Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Independent Review Panel

enzalutamide 40mg soft capsules (Xtandi®) SMC No. (1066/15)

Astellas Pharma Ltd.

05 February 2016

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

ADVICE: following an independent review panel

enzalutamide (Xtandi®) is accepted for use within NHS Scotland.

Indication under review: Treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

In a randomised, double-blind phase III study of adult men with chemotherapy naive mCRPC treatment with enzalutamide was associated with a statistically significant extended overall survival and radiographic progression free survival compared to placebo.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of enzalutamide. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

The treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

Dosing Information

The recommended dose is 160mg enzalutamide (four 40mg capsules) 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.

Product availability date

28 November 2014. Enzalutamide meets SMC end of life and orphan equivalent criteria.

Summary of evidence on comparative efficacy

Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Prostate cancer is androgen sensitive, responding to inhibition of androgen receptor signalling. Despite low/undetectable levels of serum androgen, androgen receptor signalling continues to promote disease progression. Treatment with enzalutamide decreases growth of prostate cancer cells, induces cancer cell death and causes tumour regression.[1] Enzalutamide has previously been accepted by SMC for use in men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy. This submission relates to its use in asymptomatic or minimally symptomatic patients after failure of androgen deprivation therapy (ADT) and in whom chemotherapy is not yet indicated.

Evidence to support this licence extension comes from PREVAIL, a phase III, multi-centre, double-blind, randomised, placebo-controlled study designed to assess the efficacy and safety of enzalutamide in men with asymptomatic or mildly symptomatic mCRPC that had progressed despite the use of androgen-deprivation therapy and who had not undergone chemotherapy. Enrolled patients had histologically or cytologically confirmed adenocarcinoma of the prostate with documented metastases and had prostate specific antigen (PSA) progression and/or radiographic progression in bone or soft tissue, despite receiving luteinising hormone releasing hormone (LHRH) analogue therapy or undergoing orchiectomy with a serum testosterone level of ≤1.73 nanomol/L. Patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and were either asymptomatic (score of 0 to 1) or mildly symptomatic (score of 2 to 3) according to the Brief Pain Inventory Short Form question 3 (worst pain in the previous 24 hours, scores range from 0 to 10, higher score indicates greater severity of pain). In addition they had not received prior treatment with cytotoxic chemotherapy, ketoconazole or abiraterone acetate. Patients with visceral disease and New York Heart Association class I or II heart failure were eligible for enrolment.[2]

Patients were stratified according to study site then randomised to receive enzalutamide 160mg orally daily (n=872) or placebo (n=845). Treatment continued until unacceptable side effects or confirmed radiographic progression and initiation of chemotherapy or an investigational agent. Discontinuation of study treatment due to a rise in PSA level alone was discouraged. Co-primary outcomes, measured in the intention-to-treat population were overall survival and radiographic progression-free survival (rPFS). Overall survival was defined as the time from randomisation to death from any cause for each patient. rPFS was defined as the time from randomisation to the first objective evidence of radiographic disease progression or death due to any cause within 168 days after treatment discontinuation, whichever occurred first. Radiographic disease progression included confirmed bone disease progression and soft tissue disease progression.[2]

At the planned interim analysis of overall survival (September 2013 data cut-off) after a median duration of follow-up of 22 months, 28% (241/872) of patients in the enzalutamide group and 35% (299/845) of patients in the placebo group had died, hazard ratio (HR) for risk of death 0.71 (95% confidence interval [CI]: 0.60 to 0.84), p<0.0001. Estimated median overall survival was 32.4 months and 30.2 months respectively.[2,3]

Data from an updated survival analysis with a cut-off date on 30 June 2014 was also provided by the submitting company and used in the economic case to SMC. A *post hoc* adjustment of this overall survival analysis was conducted to account for post-study treatment that differs from the treatment patients would receive in routine clinical practice.

Updated survival analysis after 784 deaths has been published in the summary of product characteristics (SPC), the median overall survival at this time point was 35.3 months in the enzalutamide group and 31.3 months in the placebo group, hazard ratio 0.77 (95% CI 0.67 to 0.88).[1]

At the May 2012 data cut-off, after a median follow up of 5.4 months in the enzalutamide group (n=832) and 3.6 months in the placebo group (n=801) (based on reverse Kaplan-Meier estimates), 14% (118/832) of patients in the enzalutamide group and 40% (321/801) of patients in the placebo group had an rPFS event. The median rPFS was not reached in the enzalutamide group and was 3.9 months in the placebo group, HR 0.19 (95% CI: 0.15 to 0.23), p<0.0001.[2,3]

The PREVAIL study was stopped by the data monitoring committee after reviewing the data from the interim co-primary efficacy and safety results and patients receiving placebo were offered enzalutamide.[2]

Enzalutamide was superior to placebo for all secondary endpoints, see table 1.[2,3]

Table 1. PREVAIL study, results of secondary endpoints (data cut-off 16 September 2013)[2,3]

	Enzalutamide (n=872)	**Placebo (n=845)**	**Hazard ratio (95% CI) p-value**
Initiation of cytotoxic chemotherapy Median time	35% (308/872) 28.0 months	61% (515/845) 10.8 months	0.35 (0.30 to 0.40) p<0.0001
First skeletal-related event Median time	32% (278/872) 31.1 months	37% (309/845) 31.3 months	0.72 (0.61 to 0.84), p<0.0001
PSA progression according to PCWG 2 criteria Median time	61% (532/872) 11.2 months	65% (548/845) 2.8 months	0.17 (0.15 to 0.20), p<0.0001
PSA decline of ≥50% from baseline in patients with ≥1 post-baseline assessment	78% (666/854)	3.5% (27/777)	p<0.0001
Objective response in patients with measurable soft tissue disease (complete plus partial responses)	59% (233/396)	5.0% (19/381)	p<0.0001

CI=confidence interval; PSA=prostate specific antigen; PCWG=Prostate Cancer Clinical Trials Working Group

Health-related quality of life was assessed using FACT-P (functional assessment of cancer therapy-prostate), a pre-specified exploratory endpoint. The time to decline in the FACT-P global score was defined as time from randomisation to first assessment with at least a 10-point decrease from baseline in the total FACT-P score. Median time until decline in FACT-P global score was 11.3 months for enzalutamide and 5.6 months for placebo; hazard ratio 0.63 (95% CI: 0.54 to 0.72), p<0.001.[2,3]

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

Summary of evidence on comparative safety

In the PREVAIL study, most patients reported an adverse event; 97% (844/871) of enzalutamide-treated patients and 93% (787/844) of placebo-treated patients. The median safety reporting period was 17.1 versus 5.4 months respectively. Any adverse event ≥ grade 3 occurred in 43% (374/871) versus 37% (313/844) of patients and any serious adverse event in 32% (279/871) versus 27% (226/844) of patients respectively. Adverse events leading to treatment discontinuation occurred in 5.6% (49/871) treated with enzalutamide and 6.0% (51/844) treated with placebo.[2]

The most common adverse events (of any grade occurring in >10% of either group) in the enzalutamide and placebo groups respectively were; fatigue (36% versus 26%), back pain (27% versus 22%), constipation (22% versus 17%), arthralgia (20% versus 16%), decreased appetite (18% versus 16%), hot flush (18% versus 7.7%), diarrhoea (16% versus 14%), hypertension (13% versus 4.1%), asthenia (13% versus 7.9%), fall (12% versus 5.3%), weight loss (11% versus 8.4%), peripheral oedema (11% versus 8.2%) and headache (10% versus 7.0%).[2]

When an adjustment for the length of exposure was made, adverse events with a higher rate in the enzalutamide group than in the placebo group were hot flush (14 versus 12 events/100 patient-years), hypertension (11 versus 7 events/100 patient-years), and falls (11 versus 9 events/100 patient-years).[2]

Summary of clinical effectiveness issues

Enzalutamide is the second treatment licensed for asymptomatic or mildly symptomatic mCRPC after failure of ADT in whom chemotherapy is not yet clinically indicated. The other medicine, abiraterone acetate (administered with a corticosteroid), was accepted for use by SMC in October 2015 and therefore was not in routine clinical use at the time of the enzalutamide submission to SMC. UK guidance at that time was watchful waiting for asymptomatic or mildly symptomatic patients and then initiation of chemotherapy (docetaxel plus prednisolone) in patients with symptomatic progression and in asymptomatic patients with rapidly rising PSA.[5] Clinical experts consulted by SMC considered that there was unmet need in this therapeutic area. Castration-resistance is a fatal transition for prostate cancer and most patients will die from disease progression.[3] Estimates of overall survival from the control group in the pivotal study suggests the median overall survival is likely to be less than three years for these patients. Enzalutamide meets SMC end of life and orphan equivalent criteria for this indication.

In PREVAIL, treatment with enzalutamide significantly extended overall survival and rPFS compared with placebo in patients who were concurrently receiving a range of treatments which could include bisphosphonates, radiation therapy, opiate analgesics and/or corticosteroids. Furthermore the benefit of enzalutamide in rPFS and overall survival was observed in all pre-specified subgroups including patients with visceral disease, who comprised 12% of the study population.[3]

The European Medicines Agency (EMA) noted, despite the immature survival data at the interim analysis, the hazard ratio suggests a large treatment benefit.[3] Patients switched to a variety of treatments following progression which limits the interpretation of overall survival data. The company has provided adjusted overall survival analysis using the Inverse Probability of Censoring Weights (IPCW) method to account for this. This analysis demonstrates a greater relative benefit for enzalutamide over placebo.[4] Updated survival analyses presented support the original study results despite the potentially confounding influence of further treatments.

Results of secondary endpoints were supportive of the co-primary endpoints. Treatment with enzalutamide significantly extended the median time to initiation of chemotherapy by 17 months compared with placebo. Clinical experts consulted by SMC considered that enzalutamide is a therapeutic advancement due to its ability to delay time to chemotherapy treatment and provide a therapeutic option in a patient group where there are no licensed treatments routinely available for use in NHS Scotland that have been shown to alter survival outcomes. Furthermore, the median time until decline in the FACT-P global score was also significantly extended by 5.7 months relative to placebo. These outcomes may have particular importance to patients.[3]

An indirect treatment comparison of enzalutamide with abiraterone acetate was included in the company's submission. Abiraterone acetate was not in routine use in NHS Scotland at the time of the enzalutamide submission to SMC therefore the indirect comparison was considered to have limited relevance.

Enzalutamide is a potent enzyme inducer so may interact with several medications. A review of patient's current medication should be undertaken before commencing enzalutamide.[1] Enzalutamide has been associated with seizures therefore caution is required when administering enzalutamide to patients with a history of seizures, predisposing risk factors or concomitant medicines that lower the seizure threshold.[1]

Clinical experts consulted by SMC considered that the introduction of this medicine in the pre-chemotherapy setting is likely to impact on service delivery in terms of increased requirement for consultant, nursing and pharmacy time.

Summary of patient and clinician engagement

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 end of life and orphan equivalent medicine, in the context of treatments currently available in NHS Scotland at the time of the enzalutamide submission to SMC.

The key points expressed by the group were:

- Patients developing mCRPC are frequently fit and relatively asymptomatic. Chemotherapy is considered on development of symptoms and represents a step change in the intensity of treatment that patients have experienced so far and has a major impact on the patient and their families.

- There are currently no other treatments routinely available for use in NHS Scotland at this stage in the treatment pathway that have been shown to alter survival outcomes.

- Enzalutamide used in the pre-chemotherapy setting offers a 17-month delay in the time to chemotherapy. This represents time with a high standard of quality of life. Evidence suggests that the duration of progression free survival is greater in the pre-chemotherapy setting compared with post-chemotherapy, where enzalutamide is currently accepted for use by SMC. Use in the pre-chemotherapy setting also offers the possibility of an improvement in survival compared with the existing treatment pathway.

- For patients who are minimally symptomatic, the possibility to delay chemotherapy with its associated toxicity and psychological impact, and also to delay the onset of severe symptoms and palliative care, has huge benefits for their sense of wellbeing and for their families and would allow them to maintain a 'normal life' for longer.

- The PACE group felt strongly that this medicine should be made available in NHS Scotland for patients at the stage in the treatment pathway before chemotherapy is clinically indicated.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing enzalutamide to best supportive care (BSC) in adult men with mCRPC who are asymptomatic or mildly asymptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. In the analysis, BSC was assumed to reflect the placebo arm of the PREVAIL study and therefore included the use of concomitant medications such as H2-antagonists, bisphosphonates and corticosteroids. The time horizon for the analysis was 10 years.

A Markov model was used to structure the analysis. The model included three main health states; stable disease, progressed disease and death. However, to allow for subsequent treatments, the progressive disease state was sub-divided into stages for post-progression 1 (PP1), post-progression 2 (PP2) and palliative care. PP1 captured patients who had progression from the stable disease state and had moved to the next line of treatment, but were yet to progress on that treatment. PP2 related to patients who had progressed on the PP1 treatment and moved to the next line of therapy but had not yet progressed on that treatment. The PP1 treatment was docetaxel for both arms of the model. The PP2 treatment was enzalutamide for patients in the BSC arm of the model but for patients in the enzalutamide arm of the model, there was no PP2 treatment option and no treatment was received. This is summarised as the following pathways: for the enzalutamide arm enzalutamide > docetaxel > palliative care and for the BSC arm BSC > docetaxel > enzalutamide.

The source of the clinical data for the economic model was the PREVAIL study in terms of the initial progressions in the model from the stable disease state. Key data used from PREVAIL related to both overall survival (OS) estimates and time to discontinuation (TTD) as a measure of progressive disease. The OS data were adjusted using the IPCW method in order to account for the use of treatments post-progression in PREVAIL that would not reflect the current treatment options in NHS Scotland. Extrapolations of TTD data were necessary and these were achieved by applying a gamma distribution to each arm of the model. Other literature sources were used for later progressions in the model. Adverse events at grade 3 and above and with an incidence of >2% in either group were included in the analysis on the basis of data from the PREVAIL study.

Utility values were taken from the EQ-5D data collected in the PREVAIL study in terms of base line utility estimates and for the estimation of the utility while in stable disease; patients on enzalutamide in stable disease had a higher utility value than BSC patients in the same health state on the basis of quality of life data collected in the clinical study. Utilities for the post-progression states and for adverse events were taken from published sources.

Costs in the model included additional tests and monitoring associated with enzalutamide treatment. Costs of adverse events and skeletal related events (SREs) were also included.

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. Under the PAS, a simple discount is offered on the price of the medicine. With the PAS, the base case incremental cost-effectiveness ratio (ICER) was £31,542 per quality adjusted life year (QALY). It is SMC policy to include the estimated QALY gain in the detailed advice document for all submissions. However, owing to commercial in confidence concerns regarding the PAS, SMC is unable to publish this figure.

In terms of the key drivers of the with PAS results, the QALY gain was driven by greater amounts of time spent in the stable disease state. As such, patients on enzalutamide spend more time in the health state with the best quality of life, and more patients are in this state. The incremental costs were predominantly driven by the incremental costs of enzalutamide in the stable disease state but with some lower costs compared to BSC in the PP1 state.

Extensive one-way and scenario-based sensitivity analysis was provided. This showed that the analysis was most sensitive to the following aspects:

- The ICER was most sensitive to changing the proportion of patients in the BSC arm who received 2nd line (docetaxel) treatment; when this was set at 0% the with- PAS ICER rose to £51,467. This would seem to be an extreme value analysis and would assume that all patients in the BSC arm moved straight to palliative care on progression. SMC expert comments provided some reassurance that if patients were fit enough to receive docetaxel they would receive it and thus expecting no patients to move to docetaxel is not likely.
- The next most sensitive variable was changing the proportion of patients in the BSC arm who went on to receive enzalutamide post-docetaxel; if this was set at 0%, the ICER rose to £37,138. Again, SMC expert responses however, provided reassurance that it would be unlikely that no patients would go on to receive enzalutamide (or abiraterone acetate) post-docetaxel and thus the base case value seemed reasonable.
- Use of a less mature set of data led to an ICER of £37,526. While this was the protocol-defined date, it seemed reasonable to use more mature data in the economic model's base case if possible to reduce the length of the extrapolation phase.
- Using unadjusted OS data increased the ICER to £36,319. It was noted that use of other forms for the extrapolation of OS or alternative methods for adjusting the OS data did not result in significant changes in the ICER (£33,552 when an alternative two-stage method of adjustment was used).
- Using rPFS rather than TTD data for progression modelling increased the ICER to £36,082. SMC experts have however generally confirmed that TTD was a reasonable measure to use for disease progression in practice.
- The company also included some analysis to show the impact of patients in the enzalutamide arm of the model being able to receive abiraterone acetate as a post-docetaxel treatment. A PAS is in place for abiraterone acetate and this was included in the analysis by using an estimate of the relevant price of abiraterone acetate. The result indicated that with the ICER increased by a modest amount. However, SMC expert comments suggested there is considerable uncertainty as to whether sequential use of these medicines would occur in practice and the results were viewed accordingly.
- Probabilistic sensitivity analysis showed a 0%, 35% and 100% chance of enzalutamide being cost-effective at willingness to pay thresholds of £20k, £30k and £50k per QALY respectively.
- The company did provide a sensitivity analysis where abiraterone acetate was the comparator therapy. However, as noted above, abiraterone acetate was not in routine use in NHS Scotland at the time of the enzalutamide submission to SMC and therefore the analysis was not considered relevant.

In terms of weaknesses in the analysis, the following were noted:

- As noted above, the results showed some sensitivity to the estimation of OS. The SMC statistical advisor noted that the IPCW model used in the analysis would depend on the predictors of switching available and produce estimates with some error depending on the fit of the model, and would thus not be a perfect fit to the data. However, the company has assumed the error in the model is zero and a perfect fit in using the IPCW estimate. The use of alternative approaches to OS estimation in sensitivity analysis was however helpful in showing the impact of making different assumptions about OS.
- There is some uncertainty associated with the treatment pathway, for example in terms of any treatments that may be given post-docetaxel if a patient was treated with enzalutamide pre-chemotherapy. While a scenario analysis was provided assuming use of abiraterone acetate in this setting, there is some uncertainty around the assumptions that have been used in the analysis, for example, in terms of the outcomes achievable if enzalutamide had been used pre-chemotherapy.

The Independent Review Panel (IRP) considered the benefits of enzalutamide in the context of its decision modifiers that can be applied when encountering high cost-effectiveness ratios and where there is increased uncertainty due to the orphan-equivalent status of the medicine and concluded that the criteria for substantial improvements in survival and quality of life were met.

After considering all the available evidence, the output from the PACE process and after application of the appropriate modifiers, the IRP was able to accept enzalutamide for use in NHS Scotland.

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

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups at the time of the enzalutamide submission to SMC.

- Submissions were received from Prostate Scotland, Tackle Prostate Cancer and Prostate Cancer UK, all are registered charities.

- Prostate Cancer UK and Tackle Prostate Cancer have received 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.

- Patients with advanced prostate cancer can experience many symptoms such as mobility issues, bone pain and in some cases metastatic spinal cord compression causing weakness and numbness in the legs. It can cause significant emotional difficulties, as it cannot be cured which impacts on the lives of patients and their families. Some patients will face financial difficulties from being restricted in their employment or unable to work.

- At present there are very limited treatment options available for these men prior to chemotherapy. Being able to use enzalutamide prior to chemotherapy would give them a treatment option giving them hope.

- As enzalutamide is taken orally in tablet form it would not require the inconvenience of hospital visits increasing the time patients can spend with their families. Any side-effects are regarded by patients as being far less of a burden than those of chemotherapy.

- Enzalutamide may prolong survival and would delay the need for chemotherapy, with its associated toxicity and psychological impact, which would allow patients to maintain as much of a normal life for as long as possible.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence published *prostate cancer; diagnosis and treatment clinical guideline number 175*, in 2014.[5] The goals of treatment in hormone-relapsed disease are: improvement of survival and quality of life with control of symptoms. Hormone-relapsed disease may be defined as such when there is radiological progression, loss of PSA control or development of disease-related symptoms. LHRH analogues are usually continued in hormone-relapsed disease since the androgen receptors on the cancer cells can remain active, and the disease may still respond to alternative agents such as corticosteroids and oestrogens. It is recommended that a corticosteroid is offered to patients with hormone-relapsed prostate cancer as a third-line hormonal therapy after androgen deprivation therapy and anti-androgen therapy. Chemotherapy (docetaxel plus prednisolone) is recommended in men with symptomatic progression and in asymptomatic patients with rapidly rising PSA.
NB: This guideline predates the availability of enzalutamide for the indication under review.

The European Association of Urology updated its Prostate cancer management guidelines, in 2015.[6]
The defining characteristics of castration-resistant prostate cancer are:
Castrate levels of serum testosterone (<50nanograms/dL or <1.7nanomol/L) plus either

1. *Biochemical progression*: Three consecutive increases in PSA (7 days apart) resulting in two 50% increases over the nadir, with PSA >2nanograms/mL or
2. *Radiological progression*: The appearance of at least two bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST.

The gold-standard treatment outcome in castration-resistant prostate cancer is overall survival, with other commonly used outcomes of improvements in quality of life, PFS and prostate cancer specific survival. Nearly all studies of treatments for castration-resistant prostate cancer have been conducted with ongoing androgen suppression, so this should be continued in these patients. In patients with metastatic castration-resistant prostate cancer, good performance status, mildly symptomatic or asymptomatic with no evidence of visceral disease, the following are suggested as first-line non-chemotherapy-based therapeutic options: abiraterone acetate, Sipuleucel T, enzalutamide. The recommendations are made on the basis of the results of placebo-controlled studies of abiraterone acetate (COU-AA-302), enzalutamide (PREVAIL) and Sipuleucel T (phase III study supporting registration). Due to a lack of head to head studies or data for different sequencing options, it is not clear how to choose the most appropriate therapeutic option.

The European Society for Medical Oncology published; *Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*, in 2015.[7] First line treatment options for patients with asymptomatic/mildly symptomatic mCRPC are abiraterone acetate or enzalutamide. Radium-223 is recommended for patients with bone-predominant symptomatic mCRPC without visceral metastases, docetaxel is recommended for men with mCRPC and Sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve mCRPC. The optimal sequence or combination of treatments is unknown.

Additional information: comparators

Watchful waiting. Abiraterone acetate has recently been accepted for use by SMC for the same indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Enzalutamide	**160mg orally once daily**	**35,551**
Abiraterone acetate plus prednisolone	abiraterone acetate 1,000mg orally once daily prednisolone 5mg orally twice daily	35,584

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 17 November 2015. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there to be 488 patients eligible for treatment with enzalutamide in year 1 rising to 526 patients in year 5 to which confidential estimates of treatment uptake were applied.

Without PAS
The company estimated the gross medicines budget impact to be £7m in year 1 rising to £15m in year 5. As no other medicines were assumed to be displaced, the net medicines budget impact was as per the gross estimates. The company also estimated other resource costs associated with monitoring and savings associated with displacement of medicines in the post-chemotherapy setting. These costs and savings were estimated at a cost of £18k in year 1 and then a saving of £2.5m in year 5. The net total budget impact was therefore estimated as £7m in year 1 rising to £12.5m in year 5. Abiraterone acetate was not in routine use in the pre-chemotherapy setting in NHS Scotland at the time of the enzalutamide submission to SMC and is therefore not taken into account in these estimates.

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

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Astellas Pharma Ltd. Summary of product characteristics for enzalutamide (Xtandi®) soft capsules. Last updated 16 January 2015.
2. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N Engl J Med. 2014; 371:424-433.
3. European Medicines Agency. European Public Assessment Report for enzulatamide (Xtandi®). EMA/CHMP/607459/2014. 23 October 2014.
4. *Commercial in Confidence**
5. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and treatment. NICE clinical guideline 175 (January 2014). www.nice.org
6. Mottet N, Bellmunt J, Briers E et al. Guidelines on prostate cancer (update March 2015) – European Association of Urology. www.uroweb.org
7. Parker C, Gillessen S, Heidenreich A, Horwich A, on behalf of the ESMO Guidelines Working Group. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2015; 26 (Supplement 5): v69-77.

This assessment is based on data submitted by the applicant company up to and including 21 May, 2015**.**

**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_statements/Policy_Statements

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.