five-dimensions, five-levels questionnaire (EQ-5D-5L). Patient experience of pain and fatigue did not differ between groups for the duration of treatment and FACT-P total scores and EQ-5D-5L data showed preservation of HRQoL in both groups[41].

A published NMA explored the treatment of mHSPC and included apalutamide[34]. It found that, while no treatment was superior to docetaxel for OS, apalutamide did show lower overall mortality rates than docetaxel plus ADT (HR 0.90; 95% CI: 0.67 to 1.22) and significantly lower disease progression rates than docetaxel plus ADT (HR 0.74; 95% CI: 0.57 to 0.95)[34].

Safety

Abiraterone acetate

The Summary of Product Characteristics (SPC) for abiraterone acetate lists the most common adverse events, reported in 1 in 10 people, to be peripheral oedema, hypokalaemia, hypertension, urinary tract infection, diarrhoea and increases in liver enzymes (ALT and/or AST)[2]. Liver function test monitoring is required prior to and during treatment. The incidence of hypertension and hypokalaemia is higher in hormone sensitive patients than in hormone resistant patients. Regular monitoring of liver function tests, blood pressure, serum potassium and fluid balance is recommended. Abiraterone acetate inhibits hepatic drug-metabolising enzymes, CYP2D6 and CYP2C8. Dose reductions and monitoring of concomitant medicines may be required when used with abiraterone[2].

Adverse events (of at least grade 3) were experienced by 63% and 47% of patients receiving abiraterone acetate and 48% and 33% of patients receiving ADT alone in the LATITUDE and STAMPEDE trials respectively[23,26]. Treatment related deaths were similar within both treatment groups, for both trials: LATITUDE for placebo 4% and abiraterone acetate 5%; STAMPEDE for placebo < 1% and abiraterone acetate 1%. In STAMPEDE, treatment related deaths in the abiraterone acetate group were due to pneumonia (n = 2), stroke (n = 2) and one each of dyspnoea, lower respiratory tract infection, liver failure, pulmonary haemorrhage and chest infection[23,26].

Adverse events (of at least grade 3) were experienced by 48% of patients receiving abiraterone acetate and 50% of patients receiving docetaxel in a follow-up publication to STAMPEDE[28]. The patterns of toxicity were different in line with the known toxicity profiles of the medicines. Neutropenia and febrile neutropenia (of at least grade 3) were most commonly reported with docetaxel, in 13% and 17% of patients respectively, compared with 1% of patients receiving abiraterone acetate[28]. Raised liver transaminases were reported in 8% of patients receiving abiraterone acetate and in 1% of patients in the docetaxel group[28].

Further limited comparative safety data for abiraterone acetate versus docetaxel has been reported in two NMAs[42,43]. There was no significant difference in the pooled relative risk of treatment related death between docetaxel and abiraterone acetate (1.438; 95% CI: 0.508 to 4.075)[42]. In one NMA, the rates of grade 3 and 4 neutropenia in the docetaxel arms and febrile neutropenia in the docetaxel arms were reported and ranged from 6.7% to 32% and 8% to 15% compared to 2% and 0.4% in the abiraterone acetate arm[42]. Both NMAs concluded that heterogeneity between adverse event rates and reporting in the treatment arms of the different studies meant that qualitative analysis was not possible[42,43].

Enzalutamide

The SPC for enzalutamide lists the most common adverse events, reported in 1 in 10 people, to be fatigue, hot flush, fractures, and hypertension[5]. Other important adverse reactions include fall, cognitive disorder, seizure and neutropenia. Enzalutamide is a potent enzyme inducer and may lead to a loss of efficacy of many commonly used medicinal products. The manufacturers advise to avoid the use of enzalutamide if the effect of any concomitant medicines is important to the patient, or if dose adjustments cannot be easily performed[5].

Adverse events (of at least grade 3) were similar within both treatment groups in ARCHES, experienced by 24.3% of patients receiving enzalutamide and 25.6% of patients receiving placebo[36].Treatment related deaths were higher for patients receiving enzalutamide (2.4%) compared with placebo (1.7%). Treatment discontinuation due to adverse events was more frequent in the enzalutamide group (7.2%) compared with placebo (5.2%)[36].

Adverse events (of at least grade 3) were experienced by 57% of patients receiving enzalutamide and 43% of patients receiving standard of care in ENZAMET[37]. None of the deaths were reported as treatment related. Treatment discontinuation due to adverse events was more frequent in the enzalutamide group than in the standard-care group (33 events and 14 events, respectively). Six patients in the enzalutamide group discontinued treatment due to seizures, no patients in the standard-care group had seizures. Febrile neutropenia was similar in both treatment groups (n = 37 with enzalutamide; n = 32 with standard care) however all but two events occurred during early docetaxel treatment[37].

A published review and meta-analysis explored the cardiovascular toxicity of abiraterone acetate and enzalutamide in castration-resistant and HSPC[44]. Abiraterone acetate and enzalutamide use was associated with an increased risk of all-grade (relative risk [RR], 1.36; 95% CI, 1.13 to 1.64; p = 0.001) and high-grade (RR, 1.84; 95% CI, 1.21 to 2.80; p = 0.004) cardiac toxicity, and all-grade (RR, 1.98; 95% CI, 1.62 to 2.43; p = 0.001) and high-grade (RR, 2.26; 95% CI, 1.84 to 2.77; p = 0.004) hypertension compared with controls. Abiraterone acetate was found to significantly increase the risk of both cardiac toxicity and hypertension, whereas enzalutamide significantly increased only the risk of hypertension[44].

Apalutamide

Adverse events listed in the SPC, reported in 1 in 10 people, include fatigue, skin rash, hypertension, hot flush, arthralgia, diarrhoea, fall and decreased weight[4]. Similarly to enzalutamide, apalutamide is also a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. The manufacturers advise to avoid the use of apalutamide if the effect of any concomitant medicines is important to the patient, or if dose adjustments cannot be easily performed[4].

Adverse events (of at least grade 3) were experienced by 42.2% of patients receiving apalutamide and 40.8% of patients receiving placebo in TITAN[39]. Treatment related deaths were higher for patients receiving placebo (3%) compared with apalutamide (1.9%). Treatment discontinuation due to adverse events was more frequent in the apalutamide group (8%) compared with placebo (5.3%)[39].

Clinical effectiveness issues

The evidence of clinical effectiveness for the treatment of mHSPC is available for all three oral agents[23,24,26-29,36,37,39]. The only agent to be directly compared with docetaxel is abiraterone acetate, however this was an opportunistic comparison and was not powered to detect differences between treatments[28]. An indirect treatment analysis concluded that all three oral agents have comparable efficacy to docetaxel, however there were differences in

the study designs and patient characteristics, making true comparisons difficult[38]. The results of the NMA are based on the unpowered subgroup analysis in the ENZAMET study[37,38].

The use of early docetaxel has become standard of care and this is reflected in the trial data. Both trials of enzalutamide allowed docetaxel; however, ARCHES allowed prior docetaxel, and treatment with enzalutamide was given after completion of docetaxel, whereas ENZAMET allowed concurrent early docetaxel[36,37]. ENZAMET did report data for patients with no planned concurrent early docetaxel but the study was not powered for this patient group and therefore is subject to a degree of uncertainty[37]. In TITAN, a small proportion of apalutamide patients had received docetaxel (10.7%) despite the majority of the population recruited considered fit enough to have received it[39].

In practice, the three oral agents and docetaxel are used in different ways; abiraterone acetate, enzalutamide and apalutamide are used until the patient develops hormone-resistant prostate cancer whilst docetaxel is given as an 18-week course. Early use of these oral agents may therefore limit future treatment options for hormone-resistant prostate cancer.

Although some comparisons of the three oral agents versus docetaxel for the treatment of HSPC have been included in the evidence for clinical efficacy and safety, it is the evidence compared to ADT alone which is likely to be of greater relevance in the context of COVID-19. When compared to ADT alone, all three oral agents showed clinical benefit in terms of PFS and OS. However the OS data for the ARCHES and TITAN trials are not yet mature[36,39]. HRQoL was preserved between patients receiving oral agent plus ADT or ADT alone.

Abiraterone acetate is currently only licensed to treat high-risk mHSPC[2]. Evidence for the off-label use of abiraterone acetate for low-risk mHSPC patients is provided by post hoc subgroup analysis of STAMPEDE trial data which was not powered for this patient group and therefore is subject to a degree of uncertainty. Treatment of either mHSPC or locally advanced HSPC are currently off-label uses of enzalutamide. Patients were stratified in ARCHES according to low and high volume disease and results indicated comparable findings across these sub-groups[36]. Patients were also stratified by Gleason score and results were consistently in favour of treatment with enzalutamide compared to ADT irrespective of the score. Apalutamide is currently only licensed to treat mHSPC[4]. TITAN broadly recruited people with mHSPC (stratified according to Gleason score, geographic region and prior docetaxel treatment) and did not stratify according to disease volume, although did report outcomes for this subgroup. There was uncertainty surrounding the OS benefit of apalutamide for patients with Gleason scores of 8 and above or low volume disease[39].

There are no subgroup analysis results for the high-risk locally advanced non-metastatic hormone sensitive subgroup of patients recruited in the STAMPEDE trial. Results presented for the non-metastatic and metastatic subgroups as a whole, receiving abiraterone acetate plus prednisolone plus ADT or ADT alone, show that the treatment effect for OS is not significantly different between these groups[26]. No published data were found for enzalutamide and apalutamide for this patient cohort.

The adverse effect profile of abiraterone acetate, enzalutamide and apalutamide differs notably from that of docetaxel in that the rate of neutropenia and febrile neutropenia is markedly higher for docetaxel. This is of significance in the context of the COVID-19 pandemic where avoiding drug-related immunosuppression is desirable. Although all three oral agents are associated with androgen suppressant side effects, there are potential differences in the adverse effects profile of these agents which may affect treatment choice. The SPC for abiraterone acetate recommends regular monitoring of liver function tests, blood pressure, serum potassium and fluid retention[2]. Due to potential interactions, medicine reviews may be necessary when starting treatment with either enzalutamide or apalutamide[4,5].

SUMMARY OF EVIDENCE OF COST-EFFECTIVENESS

NICE and SMC have both appraised abiraterone acetate for the treatment of newly diagnosed high-risk mHSPC in combination with ADT (NICE decision currently under appeal). The company provided AWTTC with the health technology assessment cost-effectiveness model submitted to SMC. In addition, the committee papers published by NICE have been reviewed.

Cost effectiveness evidence

The company's cost-effectiveness model submitted to SMC includes a cost-utility analysis (CUA) comparing abiraterone acetate plus ADT with ADT alone for the treatment of newly diagnosed, high-risk mHSPC[17]. The CUA takes the form of a partitioned survival model structure with a separate state for each line of therapy. The model is comprised of the following health states: mHSPC (progression-free); mHSPC (progressive disease); metastatic CRPC (mCRPC) first line (on/off treatment); mCRPC second line; mCRPC third line; in addition to a state for death. The model adopts a 33 year time horizon and an NHS/Personal and Social Services perspective. Costs and outcomes are discounted at 3.5%[17].

During the first line of therapy (mHSPC) patients can either be in a pre-progression or progression health state, and during the second line of therapy (first line mCRPC) patients can be in an on-treatment or off-treatment health state[17]. Afterwards, patients are assumed to stay on each line of subsequent therapy (second line and third line mCRPC) for a fixed duration. Patients can transition to death from any of the health states. The costs in the model included: treatment acquisition, monitoring, secondary care resource use and adverse events. The utilities were derived from a number of sources including the LATITUDE study for the mHSPC health state (progression free), a time-trade-off study conducted by the company and NICE TA387: abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated[17].

AWTTC manipulated the model to include the commercial arrangement for abiraterone during COVID-19 and the Patient Access Scheme (PAS) discounts for the medicines included in the model that would be used later in the treatment pathway when patients progressed to mCRPC. When compared with ADT alone [confidential data removed].

The committee papers published by NICE for the assessment of abiraterone acetate for the treatment of newly diagnosed high risk metastatic hormone-naïve prostate cancer (ID945) included analyses of the cost-effectiveness of abiraterone acetate plus ADT compared with ADT alone[20].

A life time horizon was used to estimate the cost-effectiveness of abiraterone acetate plus ADT in men with newly diagnosed high-risk mHSPC compared to docetaxel plus ADT and ADT alone from an NHS perspective[20]. Patients eligible to receive ADT alone were considered chemo-ineligible; this is defined as patients with severe liver impairment, neuropathy or thrombocytopenia/neutropenia, poor Eastern Cooperative Oncology Group (ECOG) performance status, or very frail[20]. The clinical parameters and utility values for quality of life were derived from the LATITUDE study[20]. Adverse events were derived from the literature[20].

In the company's base case analysis for patients deemed chemo-ineligible at diagnosis, when compared to ADT alone, abiraterone acetate plus ADT was associated with an ICER between £14,899 and £19,120 per quality-adjusted life-year (QALY) gained using log-logistic and Weibull extrapolation of survival, respectively[20]. These ICERs incorporate the commercial access arrangement for abiraterone acetate, but not the available commercial arrangements for subsequent therapies in the model. In updated analyses matching NICE committee's preferences and accounting for the confidential commercial arrangement of subsequent therapies within the model, the resultant cost-effectiveness estimated compared with ADT alone was likely to exceed £30,000 per QALY gained[20].

Cost effectiveness issues

SMC noted that the survival estimates provided for the comparators were likely to underestimate survival outcomes anticipated in Scottish clinical practice due to higher anticipated use of post-progression therapies such as abiraterone than those observed within the key clinical trials. This is likely to be a similar position in Wales. However, SMC noted that the company's use of more conservative assumptions highlighted that this only had a moderate influence on the ICER.

The NICE cost-effectiveness evidence is for the use of abiraterone for the treatment of high-risk mHSPC in patients deemed chemo-ineligible. This group is dissimilar to the current population who would otherwise be fit for treatment with docetaxel. Additionally, the commercial agreement in Wales is different to the NICE commercial access arrangement. The applicability of these findings are therefore subject to significant uncertainty.

No published cost-effectiveness evidence was found for abiraterone for the treatment of low-risk metastatic, or locally advanced HSPC, and no cost-effectiveness evidence was found for the use of enzalutamide or apalutamide.

BUDGET IMPACT

Table 6 details the estimated cost of abiraterone acetate plus prednisolone, apalutamide and enzalutamide per patient in Wales. These costs are based on current commercial arrangements/list price and are exclusive of VAT[2,4,5,45]. Since the original assessment there has been an update to the commercial arrangements for the three medicines. Treatment with abiraterone acetate requires monitoring of serum transaminases, blood pressure, serum potassium and fluid retention[2]. [confidential data removed] [46,47]. As docetaxel is currently not recommended due to COVID-19 this cost has not been included in the budget impact.

Table 6. Estimated cost of 12 months treatment per patient in Wales with confidential commercial arrangements for abiraterone acetate, apalutamide and enzalutamide

	Abiraterone acetate (ZYTIGA®) + prednisolone	Apalutamide (Erleada®)*	Enzalutamide (Xtandi®)†
Net medicine acquisition costs	¶¶	¶¶	¶¶
Net monitoring costs	¶¶	NA	NA
Overall net cost per patient	¶¶	¶¶	¶¶

NA: not applicable
* Assumes 7 months treatment at list price and 5 months treatment at new commercial arrangement price.
† Assumes 4 months treatment at original commercial arrangement price and 8 months treatment at new lower commercial arrangement price.
See the relevant Summary of Product Characteristics for the licensed doses and MIMS for the list prices of the oral medicines[2,4,5,45]
¶¶ confidential figure removed

Patient numbers reported by clinicians estimate that 111 patients have received one of these medicines over a period of four months since the original One Wales decision was issued in April 2020. This has been extrapolated to 200 patients starting treatment within 12 months to account for a continued rise in patient numbers (but at a slower rate of progression). Clinicians also provided information about the market share of each medicine. Table 7 details the estimated budget impact in Wales for 12 months. Based on patient numbers reported by clinicians it is assumed that abiraterone acetate plus prednisolone has 50% market uptake and apalutamide and enzalutamide each have a 25% market uptake.

Table 7. Projected Budget Impact in Wales for 12 months with confidential commercial arrangements for abiraterone acetate, apalutamide and enzalutamide

	Abiraterone acetate (ZYTIGA®) + prednisolone	Apalutamide (Erleada®)	Enzalutamide (Xtandi®)	Total	Data Source
Number of patients receiving treatment	100*	50†	50§	200	Clinical experts
Total acquisition costs of oral medicine	¶¶	¶¶	¶¶	¶¶	MIMS[45]

* It is assumed that 75 patients would receive treatment for seven months and 100 patients would receive treatment for five months at the agreed commercial arrangement price
†It is assumed that 25 patients would receive treatment for seven months at the list price and that all 50 patients would receive treatment for the remaining five months at the agreed commercial arrangement price
§ It is assumed that 25 patients would receive treatment at the original commercial arrangement price for four months, 35 patients would receive treatment for the next three months at the new lower commercial arrangement price and all patients would receive treatment for the remaining five months at the lower commercial arrangement price
See the relevant Summary of Product Characteristics for the licensed doses[2,4,5,48]
¶¶ confidential figure removed

If we assume that the market share remains the same (50% abiraterone acetate, 25% apalutamide and 25% enzalutamide) and that 200 patients will start treatment during a 12 month period, the estimated cost is [confidential data removed] using the confidential commercial arrangement prices for the three medicines.

Budget impact issues

- The budget impact assumes that the commercial arrangement for apalutamide will be active from the 1st November 2020
- The budget impact has not considered the discontinuation of therapy and mortality rates, thus assuming that all patients respond (100% success rate) for up to one year.
- Adverse event rates have not been included in the budget impact.
- Clinical experts indicate that the oral medicines may be supplied through homecare for the licensed indications. This would be associated with an admin fee of £50 per pack of medicine (equal to 28 days). These costs have not been included in the budget impact analysis. Provision by homecare would not incur VAT costs.

Commercial agreement

Commercial agreements are available in NHS Wales for abiraterone acetate, enzalutamide and apalutamide offering treatments at a reduced price during the COVID-19 pandemic.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Some of the medicines included in this report are being used for indications that are outside of their current product licence and are therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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