Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2400

enzalutamide 40mg film-coated tablets (Xtandi®)

Astellas Pharma Ltd

14 January 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission under the orphan equivalent medicine process

enzalutamide (Xtandi®) is accepted for use within NHSScotland.

Indication under review: treatment of adults with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).

Enzalutamide improved radiographic progression-free survival compared with placebo and it improved overall survival compared with placebo and an older non-steroidal anti-androgen (NSAA) in adults with mHSPC who were receiving ADT.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).[1]

Dosing Information

160mg enzalutamide (four 40mg film-coated tablets swallowed whole with water) orally once daily. The film-coated tablets should not be cut, crushed or chewed. Dose adjustment to manage adverse events are detailed in the summary of product characteristics (SPC).
Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.
Treatment with enzalutamide should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer.[1]

Product availability date

14 May 2021
Enzalutamide in this indication meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Enzalutamide is a non-steroidal androgen receptor inhibitor that competitively inhibits androgen binding and stimulation of the receptor. It decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression.[1] SMC has previously issued advice for the use of enzalutamide in castration-resistant prostate cancer (SMC2195, SMC1066/15 and SMC911/13). This submission is for patients with hormone sensitive disease.

A double-blind phase III study (ARCHES) recruited adults with metastatic prostate cancer and an Eastern Co-operative Oncology Group (ECOG) performance status score of 0 to 1. They had not received pharmacotherapy, radiotherapy or surgery for metastatic prostate cancer except (a) up to three months (or six months if also receiving docetaxel) of ADT (LHRH analogue or orchidectomy with or without anti androgens), with no evidence of disease progression or rising prostate-specific antigen (PSA); (b) up to six cycles of docetaxel completed at least 2 months previously with no evidence of disease progression during or after it; (c) one course of palliative radiotherapy or surgery for symptoms completed at least 4 weeks previously; or (d) ADT as neoadjuvant/adjuvant therapy for less than 39 months, which was completed more than 9 months before randomisation. All patients maintained ADT (LHRH analogue or bilateral orchidectomy) during the study and were equally randomised to enzalutamide 160mg orally once daily or placebo until radiographic disease progression, unacceptable toxicity or initiation of new therapy for prostate cancer. Randomisation was stratified by prior docetaxel (none versus 1 to 5 cycles versus 6 cycles) and disease volume (high versus low).

The primary outcome of radiographic progression-free survival (rPFS), was defined as the time from randomisation to first evidence of radiographic disease progression or death from any cause

within 24 weeks of study drug discontinuation. Radiographic progression was assessed by independent central review (ICR) against pre-specified criteria, which included Response Evaluation in Solid Tumours (RECIST) version 1.1 for soft tissue disease or appearance of at least two new bone lesions on bone scan. This was analysed in the intention-to-treat (ITT) population, which comprised all randomised patients.[2,3]

At the cut-off for the primary analysis (14 October 2018) median follow-up was 14.4 months.[3] Enzalutamide compared with placebo significantly increased rPFS. A parallel testing strategy was used to test overall survival and the other five key secondary outcomes. These were analysed in the hierarchy as listed in Table 1 and were significantly different, except the last one, time to deterioration in urinary symptoms. At this cut-off, the interim analysis of overall survival was not significant but it was at the final analysis at 28 May 2021 cut-off. Results are detailed in Table 1 below.[2,4]

Table 1: Primary and key secondary outcomes of ARCHES study.[2,4]

	Enzalutamide (N=574)	**Placebo (N=576)**
Time to radiographic progression (14 October 2018)		
Events	89	198
Hazard ratio (95% confidence interval)	0.39 (0.30 to 0.50), p<0.001	
Median (months)	NR	19.4
12 months radiographic PFS	84%	64%
Overall survival interim analysis (14 October 2018)		
Deaths	39	45
Hazard ratio (95% confidence interval)	0.81 (0.53 to 1.25), p=0.34	
Overall survival final analysis (28 May 2021)*		
Deaths	154	202
Hazard ratio (95% confidence interval)	0.66 (0.53 to 0.81), p<0.001	
Median	NR	NR
36 months overall survival	78%	69%
Time to PSA progression (14 October 2018)		
Events	45	189
Hazard ratio (95% confidence interval)	0.19 (0.13 to 0.26), p<0.001	
Median	NR	NR
Time to new anti-neoplastic therapy (14 October 2018)		
Events	46	133
Hazard ratio (95% confidence interval)	0.28 (0.20 to 0.40), p<0.001	
Median (months)	30.2	NR
Time to undetectable PSA (in those with measurable PSA at baseline; 14 October 2018)		
Rate	348/511 (68%)	89/506 (18%)
Difference (95% confidence interval)	50% (45% to 56%), p<0.001	
Overall response rate ICR assessed (in patients with measurable disease at baseline)		
Overall response rate	147/177 (83%)	116/182 (64%)
Difference (95% confidence interval)	19% (10% to 28%), p<0.001	

Time to deterioration of urinary symptoms (14 October 2018)		
Events	184	201
Hazard ratio (95% confidence interval)	0.88 (0.72 to 1.08), p=0.22	
Median (months)	NR	16.8

Analyses conducted at 14 October 2018 cut-off, except final analysis of overall survival, conducted at 28 May 2021. * In final analysis of overall survival 180 patients from placebo group had crossed over to enzalutamide plus ADT. NR=not reported; PSA=prostate-specific antigen; ICR= independent central review; PFS = progression-free survival

Baseline health-related quality of life scores suggest patients were generally asymptomatic with good health-related quality of life, low symptom burden, and minimal functional limitations. Mean scores by visit indicated that high levels of health-related quality of life and low levels of pain at baseline were generally maintained during the study in both groups, with no clinically meaningful differences between the groups. However, median time to deterioration on EuroQol five dimension five level (EQ-5D-5L) visual analogue scale was delayed with enzalutamide versus placebo, 11.1 versus 8.4 months, with a hazard ratio (HR) of 0.80 (95% confidence interval [CI]: 0.67 to 0.94).[5]

An open-label phase III study (ENZAMET) recruited adults with mHSPC and ECOG performance status score of 0 to 2 who had commenced first-line ADT in the preceding 12 weeks (LHRH analogue or surgical castration). Randomisation was stratified by disease volume (high versus low), study site, concomitant anti-resorptive therapy, Adult Comorbidity Evaluation (ACE27) score (0 to 1 versus 2 to 3) and early planned docetaxel use. Patients were assigned equally to enzalutamide d160mg orally once daily or older oral non-steroidal anti-androgen (NSAA; bicalutamide 50mg once daily, nilutamide 150mg once daily or flutamide 250mg three times daily, with choice of drug at the investigator's discretion) until disease progression or unacceptable toxicity. Patients were allowed up to six cycles of concomitant docetaxel (75mg/m^2) if the decision of use was made prior to randomisation and no more than two cycles had been given before randomisation. The primary outcome was OS, defined as the time from randomisation to death from any cause and this was assessed in the ITT population, which comprised all randomised patients.[2,6]

At the first interim analysis of overall survival, data cut off 28 February 2019, median follow-up was 34 months. Enzalutamide, compared with older NSAA, significantly increased overall survival. Similar results were observed in the subgroup that did not receive concomitant docetaxel (which can be considered similar to the ARCHES population and was used in the economic analyses). Secondary outcomes prostate specific antigen progression-free survival (PSA-PFS) and rPFS were improved with enzalutamide. These results are detailed in Table 2 below.[2,6]

Table 2: Primary and secondary outcomes of ENZAMET study in ITT population and without concomitant docetaxel subgroups.[2,6]

	Intention-to-treat		Without docetaxel	
	Enzalutamide (N=563)	**NSAA (N=562)**	**Enzalutamide (N=309)**	**NSAA (N=313)**
Overall survival				
Deaths	102	143	50	88
HR (95% CI)	0.67 (0.52 to 0.86)		0.53 (0.37 to 0.74)	
Median	NR	NR	NR	NR
3-year OS	80%	72%	83%	70%

Clinical progression free survival				
Events	167	320	76	174
HR (95% CI)	0.40 (0.33 to 0.49)		0.34 (0.26 to 0.44)	
3-year PFS	68%	41%		
PSA progression free survival				
Events	174	333	-	-
HR (95% CI)	0.39 (0.33 to 0.47)		0.34 (0.26 to 0.44)	
3-year PFS	67%	37%	-	-

Control = non-steroidal anti-androgen; CI = confidence interval; HR = hazard ratio; PFS = progression free survival; PSA = prostate specific antigen; NR = not reached; NSAA = older non-steroidal anti-androgen (bicalutamide 50mg once daily, nilutamide 150mg once daily or flutamide 250mg three times daily).

Health related quality of life was assessed using EORTC PR25 and QLQ-C30 questionnaires. For the latter, enzalutamide compared with NSAA was associated with greater impairments from week 4 to 156 in fatigue, least square mean difference (LSMD) 5.0 (95% CI: 3.3 to 6.7), cognitive function, LSMD of 3.9 (95% CI: 2.4 to 5.4), and physical function, LSMD of 2.5 (95% CI: 1.2 to 3.8). However, there were higher rates in the enzalutamide group of QLQ-C30 deterioration-free survival at 3 years for general health and quality of life (32% versus 18%), cognitive function (33% versus 21%), and physical function (31% versus 22%).[7]

Bayesian network meta-analyses (NMA) were presented, which compared enzalutamide-ADT with ADT alone, NSAA-ADT, docetaxel-ADT and abiraterone-ADT for a variety of outcomes, with results for OS and rPFS for the latter two comparators applied to the economic analysis. The analyses were conducted in a variety of populations, including a scenario analysis in newly-diagnosed high-risk mHSPC. This may be relevant for the comparison with abiraterone-ADT, as it is licensed for use in this subgroup of patients only. The company consider the results confidential. They conclude that the NMAs generally favoured enzalutamide treatment, however, the wide credible intervals around the hazard ratios mean this conclusion is uncertain.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review concluded that overall enzalutamide was generally well tolerated in patients with mHSPC and adverse events were in line with its established safety profile.[2]

In the ARCHES study at data cut-off 14 October 2018, adverse events were reported by 85% (487/572) and 86% (493/574) of patients in the enzalutamide and placebo groups, respectively and these were treatment-related in 53% and 47% of patients. Serious adverse events occurred in 18% and 20% of patients and were treatment-related in 3.8% and 2.8% of patients, respectively. Adverse events were the primary reason for discontinuation of study treatment in 4.9% and 3.7% of patients in the respective groups.[2,3] In the ENZAMET study at data cut-off 28 February 2019, within the enzalutamide and older NSAA groups 97% (545/563) and 93% (521/558) of patients, respectively, had an adverse event. Serious adverse events were reported by 42% and 34% of

patients and these were treatment-related in 3.0% and 0.4% of patients, respectively. Serious adverse events led to study treatment discontinuation in 11% and 9% of patients, respectively.[2,6]

In the ARCHES study within the enzalutamide and placebo groups the most frequently reported adverse events were hot flushes (27% and 22%), fatigue (20% and 15%), arthralgia (12% and 11%), back pain (7.5% and 11%) and hypertension (8.0% and 5.6%).[2] In the ENZAMET study within the enzalutamide and older NSAA groups the most frequently reported adverse events ≥grade 3 severity were: hypertension (7.6% and 4.5%), febrile neutropenia (6.6% and 5.7%), decreased neutrophil count (5.5% and 2.9%), fatigue (5.5% and 0.7%) and syncope (3.6% and 1.1%).[6]

Summary of clinical effectiveness issues

Prostate cancer is dependent on androgen for growth and survival early in the disease, therefore ADT is a primary form of therapy and comprises surgical castration by bilateral orchidectomy or medical castration with LHRH analogues. ADT can be combined with other systemic treatments to improve survival, including docetaxel (with or without prednisone or prednisolone) and abiraterone acetate (with prednisone or prednisolone),[2] which is indicated only for newly-diagnosed high-risk mHSPC.[8] In January 2020, SMC issued advice (SMC2215) that abiraterone is accepted for use within NHSScotland in this indication. SMC clinical experts have advised that abiraterone may also be used off-label in some patients with low-risk disease. During the pandemic, the COVID-19 National Cancer Medicines Advisory Group (NCMAG) issued interim advice supporting off-label use of abiraterone plus prednisolone for the treatment of newly diagnosed low risk mHSPC in adults in combination with ADT, in patients who would otherwise receive docetaxel.[9] Enzalutamide is a NSAA and other medicines in this class are licensed for the treatment of prostate cancer, including bicalutamide, flutamide and apalutamide. In the absence of a submission from the marketing authorisation holder SMC issued advice (SMC2323) in January 2021 that apalutamide-ADT is not recommended for use within NHS Scotland for the treatment of mHSPC. SMC has not issued advice on the older NSAA, bicalutamide and flutamide and clinical experts consulted by SMC have advised that these medicines are not commonly used in first-line treatment of mHSPC. They note that docetaxel-ADT and abiraterone-ADT are the main treatments.

Enzalutamide is a newer NSAA that is licensed for treatment of mHSPC in combination with ADT.[1] In this indication it meets SMC orphan equivalent criteria.

In the ARCHES study, enzalutamide-ADT compared with placebo-ADT significantly improved rPFS (HR of 0.39) at the cut-off for the primary analysis of this outcome and overall survival (HR of 0.66) in an updated analysis in 2020. In the ENZAMET STUDY, enzalutamide-ADT compared with an older NSAA-ADT improved overall survival and clinical PFS in the total study population (HR 0.67 and 0.40, respectively) and in the subgroup that did not receive concomitant docetaxel (HR 0.53 and 0.34, respectively). In both studies, medians for these outcomes could not be estimated in the enzalutamide groups.[2,3,6]

In the ARCHES study, after the primary analysis of rPFS the Data Safety Monitoring Board (DSMB) recommended that patients treated with placebo-ADT crossed over to enzalutamide-ADT. In the subsequent final analysis of overall survival 180 patients from the placebo group had crossed over

to receive enzalutamide-ADT. This, and imbalances in other post-progression anti-cancer medicines, may impact analyses of overall survival.[2-4] The ENZAMET study was terminated at an interim analysis when 52% of the pre-specified 470 deaths for the analysis of overall survival had occurred. It is possible that this early analysis may have over-estimated the eventual treatment benefit.[6] Also, there were differences across the study in post-progression treatments, with substantial proportions of patients in the NSAA-ADT group subsequently receiving enzalutamide (25% versus 0 in the enzalutamide group) and abiraterone (20% versus 8.2% in the respective groups). This may confound the assessment of overall survival, although it may be representative of practice.[2,6]

The ENZAMET study was open-label, which may affect the assessment of subjective outcomes such as safety and quality of life. Also, there was no control for multiplicity testing across the secondary outcomes.[2,6]

The ARCHES study was placebo-controlled and the ENZAMET study compared enzalutamide-ADT with older NSAA-ADTs (bicalutamide, nilutamide, flutamide) that are not commonly used in practice. There are no direct comparative data with the relevant comparators in Scottish practice: docetaxel-ADT and, in patients with newly-diagnosed high-risk disease, abiraterone-ADT.

There were limitations with the NMA that provided an indirect comparisons of enzalutamide-ADT versus docetaxel-ADT and abiraterone-ADT. There were differences across the studies in baseline demographic and disease characteristics, including previous treatments for prostate cancer and variation in methods of assessing PFS. The substantial differences in data maturity was a key limitation, with data for enzalutamide-ADT very immature relative to the comparators. It was not possible to assess heterogeneity across most of the studies of older NSAA-ADT due to limited available data. The main study, which supports the marketing authorisation of abiraterone was not included in the NMA for the total study population, but was included in a scenario analysis in high-risk disease. Across the studies in the NMA there was variation in sample size, with some very small studies included and some input data were from subgroup analysis. Statistical heterogeneity was noted for some groups of studies and there was inconsistency in the treatment effect by direct and indirect methods. The indirect comparison did not assess safety or quality of life outcomes. Overall, there is uncertainty in the results of the indirect comparison.

Clinical experts consulted by SMC consider that enzalutamide-ADT in the treatment of mHPSC is a therapeutic advance as it provides an additional therapeutic option, which may be particularly useful for patients unable to take alternatives treatment options, docetaxel-ADT or abiraterone-ADT, due to age or conditions that contraindicate their use. They consider that enzalutamide-ADT would be used in practice as an alternative to these.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of enzalutamide, as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metastatic hormone-sensitive prostate cancer is incurable and aims of treatment are to prevent disease progression and prolong overall survival. Fear of progression can cause anxiety and patients may have physical symptoms related to the site(s) of metastases and adverse events associated with ADT. Some patients have difficulties with mobility and activities of daily living; they may not be able to continue to work, socialise, fulfil family caring commitments and make plans. Altogether, the prognosis, symptoms and adverse effects of ADT have a negative psychological impact on the patient, their family and friends.

- To prolong overall survival the optimum available options are docetaxel-ADT and abiraterone-ADT, which is licensed for high-risk patients but has been available for use on a temporary basis (during the pandemic) in low-risk patients. Docetaxel is a chemotherapy that is associated with substantial side effects and risks. Some patients cannot receive either docetaxel or abiraterone due to comorbidities or concomitant medicines. There is an unmet need for additional treatment options that prolong progression-free and overall survival at this stage of disease.

- Enzalutamide provides an additional treatment option that can prolong progression-free and overall survival similar to docetaxel and abiraterone. It may be useful for patients who cannot receive these for clinical reasons and in the future when abiraterone may not be available for those with low-risk disease. Patients are aware of the overall survival benefits with enzalutamide and accessing this treatment (if they are not suitable for docetaxel or abiraterone) would provide reassurance that they are receiving the optimum treatment for their condition. This can have a substantial psychological benefit. Some patients may derive hope that prolonged progression-free and overall survival with enzalutamide may provide a bridge to a time when other new medicines become available.

- Compared with docetaxel (which is given intravenously every three weeks for six cycles and requires at least two visits to hospital each cycle), enzalutamide administration is more convenient and easier, as it is taken orally each day and the medicine can be delivered directly to the patient's home. Enzalutamide is considered by patients to have milder adverse effects than docetaxel.

- Compared with abiraterone, enzalutamide is associated with a less monitoring and lower frequency of blood tests. In contrast to abiraterone, it does not require corticosteroids to be co-administered and it does not need to be taken on an empty stomach.

Additional Patient and Carer Involvement

We received patient group submissions from Prostate Cancer UK, Prostate Scotland and Tackle Prostate Cancer. All three organisations are registered charities. Prostate Cancer UK has received less than 1% pharmaceutical company funding in the past two years, including from the submitting company. Prostate Scotland has not received any pharmaceutical company funding in the past two years. Tackle Prostate Cancer has received 32% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three organisations

participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company presented a cost-utility analysis assessing enzalutamide as an add-on treatment to ADT in adults with mHSPC. Comparisons were provided versus abiraterone plus ADT, docetaxel plus ADT, and ADT alone. SMC clinical experts confirmed that these are the relevant comparators within NHSScotland, and noted that interim advice from COVID-19 NCMAG, which allows for greater flexibility in the management of cancer during the pandemic, currently supports use of abiraterone off-label in patients with newly diagnosed low risk mHSPC who would otherwise receive docetaxel.

The economic model submittted by the company was a cohort-based semi-Markov model; this comprised six health states in total: 2 mHSPC health states (on treatment and off treatment), 3 mCRPC health states (pre-chemotherapy, chemotherapy, and post-chemotherapy), and the absorbing state of death. Patients entered the model in with mHSPC and could transition to a more advanced disease stage, or the absorbing state of death, at any time.

Relative efficacy sources used in the economic evaluation were a combination of data extrapolated directly from key clinical studies and estimates derived from the Bayesian NMA conducted by the company; specifically, the ARCHES and ENZAMET studies for enzalutamide were used to extrapolate time to discontinuation, radiographic progression free survival and overall survival for enzalutamide and ADT over the model time horizon,[4, 7] and the Bayesian NMA was used to inform the relative efficacy of the other comparators for each of these outcomes via the applicable of treatment-specific hazard ratios.

In terms of utilities, health-related quality-of-life data were collected at various points during the ARCHES study using the EQ-5D-5L questionnaire.[5] These data were subsequently 'cross walked' to a comparable EQ-5D-3L score using the algorithm developed by van Hout et al prior to being converted into health state utility values via the application of a UK tariff.[10] Disutility associated with adverse events (including skeletal related events) was also included.

Medicines acquisition costs were included for enzalutamide and comparators, and the dose and duration of each treatment was assumed to be consistent with either the key direct evidence or relevant summary of product characteristics. Other non-medicines healthcare costs estimated included disease and adverse event management resource use. The quantities of non-medicines resource use included in the analysis were based on prior NICE technology appraisals for similar indications, supplemented with expert input.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of enzalutamide. A PAS discount is also in place for abiraterone and was included in the results used for decision-making by SMC by using estimates of comparator PAS prices. SMC is unable to present the results provided by the company which used

an estimate of the PAS price for abiraterone due to commercial confidentiality and competition law issues.

The main economic results at list prices for all medicines are shown in table 3. The majority of the incremental QALYs estimated for enzalutamide appear to stem from an assumed increase in life expectancy, with a smaller proportion due to increased time spent progression free.

Table 3: Main economic results at list prices

	Abiraterone + ADT	Docetaxel + ADT	ADT
ICER (£ per QALY gain) enzalutamide-ADT versus comparator	£16,338	£69,131	£58,431

Abbreviations: ADT, androgen deprivation therapy; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

A number of individual and combined scenario analyses were requested from the company to investigate the impact of changing key structural assumptions on results. The results of these analyses are shown in Table 4 and indicate that the economic evaluation is particularly sensitive to alternative assumptions regarding the extent or existence of improvements in progression- free survival and overall survival associated with enzalutamide.

Table 4: Sensitivity analysis results at list prices

Scenario	Description	ICER (£ per QALY)	
		Abiraterone + ADT	Docetaxel + ADT
0	Base case	£16,338	£69,131
1	No difference in radiographic progression free survival	£25,980	Not applicable
2	No difference in overall survival	£24,756	£331,339
3	Scenarios 1 and 2 combined	£5,178,037	Not applicable
4	Time horizon: 10 years	£18,780	£114,338
5	Time horizon: 20 years	£16,648	£72,513

Abbreviations: ADT, androgen-deprivation therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years

The following limitations associated with the economic evaluation were noted:

- Base case overall survival extrapolations selected by the company estimated life year gains for enzalutamide versus abiraterone and docetaxel, despite the Bayesian NMA results not providing evidence of a difference in overall survival between these treatments. Table 4 scenario 2 was provided as sensitivity analysis to show the impact of removing the survival advantage. The company also provided a cost-minimisation analysis versus abiraterone-ADT,

which was helpful for the Committee to see (results cannot be presented due to commercial in confidence issues).

- The company's decision to consider the full mHSPC population means that the clinical data underpinning the economic model are calculated using full population data, masking any differences in treatment effectiveness by risk status that might exist compared to abiraterone.
- The semi-Markov model type used implicitly assumes that the probability of death is independent of a patient's disease status (stable or progressed) and their current line of treatment; however, this is a relatively common modelling complication in oncology submissions. The impact on results of using separate mortality data by disease status and treatment line is not clear.

The Committee considered the benefits of enzalutamide in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as enzalutamide is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted enzalutamide for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

In May 2019 NICE published clinical guideline number 131, Prostate cancer: diagnosis and management. This recommends offering docetaxel chemotherapy to people with newly diagnosed metastatic prostate cancer who do not have significant comorbidities as follows: start treatment within 12 weeks of starting ADT and use six 3-weekly cycles at a dose of 75 mg/m^2 (with or without daily prednisolone). Do not offer combined androgen blockade as a first-line treatment for people with metastatic prostate cancer. For people with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia with the aim of retaining sexual function, offer anti-androgen monotherapy with bicalutamide (150 mg). Begin ADT and stop bicalutamide treatment in people with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function.[11]

In June 2020, the European Society of Medical Oncology (ESMO) updated their clinical guideline on prostate cancer. This notes that ADT is recommended as first-line treatment of metastatic hormone naïve prostate cancer (mHNPC) in combination with abiraterone/prednisone or apalutamide or docetaxel or enzalutamide. Radiotherapy to the primary tumour combined with the systemic treatment is recommended for patients with low volume mHNPC. ADT alone is recommended as first-line systemic treatment of mHNPC in people who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel. For people starting on ADT, management to prevent cancer treatment-induced bone loss is recommended.[12]

In 2021, the European Association of Urology (EAU) updated their guideline on prostate cancer. In the first-line treatment of metastatic disease this includes the following recommendations:

- Offer immediate ADT to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease in symptomatic patients.
- Discuss combination therapy including ADT plus systemic therapy with all patients.
- Do not offer ADT monotherapy to patients whose first presentation is metastatic disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy and are willing to accept the increased risk of side effects.
- Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is metastatic disease and who are fit for docetaxel.
- Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is metastatic disease and who are fit enough for the regimen.[13]

Additional information: comparators

Docetaxel-ADT and abiraterone-ADT.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Enzalutamide	160mg orally once daily	35,551

Costs from BNF online on 16.9.21. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 281 patients eligible for treatment with enzalutamide in year 1 and 283 patients in year 5, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

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2. European Medicines Agency (EMA) European Public Assessment Report. Enzalutamide 40mg and 80mg film-coated tablet (Xtandi®). EMA/202601/2021, 25 February 2021. www.ema.europa.eu

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This assessment is based on data submitted by the applicant company up to and including 12 November 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.