4.02 ENZALUTAMIDE
Capsule, 40 mg
Xtandi®, Astellas Pharma Australia Pty Ltd

1 Purpose of Application

1.1 The minor resubmission sought to address issues raised by the PBAC in its consideration of the major enzalutamide submission at the March 2017 meeting.

1.2 The sponsor took the following steps to address the PBAC's concerns:

- amended the proposed restriction to include symptomatic patients as well as asymptomatic patients, and remove the requirement for opioid use;
- adjusted the mean duration of post-docetaxel treatment with enzalutamide in the watchful waiting arm of the model to 9.8 months in line with the June 2016 DUSC review;
- proposed weighting the price of enzalutamide across pre- and post-docetaxel metastatic castration-resistant prostate cancer (mCRPC) settings to achieve a weighted DPMQ of $[redacted]; and
- proposed a new risk sharing arrangement incorporating reduced caps and a weighted rebate of [redacted]% for all expenditure above the caps.

2 Requested listing

2.1 Changes to the existing listing for enzalutamide to incorporate the requested listing are shown in italics and strikethrough. Secretariat suggestions are also included.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	Castrate resistant metastatic
Condition:	Carcinoma of the prostate
PBS Indication:	Castration resistant metastatic carcinoma of the prostate
Treatment phase:	*Initial treatment*
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency

	☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	The treatment must not be used in combination with chemotherapy, *AND* *The treatment must be once in a lifetime with this drug for this condition*
Clinical criteria:	~~Patient must have failed treatment with docetaxel due to resistance or intolerance; OR~~ ~~Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel,~~ ~~AND~~ Patient must have a WHO performance status of 2 or less, AND ~~Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug~~ ~~AND~~ Patient must not have received prior treatment with abiraterone; OR Patient must have developed intolerance to abiraterone of a severity necessitating permanent treatment withdrawal.
Prescriber instructions	*A patient may qualify for PBS-subsidised treatment with this drug for this condition under this restriction once in a lifetime.* *For continuing PBS-subsidised treatment, the patient must qualify under the Continuing treatment criteria.*
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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Treatment criteria:	The treatment must not be used in combination with chemotherapy, *AND* *The treatment must be once in a lifetime with this drug for this condition*
Clinical criteria:	~~Patient must have failed treatment with docetaxel due to resistance or intolerance; OR~~ ~~Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel,~~ ~~AND~~ *Patient must have previously received PBS-subsidised treatment with this drug for this condition,* *AND* Patient must have a WHO performance status of 2 or less, AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops whils*t*~~e on~~ *being treated with* this drug *for this condition* ~~AND~~ ~~Patient must not have received prior treatment with abiraterone; OR~~ ~~Patient must have developed intolerance to abiraterone of a severity necessitating permanent treatment withdrawal.~~
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

2.2 The pre-PBAC response (p.1) stated that the indication proposed in the minor resubmission was not intended to cover both pre- and post-docetaxel settings, although the sponsor is willing to work with the PBAC and the Department on the wording of such an indication. The PBAC agreed that a broad single PBS listing for enzalutamide for mCRPC was appropriate.

2.3 The PBAC agreed with the sponsor's suggestion (pre-PBAC response, p.1) that the restriction for pre-docetaxel use of enzalutamide should include patients with a WHO performance status of 2 or less.

For more detail on PBAC's view, see section 5 "PBAC outcome."

3 Background

3.1 Enzalutamide was TGA registered on 1 July 2014 for the treatment of patients with mCRPC who have previously received docetaxel, and on 13 November 2015 for the treatment of mCRPC following failure of androgen deprivation therapy for patients in whom chemotherapy is not yet indicated.

3.2 Enzalutamide is currently PBS listed for treatment of mCRPC for patients who have failed or been considered unsuitable for docetaxel treatment.

3.3 The PBAC considered and rejected a submission for enzalutamide in November 2015 for the treatment of asymptomatic and symptomatic chemotherapy-naïve patients with mCRPC. The submission was based on a claim of overall survival benefit for enzalutamide. A submission for abiraterone in a comparable population was considered and rejected by the PBAC in July 2014.

3.4 In March 2017, the PBAC deferred recommending an extended PBS listing for enzalutamide for the treatment of mCRPC prior to docetaxel, on the basis of requiring: (i) a further price reduction so that the ICER is acceptable, with a more appropriate assumption of duration of post-docetaxel treatment with enzalutamide in the watchful waiting arm of the model;(ii) a broadening of the proposed restriction to include symptomatic patients; and (iii) a review of the financial estimates to provide a basis for a meaningful risk share arrangement to cover treatments in the pre- and post-docetaxel settings.

3.5 A summary of the key issues identified at the March 2017 meeting, the sponsor's response to the issues in the minor resubmission and the PBAC's comment on the response is shown in Table 1.

Table 1: Summary of issues identified in March 2017 consideration of the major submission

Basis for deferral	Response in minor resubmission	PBAC Comment
Indication: there is no clinical basis for excluding symptomatic patients; clinicians should decide the sequence.	Restriction now includes symptomatic patients and a stopping rule. The resubmission offers a weighted price across pre- and post-docetaxel settings, so there could now be a	The PBAC's concerns have been addressed. The PBAC considered the WHO performance status for both pre- and post-docetaxel use should be 2 or less.

Basis for deferral	Response in minor resubmission	PBAC Comment
	single enzalutamide restriction.	
The ICER is driven by cost-offsets from post-docetaxel treatment continuing until death. The pre-PBAC response reduced the duration to 14 months but this was still not consistent with the DUSC review.	The sponsor modified the post-docetaxel treatment duration to 9.8 months in line with the DUSC review. The effective DPMQ = $[redacted] to ensure an ICER of $45,000/QALY – $75,000/QALY. Note the post-docetaxel DPMQ is $[redacted] (published price $[redacted]) and the pre-PBAC response for the March meeting offered $[redacted] – the sponsor claims that this is the global floor price.	The PBAC's concerns have been partially addressed – see section 5.
The financial estimates needed to be adjusted to reflect the changes in cost-effectiveness.	Updated to include symptomatic population.	The PBAC's noted the issue was addressed.
The caps and expenditure in the pre- and post-docetaxel settings should be merged.	The sponsor proposed a weighted rebate of [redacted]% [i.e. ([redacted]% x [redacted]% pre-docetaxel) + ([redacted]% x [redacted]% post-docetaxel)] for all expenditure above the proposed subsidisation caps.	The PBAC's concerns have been partially addressed, but there is a risk that the caps won't be reached, resulting in a higher ICER. See section 5.

For more detail on PBAC's view, see section 5 "PBAC outcome."

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted that the Medical Oncology Group of Australia (MOGA) continued to express its support for the enzalutamide submission on the basis of the survival and progression-free survival benefits in the PREVAIL trial. MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefits Scale (ESMO-MCBS) for enzalutamide, which was 3 (out of a maximum of 5, where 5 and 4 represent substantial improvement) [1], based on a comparison with placebo.

Economic analysis

[1] Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 26:1547-73, 2015

4.3 In this minor resubmission, the March 2017 model was adjusted for the duration of post-docetaxel treatment with enzalutamide in the watchful waiting arm to a mean treatment time of 9.8 months, in accordance with the 2016 DUSC review.

4.4 To ensure that the ICER remained unchanged from the major resubmission $45,000/QALY – $75,000/QALY) a price of $[redacted] is required in the pre-docetaxel setting. The sponsor states this is below the global floor price of $[redacted].

4.5 To achieve a weighted DPMQ of $[redacted] across pre- and post-post docetaxel settings, the weighting of prescriptions would be approximately 64% and 36%, respectively. The minor resubmission suggests the predicted use across settings is 85% and 15%, based on rounded figures generated by the Year 1 data in the financial estimates model (86.6% and 13.4%, respectively). This results in a weighted price of $[redacted]. To achieve this weighted price, the sponsor proposes lower financial caps and additional rebates (see below).

4.6 If the exact figures from the financial estimates model were used (86.6% and 13.4%), the weighted DPMQ would be $[redacted], which has a significant impact on the financial estimates (see paragraph 4.16).

Estimated PBS usage & financial implications

4.7 The minor resubmission estimated a net cost to the PBS of more than $100 million in Year 5 of listing, with a total net cost to the PBS of more than $100 million over the first 5 years of listing. This is summarised in Table 2.

Table 2: estimated PBS usage and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	TOTAL
Total enzalutamide prescriptions, pre-docetaxel[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (86.6%)
Total enzalutamide prescriptions, post-docetaxel[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (13.4%)
TOTAL enzalutamide prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Expenditure (at $[redacted])[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	
Patient co-payments ($[redacted])[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	
Predicted Expenditure[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	

a Source: cells H15-L15 worksheet 'Cost to the PBS-RPBS', Xtandi (enzalutamide) financial implications Pricing.xlsm
b Note: cells F19- J19 worksheet 'Background & Assumptions' are adjusted to 40%, 30%, 20%, 20% and 20% respectively. Source: cells X84-AB84 worksheet 'Cost to the PBS-RPBS', Xtandi (enzalutamide) financial implications Pricing.xlsm
c Please refer to Cap and rebate calculations.xlsx.

4.8 The March 2017 submission derived the eligible population by estimating the incident mCRPC population treated with a first generation antiandrogen. The number of patients initiating on an antiandrogen were estimated from a 10% PBS sample and it was assumed that these patients had asymptomatic disease. The estimates of the annual number of incident patients ranged from [redacted] to [redacted] between 2011 and 2015. The incident population over the forward estimates period was projected using a logarithmic extrapolation of the estimates for 2011 to 2015. It was assumed that 87% of patients were treated with an antiandrogen. This was based on the proportion of participants in the PREVAIL trial at baseline who had received a first generation antiandrogen. To estimate the eligible population, including untreated patients, the number of forecasted incident patients was divided by 87%. The total eligible asymptomatic population was estimated to be [redacted] in Year 1 to [redacted] in Year 5. In its advice to the PBAC for the March 2017 submission, DUSC considered that the forecast of the eligible population was uncertain. This was mainly because of insufficient detail being provided in the analysis report for the 10% PBS sample to allow DUSC to fully evaluate the financial estimates. The PSCR and Pre-PBAC response for the March 2017 submission and the minor submission have not provided further details on the analyses undertaken from the 10% sample. As such, the forecasts of the eligible population remain uncertain.

4.9 In the resubmission, the eligible population was revised to include both asymptomatic and symptomatic patients in the pre-docetaxel setting, where 'symptomatic' included those with moderate and severe symptoms. A prevalent pool of symptomatic patients was estimated based upon the 'Changing Treatment Landscape for Castration Resistant Prostate Cancer: An Australian Multi-Centre Retrospective Study'. Based on this source, the minor submission estimated that 31% of the incident mCRPC population would have moderate to severe symptoms. The sponsor then assumed that 69% of mCRPC patients were asymptomatic. The eligible population with moderate to severe symptoms was estimated by dividing the estimate for the asymptomatic population by 69% and multiplying by 31%. For example, the Year 1 estimate was calculated as ([redacted] / 69%) x 31% = [redacted] symptomatic mCRPC patients. If the definition of 'symptomatic' was broadened to include people with mild symptoms, the total patient numbers would increase from [redacted] to [redacted].

4.10 As for the economics model, the average time of post-docetaxel therapy for enzalutamide in the financial estimates model was revised to 9.8 months.

4.11 The uptake assumptions were unchanged from the March 2017 submission. The first year is assumed to be 60%, the second year 70% with an annual uptake of 80% thereafter. For the March 2017 submission, DUSC considered that the treatment uptake assumptions were likely to have been underestimated. DUSC noted there was

a high uptake of enzalutamide in the post-chemotherapy setting, and clinicians were experienced with the use of enzalutamide.

Risk-Sharing Arrangement

4.12 In its consideration of the major submission in March 2017, the PBAC considered that risk-sharing arrangements (RSAs) should take account of the once in a lifetime use of enzalutamide, either by merging caps for both pre- and post-docetaxel settings or reducing the caps for the existing RSA for the post-docetaxel setting in accordance with the modelled cost-offsets. The total financial caps for the group of three drugs (enzalutamide, abiraterone and cabazitaxel) should be based on the percentage proposed use pre-docetaxel and post-docetaxel (accounting for the different duration of therapy in the pre- and post-docetaxel settings). The PBAC proposed a 100% rebate be considered beyond the total cap, given the increase in total expenditure from the earlier line of treatment which is associated with longer duration of therapies (March 2017, Public Summary Document (PSD), paragraph 6.47).

4.13 In the resubmission, the sponsor has proposed subsidisation caps and a rebate to ensure that the average weighted DPMQ is $[redacted].

4.14 Based on the estimated distribution of prescriptions in the pre- and post-docetaxel settings, the sponsor proposes a weighted rebate of [redacted] for all expenditure above the proposed subsidisation caps.

4.15 To achieve an average price of $[redacted] with a [redacted]% rebate, the subsidisation caps have been reduced by [redacted]% from the predicted expenditure (see Table 3).

Table 3: adjusted subsidisation caps

	Year 1	Year 2	Year 3	Year 4	Year 5
TOTAL enzalutamide prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Predicted Expenditure	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduced Expenditure cap	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Predicted rebate above expenditure cap (at 91%)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net expenditure	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Average price	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

4.16 If the weighted DPMQ were $[redacted] (see paragraph 4.6), the expected expenditure would be closer to $30 – $60 million in Year 1, which is equal to the reduced expenditure cap shown in Year 1 in Table 2. Therefore, in this scenario, the Government would not benefit from the proposed adjusted subsidisation caps.

4.17 There are currently two RSAs that cover the mCRPC medicines. Abiraterone and enzalutamide currently share a single RSA. Cabazitaxel has a separate RSA which is close to the end of its term. Achieving the expected average price is contingent on expenditure reaching the proposed caps. In addition, if the pre- and post-docetaxel proportions more accurately follow the proportions identified during the clinical trials then the average price will be significantly lower.

For more detail on PBAC's view, see section 5 "PBAC outcome."

5 PBAC Outcome

5.1 The PBAC deferred a recommendation on the proposal for an extended PBS listing for enzalutamide for the treatment of metastatic castrate-resistant prostate cancer (mCRPC) prior to docetaxel, on the basis that the proposal to achieve a cost-effective listing was unacceptable. The PBAC advised that further negotiations between the sponsor and the Department regarding the proposed price of enzalutamide, the proposed financial caps, and the size of the patient population are required, to ensure that the ICER is acceptable.

5.2 The PBAC noted that, in line with its request from the March 2017 meeting, the sponsor had amended the proposed restriction to include both symptomatic and asymptomatic patients, and to remove the requirement for monitoring opioid use. The PBAC agreed with the suggestion that a broad single PBS listing for enzalutamide for mCRPC for both pre- and post-docetaxel use would be appropriate, and it should include patients with a WHO performance status of 2 or less, as per the current listing in the post-docetaxel setting. The PBAC considered a telephone Authority would be appropriate.

5.3 The PBAC noted that, the 'once in a lifetime' criterion would need to be included in the enzalutamide restriction, and the post-docetaxel restriction for abiraterone would also need to be amended to make the 'once in a lifetime' criterion clear.

5.4 The PBAC noted that the sponsor had adjusted the duration of post-docetaxel treatment with enzalutamide in the watchful waiting arm of the economic model to 9.8 months, in accordance with the 2016 DUSC review. Achieving the cost-effective price for enzalutamide ($[redacted] in the pre-docetaxel setting) would be contingent on a rebate being triggered once expenditure reached the proposed caps. However, the PBAC considered this proposal was not acceptable in this circumstance as there is substantial risk that the caps may not be reached.

5.5 The PBAC considered that the size of the patient population is uncertain (see paragraphs 4.8 and 4.9), and the ICER will increase if the proposed caps are not reached. The PBAC noted that if the number of enzalutamide scripts is 10-20% lower

than predicted, the ICER would increase to $85,000/QALY - $120,000/QALY, significantly higher than the ICER proposed at the March 2017 PBAC meeting $45,000/QALY – $75,000/QALY) which the Committee requested be retained in future resubmissions.

5.6 The PBAC noted emerging evidence from the Latitude and Stampede trials supporting the use of abiraterone earlier in castrate-sensitive prostate cancer. The PBAC considered that earlier use of abiraterone could affect the likelihood that the proposed financial caps for enzalutamide are reached, and the efficacy of enzalutamide would be reduced in patients who have been previously exposed to abiraterone (in combination with ADT).

5.7 The PBAC also considered in light of the emerging evidence for abiraterone, there is a risk that there will be further changes in the position of enzalutamide in the treatment algorithm, and the expenditure caps would not hold over a five year period. As noted above, small reductions in the number of scripts has a substantial impact on the cost-effectiveness of enzalutamide in the pre-docetaxel setting.

5.8 Given that achieving the proposed price for enzalutamide is dependent on reaching the proposed expenditure caps, and the caps are reliant on an uncertain patient population, the PBAC was not satisfied that the proposed ICER would be achieved. The PBAC therefore agreed that the Department should enter into further negotiations with the sponsor regarding the size of the patient population, how current expenditure compares with predicted growth in expenditure, the proposed price and the risk share arrangement to ensure that the ICER remains acceptable.

5.9 The PBAC noted that this submission is not eligible for an Independent Review, as the submission was not rejected.

Outcome:
Deferred

6 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

7 Sponsor's Comment

Astellas will consider the issues raised by the PBAC and continue to investigate options to improve access to enzalutamide for metastatic castration resistant prostate cancer, chemotherapy-naïve patients.