Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2195

enzalutamide 40mg soft capsules (Xtandi®)

Astellas Pharma Ltd

06 September 2019

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 considered under the orphan equivalent process

enzalutamide (Xtandi®) is not recommended for use within NHSScotland.

Indication under review: The treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).

In a phase III study in men with high-risk non-metastatic CRPC enzalutamide was superior to placebo for metastasis-free survival. High-risk was defined as prostate specific antigen (PSA) doubling time ≤10 months and PSA ≥2 nanograms/mL. Both groups received on-going androgen-deprivation therapy or had undergone bilateral orchiectomy. Overall survival data are immature.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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

Chairman
Scottish Medicines Consortium

Indication

The treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC). High risk is defined as prostate specific antigen (PSA) doubling time (PSADT) ≤10 months and PSA ≥2 nanograms/mL.[1]

Dosing Information

The recommended dose is 160mg enzalutamide (four 40mg soft capsules or 40 mg film-coated tablets or two 80 mg film-coated tablets) as a single oral daily dose. Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

If a patient misses taking enzalutamide at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120mg or 80mg) if warranted.

Treatment with enzalutamide should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer.[1]

Product availability date

23 October 2018

Enzalutamide meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Enzalutamide is an androgen receptor inhibitor that blocks several stages in the androgen receptor signalling pathway to decrease the growth of prostate cancer cells and it can induce cancer cell death and tumour regression.[2, 3] Enzalutamide has previously been accepted by SMC for the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (SMC 1066/15) and adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy (SMC 911/13).

Key evidence for this indication is from PROSPER, a double-blind, randomised, placebo-controlled, phase III study. PROSPER recruited men with asymptomatic, high-risk, non-metastatic, pathologically confirmed CRPC with rising PSA. Patients were required to have a PSA doubling time ≤10 months and PSA level ≥2 nanograms/mL. Recruited patients had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 and were receiving on-going androgen-deprivation therapy with a gonadotropin releasing hormone agonist or antagonist or had undergone bilateral orchiectomy.[1-3] Patients receiving bisphosphonates or denosumab must

have had a stable dose for at least 4 weeks before randomisation and continued treatment until metastatic disease progression was confirmed by central radiographic review.[3]

Patients were randomised in a 2:1 ratio to receive enzalutamide 160mg oral daily (n=933) or placebo (n=468). Patients continued to receive androgen deprivation therapy if they had not had a prior bilateral orchiectomy. Patients were stratified according to the PSA doubling time (<6 months or ≥6 months) and previous or current use of a bone-targeting agent (yes or no). Treatment continued until radiographic progression, assessed by central independent blinded radiographic review. Discontinuation based on clinical progression or toxic effects was allowed but stopping solely due to an increase in PSA level was discouraged.[2, 3]

The primary outcome, assessed in all randomised patients, was metastasis-free survival. This was defined as the time from randomisation to radiographic progression (assessed by central independent blinded radiographic review) or as the time to death from any cause during the period from randomisation to 112 days after the discontinuation of study treatment without evidence of radiographic progression, whichever occurred first.[2, 3] At the time of the primary analysis 23% (219/933) of patients in the enzalutamide group and 49% (228/468) in the placebo group had a primary outcome event. The median metastasis-free survival was significantly longer in the enzalutamide group compared with the placebo group. [2, 3]

The key secondary outcomes were time to PSA progression (defined as the time to a 25% or greater increase in PSA and an absolute PSA increase of 2 ng/mL), time to the first use of a subsequent antineoplastic therapy and overall survival.[2, 3] Superiority of enzalutamide over placebo was demonstrated for time to PSA progression and time to the first use of a subsequent antineoplastic therapy.[2] In the enzalutamide group, 15% of patients discontinued the trial regimen and received subsequent antineoplastic therapy compared with 48% of the placebo group.[3] Neither of the interim analyses for overall survival provided evidence of a statistical difference between enzalutamide and placebo. [2-4] Further details are included in Table 1.

Table 1: Primary and key secondary outcomes from PROSPER. [2-4]

	Enzalutamide (n=933)	Placebo (n=468)	Hazard ratio (95% confidence interval)
Median metastasis-free survival (months)	36.6	14.7	0.29 (0.24 to 0.35) p<0.001
Median time to PSA progression (months)	37.2	3.9	0.07 (0.05 to 0.08) p<0.001
Median time to the first use of a subsequent antineoplastic therapy (months)	39.6	17.7	0.21 (0.17 to 0.26) p<0.001

Deaths at the first interim analysis for overall survival (165 patients had died [30% of the deaths specified for the final overall survival analysis])	11%	13%	0.80 (0.58 to 1.09) p=0.150
Deaths at the second interim analysis for overall survival (288 patients had died [48% of the deaths specified for the final overall survival analysis])	20%	22%	0.83 (0.65 to 1.06) p=0.134

There were no differences identified between groups for time to degradation of the Functional Assessment of Cancer Therapy - Prostate (FACT-P) global score. The median time to degradation of FACT-P was 11.1 months in both groups. The proportions of patients with score degradation in the enzalutamide and placebo groups were 54% and 51% respectively. [2, 3]

STRIVE was a randomised, double-blind phase II study in patients with non-metastatic or metastatic CRPC. Patients were randomised equally to receive enzalutamide 160mg daily (n=198) or bicalutamide 50mg daily (n=198). Patients continued to receive androgen deprivation therapy if they had not had a prior bilateral orchiectomy.[2, 5] The primary outcome was investigator assessed progression-free survival (PFS). In the subgroup of patients with non-metastatic disease (enzalutamide n=70, bicalutamide n=69), median PFS was not reached in the enzalutamide group and was 8.6 months in the bicalutamide group, hazard ratio (HR) 0.24 (95% CI: 0.14 to 0.42, p<0.001).[2, 5]

Summary of evidence on comparative safety

The European Medicines Agency (EMA) concluded that enzalutamide appears to be well tolerated and that the safety profile in patients with non-metastatic CRPC seems to be similar to that reported in previous clinical studies, with no major safety concerns.[2]

In the key PROSPER study, adverse events were reported by 87% of the enzalutamide group and 77% of the placebo group. These were considered serious in 24% and 18% of the enzalutamide and placebo groups respectively. Adverse events leading to discontinuation of treatment occurred in 9.4% and 6.0% and leading to death in 3.4% and 0.6% of the groups. The most common adverse events were fatigue (33% and 14%), hot flush (13% and 7.7%), nausea (11% and 8.6%), diarrhoea (10% in both groups), hypertension (12% and 5.1%), fall (11% and 4.1%), dizziness (10% and 4.3%), and decreased appetite (10% and 3.9%). Major cardiovascular events were reported in 5.2% of patients in the enzalutamide group and 2.8% in the placebo group. Less than 1% of patients experienced a convulsion.[3]

Summary of clinical effectiveness issues

CRPC is defined as prostate cancer that progresses despite castrate levels of testosterone while on treatment with a luteinising hormone-releasing hormone (LHRH) analogue (for example leuprorelin) or following bilateral orchiectomy. PSA doubling time is considered to be a useful prognostic factor in identifying patients with non-metastatic CRPC at a high risk of developing metastases. Treatments are currently very limited for patients with high-risk non-metastatic CRPC and watchful waiting is an option.[2] Androgen deprivation therapy can be continued and bicalutamide or dexamethasone may be used out with their licence. Apalutamide, another androgen receptor inhibitor, has recently received marketing authorisation for men with non-metastatic CRPC who are at high risk of developing metastatic disease. After progression to metastatic CRPC, the majority of patients are likely to receive enzalutamide or abiraterone.

Clinical experts consulted by SMC considered that enzalutamide fills an unmet need in this therapeutic area as there are very limited treatment options. Enzalutamide meets SMC orphan equivalent criteria for this indication.

In the key PROSPER study, metastasis-free survival was significantly longer in patients in the enzalutamide group compared with the placebo group. The EMA considered that delaying onset of metastasis is valuable from a patient and clinical point of view. Prolonged metastasis-free survival may delay symptoms and deteriorating quality of life, reduce patients' anxiety about prognosis and delay the need for subsequent treatments for metastatic disease. Time to PSA progression and time to first use of new antineoplastic treatment were also longer in the enzalutamide group. The EMA also noted that delaying the onset of metastasis has not been linked with an increase in overall survival.[2] Overall survival data from the PROSPER study are immature and it is unclear whether treatment with enzalutamide in this patient group improves survival.[2, 3]

It is not possible to determine from the PROSPER study whether enzalutamide pre- or post-progression will give the most benefit to patients. The EMA noted that PFS2 (time to second objective disease progression) was not included as an outcome and this may have helped to address this concern. It is unclear how prescribing enzalutamide in non-metastatic CRPC would influence later therapy.

Patients with significant cardiovascular disease were excluded from the PROSPER study and enzalutamide was associated with a higher rate of cardiovascular events than the control group. This may be relevant in the Scottish population. Patients in the control group did not receive enzalutamide after progression which may not reflect current practice. Treatments received after progression can confound survival outcome results. In addition, the proportion of patients who received post-progression treatment in the PROSPER study may be lower than clinical practice in Scotland.

Enzalutamide in addition to androgen deprivation was compared with placebo plus androgen deprivation in the key study which is a relevant comparator. Treatment options are limited in this patient group and watchful waiting with continued androgen deprivation therapy is considered an option. Available evidence from the STRIVE study provides efficacy data for enzalutamide versus bicalutamide although there is a lack of robust evidence in this patient group and bicalutamide may be a less relevant comparator.

Clinical experts consulted by SMC considered that enzalutamide is a therapeutic advancement due to significantly improving metastasis-free survival and also noted that the overall survival data are immature. There may be service implications associated with the introduction of enzalutamide due to monitoring requirements.

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:

- Although prostate cancer is a common cancer in men, the number of patients with high-risk non-metastatic CRPC is very small. This is an incurable condition that will progress to metastatic disease. The impact is mainly psychological at this stage and patients may experience anxiety about a rising PSA.

- There are currently no other medicines licensed for this indication. Patients are usually monitored for the development of metastases before they receive further treatment.

- Although no improvement in overall survival was identified for patients receiving enzalutamide, PACE patient group participants advised that patients and their families value a delay in disease progression.

- Enzalutamide is already used in the metastatic setting. PACE clinicians stated that if patients received enzalutamide for high-risk non-metastatic CRPC they would not be able to receive this treatment for metastatic disease. PACE participants considered that there is uncertainty about which patient population would benefit most from enzalutamide.

- The availability of enzalutamide for high-risk non-metastatic CRPC would allow patients to choose whether they want to receive treatment at this point. It may be of benefit to patients who have anxiety about their condition or the small number of patients who are experiencing local symptoms.

- Enzalutamide is taken orally but patients would be required to attend additional clinic appointments and it may be associated with side effects, for example fatigue and cognitive impairment.

Additional Patient and Carer Involvement

We received patient group submissions from the Edinburgh and Lothian Prostate Cancer Support Group, Prostate Cancer UK, Prostate Scotland and Tackle Prostate Cancer. All four organisations are registered charities. In the past two years, Prostate Cancer UK has received less than 0.15% pharmaceutical company funding, with none from the submitting company. Tackle Prostate Cancer has received 60% pharmaceutical company funding in the past two years, including from the submitting company. Edinburgh and Lothian Prostate Cancer Support Group and Prostate Scotland have not received any pharmaceutical company funding in the past two years. Representatives from all four 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 submitting company presented a cost-utility analysis evaluating the use of enzalutamide for the treatment of adult men with high-risk (PSA doubling time ≤10 months and PSA ≥2 ng/mL) non-metastatic castration-resistant prostate cancer. Enzalutamide was evaluated as an add-on treatment to androgen-deprivation therapy (ADT), compared to androgen-deprivation therapy alone.

The economic model used a semi-Markov model structure. This comprised five health states in total: one non-metastatic health state (nmCRPC), three metastatic (PD1: progressed disease 1 [pre-chemo], PD2: progressed disease 2 [chemo], PD3: progressed disease 3 [post-chemo]) and an absorbing state of death. Patients entered the model in nmCRPC and could transition to a more advanced disease stage, or die at any time. The majority of transition probabilities were derived from the PROSPER study, with the exception of movement from PD1-3 which was based on expert opinion. Although overall survival data were available from the PROSPER study, the company conducted a post-hoc analysis to convert these into pre-progression survival (PrePS) and post-progression survival (PPS). However, an alternative scenario was provided where a single overall survival (OS) curve was applied, resulting in a broad range of projections of long-term survival. A 20 year time horizon was applied.

Health state utility values were collected from the PROSPER study and other relevant clinical trials using EQ-5D questionnaire, and valued using either the -3L UK tariff or crosswalk algorithm, as appropriate. Utility estimates were derived from relevant clinical trials (nmCRPC: 0.85, PD1: 0.81, PD2: 0.80, PD3: 0.69, end-of-life: 0.59).

The model included the following categories of healthcare resources: medicines acquisition, concomitant medications, adverse event and skeletal-related events (SREs), end-of-life care, imaging and routine management. The dose of enzalutamide and ADT included in the nmCRPC state were assumed to be according to licence and did not account for relative dose intensity. Treatment duration was obtained from the PROSPER clinical study. The distribution of post-progression treatments, and durations of treatment, was estimated based on the input of a single clinical expert interviewed by the company. Rates of adverse events and SREs was estimated

based on rates reported in relevant clinical studies. Sources for assigning costs to the different resource components were generally appropriate and relevant to NHS Scotland.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Abiraterone is used as a subsequent therapy in the comparator arm of the model. A PAS discount is in place for abiraterone and this was included in the results used for decision-making by SMC by using estimates of the comparator PAS price. The base case results and key sensitivity analyses at list price are presented in the tables below.

The results presented do not take account of the PAS for abiraterone or the PAS for enzalutamide but these were considered in the results used for decision-making at SMC. 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.

Table 1: Base-case cost-effectiveness results (list price)

Outcome	**Enzalutamide**	**ADT**
Total costs	£170,131	£76,435
Total Quality adjusted life years (QALYs)	4.17	3.18
Incremental cost –effectiveness ratio (ICER)(incremental cost/QALY gained)		£94,502

The company conducted a range of sensitivity analyses, including one-way deterministic analyses varied across 95% confidence intervals, probabilistic sensitivity analyses, and a number of scenario analyses.

The model was relatively stable to application of alternative utilities, incorporation of enzalutamide wastage and alternative first-line treatment distributions. The choice of alternative distributions for PrePS did not overly affect the ICER (although this structural assumption introduced some uncertainty). The key uncertainties were associated with the use of a single overall survival curve, which potentially represents the more appropriate approach to modelling survival, and the modelling of subsequent treatments (Table 2).

Table 2: Key scenario analyses (list price)

Scenario number	**Description**	**ICER (£/QALY)**
1	Use of single OS curve: Weibull (company selected)	£136,797
2	Use of single OS curve: log-normal	£76,875
3	Use of single OS curve: gompertz	£270,369
4	Removal of subsequent metastatic health states (PD2 and PD3)	£68,858

ICER: incremental cost-effectiveness ratio

The methods used in the base case analysis were largely appropriate. However, the main weaknesses with this analysis are ultimately associated with the approach to modelling survival, with the majority of incremental QALYs gained after 5 years in the model:

- A non-standard approach has been applied which separates pre- and post-mCRPC survival on the assumption of a significant overall survival benefit, despite the absence within the ITT population. The reliance on time to treatment discontinuation as a surrogate for progression creates uncertainty in the classification of mortality events as pre- or post-metastatic progression: the use of a single overall survival curve removes this uncertainty. As shown in table 6, there is variability in the ICER when taking this approach.
- The extrapolation of survival benefit results in a significant improvement in projected overall survival for enzalutamide. The available overall survival data are immature, and reduced predictions in incremental QALY gain result in higher ICERs (Scenario 3).
- The immature overall survival data are derived from the PROSPER study, where fewer placebo patients received enzalutamide and abiraterone than expected in current clinical practice. Therefore, the analysis included the costs of these post-progression treatments without fully incorporating the potential survival benefits for placebo patients.
- The model was sensitive to changes in the assumed treatment pathway for mCRPC, which were based on estimates from a clinical expert. However, Scenario 4 represents an arbitrary change, therefore is potentially an upper estimate of the influence of changes in this assumption.

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 was unable to accept enzalutamide for use in NHSScotland.

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

Additional information: guidelines and protocols

The European Association of Urology published an updated guideline on prostate cancer in 2019. The guidance makes the following recommendation for non-metastatic castrate-resistant disease: Offer apalutamide or enzalutamide to patients with non-metastatic CRPC and a high risk of developing metastasis (PSADT <10 months) to prolong time to metastases.[6]

The National Institute for Health and Care Excellence (NICE) published Prostate cancer: diagnosis and management (NG131) in May 2019. The guidance does not make any specific recommendations on the treatment of patients with high-risk non-metastatic CRPC.[7]

Additional information: comparators

Continued androgen deprivation, watchful waiting, potentially bicalutamide (off-label) in some patients.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
enzalutamide	**160mg orally daily**	**35,551**
Bicalutamide*	150mg orally daily	111

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 03 June 2019. *off-label use. Costs do not take any patient access schemes into consideration.*

Additional information: budget impact

The submitting company estimated there would be 73-74 patients eligible for treatment with enzalutamide each year to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the PAS budget impact estimates due to commercial in confidence issues.

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

References

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2. European Medicines Agency. (EMA) European Public Assessment Report. Enzalutamide (Xtandi®) 20/09/2018, EMEA H-C-002639-II-0039-G. www.ema.europa.eu.
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4. Medivation Pfizer. Clinical Study Report - PROSPER: a multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in patients with nonmetastatic castration-resistant prostate cancer. 8 December 2017.
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6. Mottet N, van den Bergh RCN, Briers E, et al. European Association of Urology prostate cancer guideline, 2019. Available at: https://uroweb.org/guideline/prostate-cancer/ (Accessed 14/05/19).
7. National Insitute for Health and Care Excellence. Prostate cancer: diagnosis and management (NG131), 2019. Available at: https://www.nice.org.uk/guidance/ng131 (Accessed 14/05/19).

This assessment is based on data submitted by the applicant company up to and including 12 July 2019.

**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: https://www.scottishmedicines.org.uk/media/3572/20180710-release-of-company-data.pdf*

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.