# 7.02 ENZALUTAMIDE, Capsule 40 mg, Xtandi®, Astellas.

## 1 Purpose of Application

1.1 This resubmission requested an Authority Required listing for enzalutamide for treatment of metastatic castration-resistance prostate cancer (mCRPC) in "asymptomatic" patients who have not yet had docetaxel. The November 2015 submission of enzalutamide was for both 'asymptomatic' and 'symptomatic' patients in a similar setting.

## 2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer | |
|---|---|---|---|---|---|
| ENZALUTAMIDE<br>capsule, 40 mg, 112 | 1 | 2 | $3,701.18 (published)<br>$[redacted] (effective) | Xtandi | Astellas Pharma |

| | |
|---|---|
| **Category / Program** | GENERAL – General Schedule (Code GE) |
| **Prescriber type:** | ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives |
| **Episodicity:** | - |
| **Severity:** | Castration resistant metastatic |
| **Condition:** | ~~Castration-resistant metastatic~~ Carcinoma of the prostate |
| **PBS Indication:** | Castration-resistant metastatic carcinoma of the prostate |
| **Treatment phase:** | Initial and continuing |
| **Restriction Level / Method:** | ☐Restricted benefit<br>☒Authority Required - In Writing<br>☒Authority Required - Telephone<br>☒Authority Required – Emergency<br>☒Authority Required - Electronic<br>☐Streamlined |
| **Treatment criteria:** | The treatment must not be used in combination with chemotherapy |
| **Clinical criteria:** | ~~Patient must not have had prior treatment with docetaxel~~<br>~~AND~~<br>Patient must have a WHO performance status of 1 or less<br>AND<br>Patients must not have evidence of cancer related pain which requires the use of opioid medications<br>AND<br>Patient must not have received prior treatment with abiraterone |
| **Administrative Advice** | Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).<br><br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au<br><br>Applications for authority to prescribe should be forwarded to:<br>Department of Human Services<br>Prior Written Approval of Complex Drugs<br>Reply Paid 9826<br>GPO Box 9826<br>HOBART TAS 7001 |

2.2 The basis for this proposed listing was cost-effectiveness versus watchful waiting (which included hormonal manipulations with first-generation anti-androgens). Enzalutamide is already listed on the PBS for mCRPC patients post docetaxel

treatment and for patients who are judged to be unsuitable for docetaxel. The proposed restriction is identical to the current listings of enzalutamide in terms of maximum quantities, number of repeats and the published price. The resubmission did however propose a lower effective price ($[redacted] DPMQ) for the new population. The effective DPMQ for the existing listing would remain unchanged ($[redacted] DPMQ).

2.3 The PBAC noted a further [redacted]% price reduction was offered in the Pre-PBAC response, resulting in a proposed effective DPMQ in the new setting of $[redacted].

2.4 There are a number of differences in this requested restriction compared to the requested restriction in the November 2015 submission: i) the resubmission specifically precluded access by symptomatic patients, eligible "asymptomatic" patients are to be identified via a lack of opioid use for pain and a WHO performance status of 1 or less (previously 2 or less) and ii) a separate stopping rule requiring patients to stop treatment post disease progression was removed. These have important implications for clinical practice and PBS utilisation. The Pre-Sub-Committee Response (PSCR) stated that the stopping criteria was inadvertently omitted from the proposed restriction; the sponsor agreed that stopping criteria should be included and based upon the definition of progression in the PREVAIL trial.

2.5 The proposed restriction identifies 'asymptomatic' patients by a lack of opioid use for pain. The ESC considered this definition of 'asymptomatic' was vague, open to clinician interpretation and, if used as a basis for restriction, could distort clinical practice by delaying opioid use. In contrast, the definition used in the PREVAIL trial was a pain score of <4 on the Brief Pain Inventory. The sponsor's PSCR stated that the Brief Pain Inventory is not routinely used in Australia, and that the use of opioid medication is a practical and measurable alternative, as it can be determined by the Department of Human Services (DHS) at the time of the initial authority application. The ESC did not consider this request of DHS would be reasonable or effective, and the use of opioids in this population may or may not relate specifically to cancer pain.

2.6 The PBAC considered treatment should not be restricted to asymptomatic patients.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 3 Background

3.1 **TGA status at time of PBAC consideration:** enzalutamide was TGA registered on 1 July 2014 for the treatment of patients with metastatic castration resistant prostate cancer who have previously received docetaxel, and on 13 November 2015 for the treatment of metastatic castration resistant prostate cancer following failure of androgen deprivation therapy for patients in whom chemotherapy is not yet indicated.

3.2 Enzalutamide is currently PBS-listed for mCRPC where the patient

- has failed treatment with docetaxel due to resistance or intolerance; OR
- is unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel.

Abiraterone currently has an identical listing, and each of the listings include wording precluding use of one after the other unless the patient develops intolerance at a severity necessitating permanent treatment withdrawal.

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

3.4 The PBAC rejected the previous submission because it considered the purpose of treatment would be to maintain a better quality of life for longer by either:

- In asymptomatic patients – delaying symptoms from developing, or
- In symptomatic patients considered suitable for docetaxel – delaying the toxicities of chemotherapy.

3.5 Neither of these patient groups would be considered to benefit substantially in survival from the earlier treatment with novel hormonal therapies. This is in contrast to the entire basis of the previous submission which was a claim of overall survival advantage. However, by focussing only on the asymptomatic patients, the resubmission does not reflect the intent of the PBAC recommendation. This raises a number of issues:

- how "asymptomatic" is defined for the purposes of the restriction and whether this may distort clinical practice (e.g. by delaying opioid use)
- the reasoning for denying symptomatic patients this clinical option
- the applicability of the PREVAIL trial population (a large proportion of patients were using opioid medications by the end of PREVAIL, and they continued treatment until disease progression; up to 39.4% and 34.8% in the enzalutamide and placebo arms, respectively)
- the modelled benefit for asymptomatic patients being based on time to cytotoxic chemotherapy, rather than occurrence of symptoms.

3.6 A summary of the previous and current submissions is presented in Table 1.

**Table 1: Summary of the previous submission and current resubmission**

| | Enzalutamide November 2015 | Current resubmission |
|---|---|---|
| Requested PBS listing | Asymptomatic and symptomatic chemotherapy naïve mCRPC | Asymptomatic chemotherapy naïve mCRPC |
| Requested price | $[redacted] (DPMQ, effective price); Same as for the current (post docetaxel listing) listing. | $[redacted] (DPMQ, effective price); no change to current listing DPMQ effective price. Pre-PBAC effective price proposed: $[redacted]. |
| Main comparator | Watchful waiting and docetaxel (and abiraterone if listed for same indication), depending on symptom status and disease progression.<br>**PBAC Comment:** watchful waiting is appropriate for asymptomatic patients; and docetaxel is appropriate for symptomatic patients (Paragraph 7.1). | Watchful waiting for asymptomatic patients. |
| Clinical evidence | Seven RCTs: Enzalutamide in PREVAIL (N=1717); abiraterone in COU-AA-302 (N=1088); docetaxel in TAX-327 (N=672) and Ye 2013 (N=220); mitozantrone in Tannock 1996 (N=161), Kantoff 1999 (N=242) and Berry 2002 (N=119).<br>**PBAC Comment:** All of the trials generally have low risk of bias with respect | One RCT: PREVAIL (N=1717) |

| | Enzalutamide November 2015 | Current resubmission |
|---|---|---|
| | to the outcome overall survival (Paragraph 6.8). | |
| Key effectiveness data | To control for subsequent treatment in PREVAIL, two adjustments to PREVAIL data were made using the IPCW method. Both made a moderate impact on overall survival in favour of enzalutamide:<br>• ITT, HR = 0.767 (95%CI: 0.666, 0.882)<br>• IPCW (doc is not a switch), HR = 0.660 (95%CI: 0.565, 0.772)<br>• IPCW (doc is a switch), HR = 0.470 (95%CI: 0.341, 0.592)<br>Adjusted data were used for the nominated comparators:<br>• Watchful waiting: PREVAIL IPCW (doc is not a switch)<br>• Docetaxel: Indirect comparison of PREVAIL IPCW (doc is a switch) v meta-analysis of TAX-327 and Ye 2013; indirect HR = 0.66 (0.47, 0.92)<br>**PBAC Comment:** Adjusting for switching for watchful waiting and the indirect comparison for docetaxel were not appropriate, favouring enzalutamide (Paragraphs 6.14 and 7.5). No evidence was presented that the order in which enzalutamide or docetaxel are used in a treatment algorithm results in treatment modification to support the contention that enzalutamide to docetaxel is superior to docetaxel to enzalutamide (Paragraph 6.18). Given patients would not benefit substantially in survival, the PBAC considered the impact on quality of life from delaying disease symptoms (such as pain, fractures, and spinal cord compression) and delaying toxicities from chemotherapy were of most relevance to this patient population (Paragraphs 7.2 and 7.6). | Given PREVAIL does not inform the current and proposed treatment algorithms, and in light of PBAC comments regarding the clinical claim, the submission focused on secondary quality of life outcomes in PREVAIL. The outcome modelled was time to initiation of cytotoxic chemotherapy:<br>• ITT, HR=0.349 (95%CI: 0.303, 0.403) |
| Key safety data | No safety concerns.<br>**PBAC Comment:** None. | No safety concerns. |
| Clinical claim | Enzalutamide superior effectiveness in terms of overall survival compared to watchful waiting and docetaxel; non-inferior safety to watchful waiting but superior safety to docetaxel.<br>**PBAC Comment:** The PBAC considered, in light of input from clinicians and consumers, patients would <u>not</u> benefit substantially in survival from earlier treatment with enzalutamide [in a treatment algorithm], this is in contrast to the entire basis of the submission (Paragraph 7.3). The goal of earlier treatment is to maintain better quality of life for longer. For asymptomatic patients, the benefit is delaying symptoms from developing; for symptomatic patients, the benefit is delaying the toxicities of chemotherapy (Paragraph 7.2). | Enzalutamide superior effectiveness in terms of quality of life, pain progression, delaying subsequent treatment and progressive disease compared to watchful waiting; non-inferior safety to watchful waiting. |
| Economic evaluation | Cost-utility models comparing algorithms:<br>• Analysis A (enzalutamide → docetaxel → palliative care versus watchful waiting → docetaxel → palliative care), $45,000/QALY - $75,000/QALY (10 years).<br>• Analysis C (enzalutamide → docetaxel → palliative care versus docetaxel → abiraterone → palliative care), $45,000/QALY - $75,000/QALY (10 years).<br>**PBAC Comment:** The models were driven by assumptions about progression free survival which were not justified, and the PBAC did not consider Analysis A or C appropriately reflect the value (i.e., not overall survival) of early enzalutamide [in a treatment algorithm] (Paragraph 7.7). | Cost-utility model comparing algorithm: enzalutamide → docetaxel → best supportive care versus watchful waiting → docetaxel → enzalutamide or abiraterone, $45,000/QALY - $75,000/QALY (10 years). |
| Number of scripts | 10,000 – 50,000 scripts in Year 1 increasing to 10,000 to 50,000 scripts in Year 5.<br>**PBAC Comment:** DUSC considered the eligible population (*and hence number of scripts*) was likely underestimated (Paragraph 6.38). | 10,000 to 50,000 scripts in Year 1 increasing to 50,000 to 100,000 scripts in Year 5. |
| Estimated cost to PBS | $10 - $20 million in Year 1 increasing to $30 - $60 million in Year 5 for a total of more than $100 million over the first 5 years of listing.<br>**PBAC Comment:** DUSC considered the financial estimates model was poorly structured and did not adequately inform the budget impact estimates | $30 - $60 million in Year 1 decreasing to $20 - $30 million in Year 5 for a total of more than $100 million over |

| | Enzalutamide November 2015 | Current resubmission |
|---|---|---|
| | (Paragraph 6.38). | the first 5 years of listing. |
| PBAC decision | Reject. | - |

Source: Compiled during the evaluation using PBAC minutes November 2015 and the current enzalutamide submission, March 2017.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 4 Clinical place for the proposed therapy

4.1 Metastatic castrate resistant prostate cancer (mCRPC) is an advanced cancer of the prostate gland that has spread to the lymph nodes, bones or other organs of the body and is no longer sensitive to hormonal castration (surgical or medical). The submission proposed that upon diagnosis, asymptomatic patients in Australia would undergo a period of watchful waiting (including hormonal manipulation with first-generation anti-androgens), unless the patient is not suitable for chemotherapy, in which case enzalutamide may be initiated. Once symptoms develop, patients who are suitable for chemotherapy will receive docetaxel, post docetaxel they are then eligible for other PBS listed treatments such as cabazitaxel, enzalutamide or abiraterone (all these treatments have demonstrated benefits in patient survival). If enzalutamide is to be listed as requested, it will replace watchful waiting in 'asymptomatic' patients who are not already eligible for PBS enzalutamide treatment (however post docetaxel enzalutamide/abiraterone will then be precluded).

4.2 The ESC noted the treatment landscape for advanced prostate cancer is rapidly evolving and the treatment decisions are complex and depend on clinical factors, for example docetaxel may be recommended for asymptomatic patients with rapidly progressing disease and may also be used even earlier in the algorithm in patients with hormone-sensitive metastatic disease given results of recent trials.

4.3 The ESC noted that no clinical reasoning was provided for excluding symptomatic patients, and that it creates inequity, particularly as the PBAC previously considered symptomatic patients could benefit from delaying the toxicities of chemotherapy. The sponsor's PSCR stated that there are no clinical data available for the clinical effectiveness of enzalutamide for the treatment of symptomatic patients prior to chemotherapy.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 5 Comparator

5.1 The submission nominated watchful waiting as the comparator. The ESC considered this comparator would be better described as 'active surveillance' rather than 'watchful waiting' given the patients are closely monitored and receive medical interventions, such as anti-androgen deprivation therapy. The PBAC had previously considered enzalutamide versus watchful waiting to be the appropriate comparison for asymptomatic patients (and enzalutamide versus docetaxel for symptomatic

patients). The PBAC had previously stated being interested in the change in the treatment algorithm, specifically enzalutamide before docetaxel versus enzalutamide after docetaxel. The resubmission presented a modelled comparison between two treatment algorithms: enzalutamide → docetaxel → best supportive care versus watchful waiting → docetaxel → enzalutamide or abiraterone.

5.2 The ESC agreed that watchful waiting (or active surveillance) was the appropriate comparator for this submission. The intention may be that treatment with enzalutamide before chemotherapy would preclude treatment with enzalutamide or abiraterone after chemotherapy, however, the ESC noted clinical trials are underway for re-treatment with enzalutamide, both pre-chemotherapy and post-chemotherapy (NCT02116582). The current PBS listing for enzalutamide states 'patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug'; this could be open to interpretation for re-treatment. The algorithm will potentially be enzalutamide → docetaxel → abiraterone (or enzalutamide).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 6 Consideration of the evidence

### *Sponsor hearing*

6.1 There was no hearing for this item.

### *Consumer comments*

6.2 The PBAC noted and welcomed the input from individuals (90), health care professionals (7) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of potential benefits of treatment with enzalutamide prior to chemotherapy, including delaying disease progression, providing another treatment option for elderly and/or frail men who can't tolerate chemotherapy, delaying the toxicity associated with chemotherapy and the time spent away from family and friend during chemotherapy treatments, enhancing quality of life and extending life.

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

6.4 The PBAC recalled during the sponsor hearing in November 2015 the goal of earlier treatment with the novel hormonal therapies (enzalutamide or abiraterone) was

[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

discussed as delaying symptom development and chemotherapy toxicities, rather than improving survival.

### *Clinical trials*

6.5 The resubmission was based on one head-to-head trial comparing enzalutamide to placebo for watchful waiting (PREVAIL, n=1717). This trial was presented in the previous submission to support a comparison with watchful waiting; other trials included in the previous submission to facilitate comparisons with docetaxel and abiraterone were excluded.

6.6 Details of the trial presented in the resubmission are provided in the table below.

**Table 2: Trial and associated reports presented in the resubmission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Direct randomised trial** | | |
| PREVAIL | PREVAIL clinical study report FINAL: A multinational Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy | 28 February 2014 (Data cut off 16 Sept 2013) |
| | PREVAIL addendum report FINAL: A multinational Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy | 19 December 2014 (Data cut off 1 Jan 2014) |
| | Beer TM, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. | *New England Journal of Medicine* 2014; 371 (5):424-433 |
| | Beer TM, et al. Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. | *European Urology* 2016; (article in press) |
| | Loriot Y, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): Results from a randomised, phase 3 trial. | *The Lancet Oncology* 2015; 16 (5):509-521 |

Source: Table B.2-3, pp42-45 of the submission

6.7 The key features of the direct randomised trial are summarised in the table below.

**Table 3: Key features of the included evidence**

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|---|---|---|---|---|---|---|
| **Enzalutamide ± prednisolone versus placebo ± prednisolone** | | | | | | |
| PREVAIL | 1717 | R, DB, PG, PC / 31.0mths (final) | Low[a] | mCRPC; asymptomatic or mildly symptomatic; chemotherapy naive | Co-primary: OS, rPFS | Time to initiation of cytotoxic chemotherapy |

R=randomised; DB=double blind; PG=parallel group; PC=placebo-controlled; OS=overall survival; rPFS=radiographic progression-free survival.

[a] placebo cross-over after interim analysis

Source: compiled during the evaluation

6.8 The ESC noted that the PREVAIL ITT population may not be applicable to the proposed PBS population, as PREVAIL may have included patients unsuitable for chemotherapy and thus eligible for enzalutamide under the current PBS listings. The

PSCR states that while the PREVAIL trial did not exclude patients unsuitable for chemotherapy, only 4.7% of the ITT population did not receive cytotoxic chemotherapy as subsequent treatment. It is unknown whether these patients were unsuitable for chemotherapy, but the sponsor argued that given it was only a small proportion of the total ITT population, the ITT population as a whole can be considered to be applicable to the proposed PBS restriction.

***Comparative effectiveness***

6.9 In its consideration of the previous submission, the PBAC considered chemotherapy-naïve patients would not benefit substantially in survival from earlier treatment with enzalutamide in a treatment algorithm, which was not captured by the comparison presented in PREVAIL. In November 2015, the PBAC considered the overall survival gain of 4 months in PREVAIL did not represent a significant gain in survival compared to enzalutamide in the post-docetaxel setting (4.8 months in AFFIRM); but noted the differences in study designs and severity of patients in the trials in making this comparison.

6.10 In November 2015, the PBAC considered the purpose of earlier treatment with enzalutamide was maintaining quality of life for longer by i) delaying disease symptoms (such as pain, fractures and spinal cord compression) and ii) delaying or reducing time with toxicities from chemotherapy. The former was considered of most relevance to an asymptomatic population.

6.11 Table 4 presents a summary of results for secondary and exploratory (post-hoc) outcomes in PREVAIL that related to i) delaying subsequent treatment, ii) health-related quality of life and delaying symptoms, iii) pain progression and iv) delaying disease progression. These were mostly secondary and exploratory (post-hoc) outcomes from the trial as the primary intention of the trial was to determine a difference in survival for enzalutamide versus placebo as first line treatment in asymptomatic chemotherapy naïve men.

**Table 4: Results of PREVAIL that relate to i) delaying subsequent treatment, ii) health-related quality of life and delaying symptoms, iii) pain progression and iv) delaying disease progression.**

| Outcome | Median time, months (95%CI) | | Absolute difference, months (95% CI) | Relative difference HR (95% CI) |
|---|---|---|---|---|
| | Enzalutamide | Placebo | | |
| Time to initiation of cytotoxic chemotherapy | 28.0 (25.8,NYR) | 10.8 (9.7,12.2) | 17.2 months | 0.349 (0.303, 0.403) |
| Time to post-baseline antineoplastic therapy[d] | 22.8 (20.5,25.2) | 7.4 (6.6,8.2) | 15.4 months | 0.273 (0.240, 0.311) |
| Time to deterioration of FACT-P (total score) | 11.3 (11.1,13.9) | 5.6 (5.5, 5.6) | 5.7 months | 0.625 (0.542, 0.720) |
| Time to deterioration of FACT-P (pain scores)[a] | 8.3 (NR) | 2.8 (NR) | 5.5 months | 0.58 (0.51, 0.67) |
| Time to EQ-5D utility index deterioration[a] | 19.2 (NR) | 11.1 (NR) | 8.1 months | 0.62 (0.52, 0.72) |
| Time to EQ-5D VAS deterioration[a] | 22.1 (NR) | 13.8 (NR) | 8.3 months | 0.67 (0.56, 0.80) |
| Radiographic progression free survival^ | NR (13.8,NYR) | 3.9 (3.7,5.4) | NYR | 0.186 (0.149, 0.231) |
| Time to first skeletal-related event | 31.1 (29.5,NYR) | 31.3 (23.9,NYR) | -0.2 months[b] | 0.718 (0.610, 0.844) |
| Time to PSA progression | 11.2 (11.1,13.7) | 2.8 (2.8,2.9) | 8.4 months | 0.169 (0.147, 0.195) |
| Time to treatment discontinuation | [redacted][c] ([redacted], [redacted]) | [redacted] ([redacted], [redacted]) | [redacted] | [redacted] ([redacted], [redacted]) |

Abbreviations: PSA=prostate surface antigen; VAS=visual analogue scale; FACT-P=functional assessment of cancer therapy – prostate, NYR=not yet reached, NR=not reported.

[a] post-hoc analysis by Loriet et al (2015) ^this was a co-primary outcome.

[b] few patients remained at risk when medians were reached; 25th percentile results were 16.6 months versus 10.1 months in favour of enzalutamide; the hazard ratio indicated a statistically significant 28% reduction in risk of event.

[c] estimate differs slightly to median treatment duration reported in PREVAIL

[d] include both cytotoxic chemotherapy and non-cytotoxic therapies.

Source: constructed during the evaluation from sources presented in the submission.

6.12 The ESC noted that time to initiation of cytotoxic chemotherapy is the outcome relied on for the modelled economic evaluation. Given the PBAC had considered that the focus of any comparison between enzalutamide and watchful waiting should be on differences in the time to development of symptoms, time to initiation of cytotoxic chemotherapy may not capture the benefits of earlier enzalutamide treatment in asymptomatic patients. Additional relevant outcomes for assessing time to development of symptoms may include time to deterioration of FACT-P (pain scores) and time to first skeletal-related event. The PSCR stated that patients were required to demonstrate radiographic disease progression or a skeletal event prior to chemotherapy, and therefore time to chemotherapy is an appropriate surrogate measure for time to development of symptoms.

6.13 The median gain of 17.2 months for time to initiation of cytotoxic chemotherapy is much longer than for both the gain in time to deterioration of FACT-P (pain scores) (5.5 months) and time to first skeletal-related event (6.5 months at the 25th percentile, with few patients remaining at risk when medians were reached). This indicates patients may spend considerable time in pain prior to commencing chemotherapy, and in clinical practice, patients may also experience some relief in symptoms from radiotherapy.

***Comparative harms***

6.14 The safety data reported for the PREVAIL trial remains unchanged from the previous submission. A statistically significant greater proportion of patients treated with enzalutamide compared with placebo experienced (RR [95% CI)]:

- Any adverse event: 1.04 [1.02, 1.06];
- Any grade ≥3 adverse event: 1.16 [1.03, 1.30]; and
- Any serious adverse event: 1.20 [1.03, 1.39].

Statistically significantly fewer patients treated with enzalutamide experienced any adverse event leading to permanent discontinuation compared with placebo (0.66 [0.55, 0.80]).

6.15 Among those treated with enzalutamide, specific adverse events occurring more frequently within the first 90 days included hot flush (2.02 [1.50, 2.73]) and hypertension (3.07 [1.82, 5.17]) and those occurring less frequently within the first 90 days included back pain (0.61 [0.46, 0.81]) and decreased appetite (0.66 [0.48, 0.90]), compared with those treated with placebo.

***Benefits/harms***

6.16 The trial evidence presented in the submission does not specifically provide a comparison of the current (i.e., enzalutamide after docetaxel) versus proposed (enzalutamide before docetaxel) clinical management algorithms, which was of interest to the PBAC. However, on the basis of direct evidence presented by the resubmission the comparison of enzalutamide and watchful waiting, or 'placebo', in the PREVAIL trial in asymptomatic or mildly symptomatic, chemotherapy naïve mCRPC patients over a maximum duration of exposure of 31 months resulted in significant increases in additional time:

- before initiation of cytotoxic chemotherapy (median of approximately 17.2 months)
- before onset of cancer pain (median of approximately 5.5 months)
- on treatment (either enzalutamide or placebo), which may be related to time to 'disease progression' (median of approximately 13.1 months).

***Clinical claim***

6.17 The submission described enzalutamide as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo (for watchful waiting) in asymptomatic chemotherapy-naïve men with mCRPC. Although the trial evidence in PREVAIL does not specifically provide a comparison of the current and proposed algorithms, the results of PREVAIL were claimed to support that as a first line treatment until disease progression (ignoring effects of subsequent therapies and survival benefits) enzalutamide versus placebo in asymptomatic chemotherapy naïve patient mCRPC may:

- Delay subsequent treatment, including delaying time to initiation of cytotoxic chemotherapy and time to first post-baseline antineoplastic therapy;
- Improve quality of life and delay symptoms as measured by EQ-5D and FACT-P instruments;
- Delay onset of cancer pain;

- Delay disease progression as measured by radiographic progression free survival, time to skeletal-related events, time to prostate surface antigen (PSA) progression, PSA response and best overall tissue response.

6.18 The submission also described enzalutamide as non-inferior in terms of comparative safety over placebo (for watchful waiting), however a claim of inferior comparative safety of enzalutamide compared with placebo may be more appropriate as a statistically significantly greater proportion of those treated with enzalutamide experienced any, any grade ≥3 and any serious adverse event, compared with placebo.

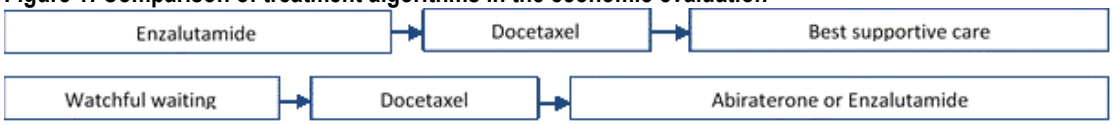
6.19 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.20 The PBAC noted the statistically significantly greater proportion of adverse events with enzalutamide. However, the harms from enzalutamide treatment were considered manageable.

***Economic analysis***

6.21 The submission presented an updated modelled economic analysis to estimate the incremental cost-effectiveness of enzalutamide before docetaxel without watchful waiting (proposed algorithm) compared with enzalutamide or abiraterone after docetaxel with watchful waiting (current algorithm) based on the ITT population of PREVAIL (Figure 1):

**Figure 1: Comparison of treatment algorithms in the economic evaluation**




6.22 Table 5 provides a summary of the model structure.

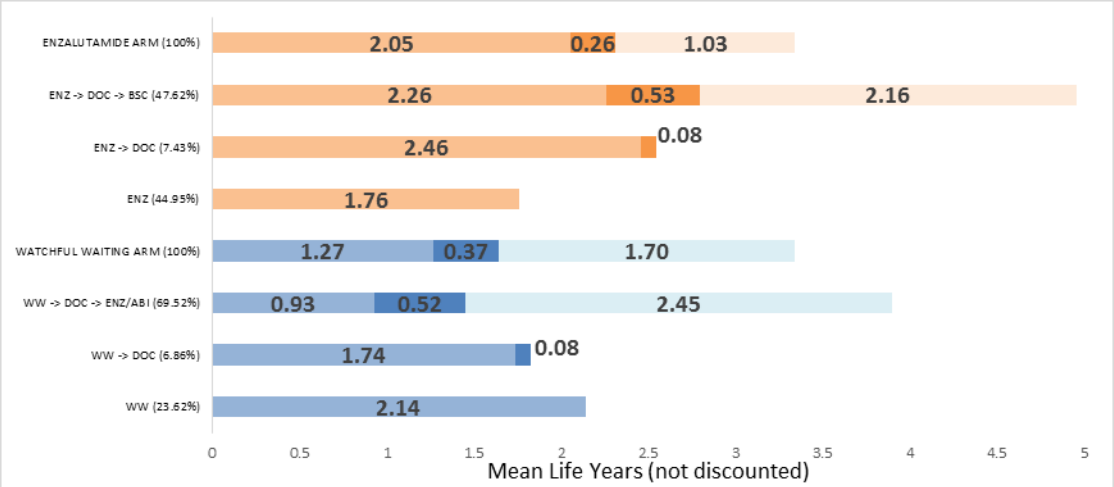
**Table 5: Summary of model structure and rationale**

| Component | Summary |
|---|---|
| Time horizon | 10 years in the model base case versus maximum of 44 months of survival data in PREVAIL |
| Outcomes | QALYs |
| Methods used to generate results | Cohort expected value analysis |
| Health states | A Markov model with three alive health states was presented. Patients enter the model in "Alive on first treatment" and may transition to a subsequent treatment tunnel state. Patients were assumed to commence second-line docetaxel for the first 6 months of the tunnel state ("Alive on second treatment") before transitioning to the third-line therapy thereafter ("Alive on third treatment"). Patients may transition to "Dead" during any cycle of the model. |
| Cycle length | 1 month |
| Half cycle correction | Yes |
| Discount rate | 5% for costs and outcomes |
| Transition probabilities | The model assumed patients in both arms of the model have equivalent survival, derived from overall survival (OS) in the enzalutamide arm of PREVAIL. The transition to the subsequent treatment tunnel state was informed by the time to initiation of cytotoxic chemotherapy in PREVAIL and was the treatment effect in the model. |

Source: compiled during the evaluation

6.23 Figure 2 summarises the mean years (not discounted) on treatment and the proportion of patients who received one- two- and three- lines of treatment in the model. Although mean overall survival was assumed equivalent, the mean time on treatment and proportions who received subsequent therapies varied across arms; the model implied that enzalutamide will both displace and replace docetaxel.

**Figure 2: Mean years (not discounted) and proportion of patients on treatment (≡in health states) by model arm and treatments received**




Legend: progression through three alive health states, alive on first treatment (light blue/orange) → alive on second treatment (dark blue/orange) → alive on third treatment (pale blue/orange)
Source: constructed during the evaluation

6.24 The PREVAIL trial data has been repurposed to provide a measure of quality of life benefit from delayed cytotoxic chemotherapy, using time in the different treatments as a proxy for progression.

6.25 The modelled economic evaluation (based on the time to chemotherapy outcome in PREVAIL ITT) predicted that the average delay in time to disease progression is 9.4 months for enzalutamide versus watchful waiting over the estimated mean survival of 40.1 months. Table 6 presents a comparison of the mean time on treatment in the economic model and trial evidence, before and after docetaxel; time on enzalutamide after docetaxel may have been significantly overestimated in the model.

**Table 6: Average time on treatment reported in the clinical evidence and predicted by the model, before and after docetaxel**

| | Trial evidence | | | Economic model |
|---|---|---|---|---|
| | Source | Treatment duration (Safety) | Time to chemotherapy (ITT) | (Sections D and E) |
| **Pre-docetaxel** | | | | |
| Enzalutamide | PREVAIL | 16.6 months (median); 15.8 months (mean) | 28.0 months (median)[a] | [redacted] months (median); [redacted] months (mean) |
| Placebo / watchful waiting | | 4.6 months (median); 7.0 months (mean) | 10.8 months (median)[a] | [redacted] months (median); [redacted] months (mean) |
| **Post-docetaxel** | | | | |
| Enzalutamide | AFFIRM | 8.3 months (median); 8.5 months (mean) | - | [redacted] months (median)[b]; [redacted] months (mean)[b] |
| Placebo / watchful waiting | | 3.0 months (median); 4.3 months (mean) | - | [redacted] months (median)[b]; [redacted] months (mean)[b] |

[a] Patients who did not start cytotoxic chemotherapy at the time of analysis data cut-off were censored at date of last assessment indicating no evidence of cytotoxic chemotherapy usage

[b] Time in health state for the proportion who enter the post-docetaxel health state, 69.52% received post-docetaxel enzalutamide (watchful waiting arm) and 47.62% received post-docetaxel best-supportive care / placebo (enzalutamide arm)

Source: constructed during the evaluation

6.26 Table 7 summarises the key drivers of the model. The model was driven by i) significant cost-offsets associated with assumed life-long treatment with enzalutamide or abiraterone after docetaxel in the watchful waiting arm, and ii) any parameter that varied the incremental difference in mean time before and after chemotherapy which impacted on the accrual of those cost-offsets.

**Table 7: Key drivers of the model**

| Description | Method/Value | Impact |
|---|---|---|
| Duration on third-line enzalutamide or abiraterone | The model assumed patients will remain on third-line treatment until death; the median time on enzalutamide or abiraterone post docetaxel in the watchful waiting arm was [redacted] months. This was likely significantly overestimated resulting in significant cost-offsets in the watchful waiting arm. By comparison, patients remained on enzalutamide and abiraterone for a median duration of 8.5 and 7.3 months in post-docetaxel trials AFFIRM and COU-AA-301 respectively. | High, favoured enzalutamide |
| Time to subsequent treatment (on first treatment) | This was based on the time to initiation of cytotoxic chemotherapy (TTC) in PREVAIL. This likely overestimated the time spent in the "alive on first-treatment" health state because: i) subsequent therapy after discontinuation was not stipulated in PREVAIL and may or may not have included cytotoxic chemotherapy, and ii) not all patients enrolled in PREVAIL may have been suitable for cytotoxic chemotherapy in the future. TTC is considerably longer in PREVAIL compared with time to discontinuation (TTD) and time to first post-baseline antineoplastic therapy. The ICER decreases if less time is spent on first-line treatment because more time will be spent on third-line treatment associated with considerable cost-offsets. | High, did not favour enzalutamide |
| Time to subsequent treatment (on second treatment) | The model assumed patients remain on second-line docetaxel for a maximum of 6 months before commencing third-line treatment, on the basis of mean time on docetaxel in the 10% PBS sample. The ICER increases as the assumed time on docetaxel increases due largely to fewer cycles on third-line treatment and associated cost-offsets. Time on docetaxel may not be a reasonable proxy for disease progression on docetaxel in the model given patients typically cease treatment with docetaxel after a maximum of 10 doses regardless of disease progression. | Low-Moderate, favoured enzalutamide |
| Time horizon | The model assumed a 10 year time horizon on the basis of capturing costs and outcomes until death. Given TTC likely delayed the time until patients reached the "alive on third-treatment" health state, a long time horizon had favoured enzalutamide as larger costs offsets accrue in later years. 10 years may not be a reasonable time horizon as benefits of treatment are more likely to be experienced in the first few years; the ICER was not sensitive to halving the time horizon when the transition to subsequent therapy was informed by TTD. | High, favours enzalutamide (low in combination with TTD) |

Source: compiled during the evaluation

6.27 The key driver of the model was the assumed life-long treatment with enzalutamide or abiraterone after docetaxel in the watchful waiting arm. Given the current listings of enzalutamide/abiraterone require patients to cease treatment after disease progression, this assumption is not reasonable and considerably favours enzalutamide. Although the PSCR noted the public summary document for abiraterone in July 2012 mentions PBAC's concern that abiraterone use may continue well beyond disease progression, the assumption of 100% use beyond progression is unreasonable, considerably favours enzalutamide and has a substantial impact on the ICER. For this reason, and given that no difference in survival was assumed and time to discontinuation data indicated the vast majority of patients would cease enzalutamide by 5 years, a 10 year time horizon may not be appropriate (see Figure 3).

6.28 Table 8 summarises the results of the modelled economic evaluation. The base case ICER was estimated to be $45,000/QALY gained - $75,000/QALY gained. The ICER falls considerably following extrapolation from 3.7 years to 10 years due to the accrual of significant cost-offsets in the watchful waiting arm, associated with the assumption that patients remain on third-line enzalutamide (or abiraterone) after docetaxel until death (i.e., up to 114 months permitted in first 120 months).

**Table 8: Results of the stepped economic evaluation (discounted)**

| Step and component | Enzalutamide arm (ENZ -> DOC -> WW) | Watchful waiting arm (WW -> DOC -> ENZ/ABI) | Increment |
|---|---|---|---|
| Step 1: trial based economic evaluation (outcome measured in QALYs)<br>Time horizon of 3.7 years (44 months)<br>• Drug costs (incl. consultations for docetaxel) | | | |
| Costs | $ [redacted] | $ [redacted] | $ [redacted] |
| QALY | [redacted] | [redacted] | [redacted] |
| **Incremental cost/extra QALY gained** | | | **$** [redacted] |
| Step 2: Modelled economic evaluation including all resource utilisation<br>• Time horizon of 3.7 years (44 months)<br>• All costs (drug costs, tests and consultations) | | | |
| Costs | $ [redacted] | $ [redacted] | $ [redacted] |
| QALY | [redacted] | [redacted] | [redacted] |
| **Incremental cost/extra QALY gained** | | | **$** [redacted] |
| Step 3: Modelled economic evaluation extrapolated to 10 years<br>• Time horizon of 10 years (120 months)<br>• All costs (drug costs, tests and consultations) | | | |
| Costs | $ [redacted] | $ [redacted] | $ [redacted] |
| QALY | [redacted] | [redacted] | [redacted] |
| **Incremental cost/extra QALY gained** | | | **$** [redacted] |

Source: Tables D.5.1, D.5.2 and D.5.3, pp212 to 213 of the submission

The redacted table shows ICERs in the range of $45,000/QALY gained - $200,000/QALY gained.

6.29 Figure 3 illustrates the relationship between the estimated ICER and the maximum number of months that patients are permitted to receive enzalutamide or abiraterone after docetaxel in the modelled economic evaluation.

**Figure 3: Modelled ICER varying the maximum number of cycles that costs for enzalutamide or abiraterone are assigned in the alive (on third treatment) health state**

Source: constructed during the evaluation

The redacted figure show that over the time range of 0 to 120 months, the ICER ranges from $45,000/QALY - more than $200,000/QALY.

6.30 Assuming a maximum of eight months on enzalutamide or abiraterone post-docetaxel in-line with the trial evidence (in the post docetaxel setting), increased the ICER from $45,000/QALY - $75,000/QALY (base case) to more than $200,000/QALY.

6.31 Overall, the ESC considered that the use of time to cytotoxic chemotherapy as the main clinical outcome and the use of the 10 year time horizon were likely to result in an overestimate of the cost-effectiveness of enzalutamide in the proposed setting.

6.32 The pre-PBAC response presented a revised base case economic evaluation. In the revised base case, the duration of treatment with enzalutamide and abiraterone in the post-docetaxel setting was reduced to 14 months, based on a 10% PBS sample of enzalutamide and abiraterone use, and the total cost of chemotherapy-naïve treatment with enzalutamide was revised using the outcome of time to discontinuation of study drug. This had the overall effect of increasing the ICER, and the sponsor proposed an [redacted]% price reduction on the effective DPMQ (to $[redacted]) in order to maintain the ICER of $45,000/QALY gained - $75,000/QALY gained.

6.33 There is no description in the pre-PBAC response or accompanying Prospection report of the methods that were used to derive the revised average time on post-docetaxel therapy of 14 months. The PBAC noted data from the June 2016 DUSC review of prostate cancer medicines found that there was a mean number of 9.5 scripts for abiraterone. When this analysis was updated to include data up to December 2016, with the same initiating cohort (i.e. 6 month initiating cohort on abiraterone between October 2013 to March 2014), including treatment breaks and

capturing switching between abiraterone and enzalutamide, the mean number of scripts was [redacted].

6.34 The PBAC also noted the ESC concerns with the 10 year time horizon, however, accepted that 10 years was considered appropriate during evaluation of the previous submission for enzalutamide in this earlier treatment setting and therefore, the 10 year time horizon would be acceptable.

***Drug cost/patient/year***

6.35 $[redacted] /patient/year assuming an effective DPMQ of $[redacted]/script (28 days) and 13.04 scripts/patient/year (365.25/28). Based on the revised price of $[redacted] in the pre-PBAC response, the drug cost/patient/year would be $[redacted].

6.36 When considering the mean duration of treatment of 15.8 months in PREVAIL, the estimated cost per course of enzalutamide was estimated to be $[redacted] per patient. This estimate does not include any cost-offset associated with a reduction in treatment with first-generation anti-androgens while watchful waiting or treatment with enzalutamide or abiraterone post-docetaxel. By comparison, the cost for enzalutamide in the post-docetaxel setting was estimated to be $[redacted] per patient, assuming an effective DPMQ of $[redacted]/script and a mean duration of treatment of 8.5 months as per the AFFIRM trial.

***Estimated PBS usage & financial implications***

6.37 This resubmission was considered by DUSC. In November 2015, DUSC considered the financial model in the previous submission was structurally flawed and too unreliable to project the financial implications of the enzalutamide listing and its impact on existing therapies.

6.38 The resubmission presented an updated mixed epidemiological and market share approach to estimate the cost to government of the proposed listing of enzalutamide in asymptomatic chemotherapy naïve patients with mCRPC who are not currently eligible for enzalutamide (i.e., those who are suitable for future docetaxel).

6.39 The modelled economic evaluation presented in Section D was used to estimate all resource utilisation under the two scenarios: i) current algorithm (watchful waiting → docetaxel → enzalutamide or abiraterone) and ii) proposed algorithm (enzalutamide → docetaxel → best supportive care). The difference between the two is the incremental cost of listing. Table 9 summarises the net financial implications of the proposed enzalutamide listing on PBS.

**Table 9: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | |
| 1st line enzalutamide scripts | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 2nd line docetaxel scripts | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 2nd line prednisolone scripts | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 2nd line dexamethasone scripts | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 3rd line enzalutamide scripts | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 3rd line abiraterone scripts | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| IV infusions | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Consultations | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PSA tests | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ALP / LDH tests | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| CT scans | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Bone scans | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated cost to PBS/MBS** | | | | | |
| Cost to PBS/RPBS for 1st-line enzalutamide | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] |
| Cost to PBS/RPBS for other drugs | -$[redacted] | -$[redacted] | -$[redacted] | -$[redacted] | -$[redacted] |
| Cost to MBS for monitoring | -$[redacted] | -$[redacted] | -$[redacted] | -$[redacted] | -$[redacted] |
| **Estimated total net cost** | | | | | |
| Net cost to government | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] |

Source: Compiled during the evaluation

The redacted table shows that at year 5 the net cost to government is $20 - $30 million.

6.40 Given the economic model was used to estimate the financial impact of the proposed listing, the estimates were driven by i) significant cost-offsets associated with assumed life-long treatment with enzalutamide or abiraterone after docetaxel in the watchful waiting arm, and ii) any parameter that varies the incremental difference in mean time before and after chemotherapy (eg time on first treatment) which impact on the accrual of those cost-offsets.

6.41 The following issues were identified during evaluation:

- The number of scripts of first-line enzalutamide (proposed algorithm) was likely overestimated because the use of time to chemotherapy (TTC) in PREVAIL likely overestimated duration on first-line therapy; the mean time on treatment in the model was [redacted] months versus 15.8 months in PREVAIL;
- As a flow on, the reduction in the number of scripts of second-line docetaxel (and concomitant dexamethasone / prednisolone) may therefore be overestimated with greater impact in the enzalutamide arm; and
- the reduction in number of scripts of third-line enzalutamide (and abiraterone) was also a likely overestimate, particularly in the latter years, because the model assumed patients remain on treatment until death; the mean time on treatment (for those who received treatment) in the model was [redacted] months versus 8.5 months in post docetaxel trial evidence.

6.42 Additional issues raised by DUSC were also noted:

- The uptake rates were assumed to be 60% in the first listing year plateauing at 80% from the third year of listing. DUSC considered that the treatment uptake

assumptions were likely to have been underestimated based on experience with the high uptake of enzalutamide in the post-chemotherapy setting and clinical experience with this agent;
- Prescribers may use non-opioid analgesia in order to access enzalutamide which may result in suboptimal pain management for some patients; and
- Asymptomatic patients who progress on enzalutamide and who are ineligible for chemotherapy were not explicitly considered in the proposed treatment algorithm. It is unclear whether these patients would be precluded from further treatment with abiraterone or enzalutamide.

6.43 As a sensitivity analysis, limiting the maximum duration of post docetaxel enzalutamide or abiraterone to 8 months in the watchful waiting arm in-line with trial evidence increased the net cost over 5 years to more than $100 million (+78.87%), compared to the base case estimate of more than $100 million.

6.44 Based on the revisions to the economic model provided in the pre-PBAC response and the [redacted]% price reduction offered, the cost to the PBS/RPBS for 1st line enzalutamide was revised:

**Table 10: revised estimated financial implications**

| Estimated cost to PBS/RPBS | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| March 2017 submission | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] |
| Pre-PBAC response revised estimates | $[redacted] | $[redacted] | $[redacted] | $[redacted] | $[redacted] |

The redacted table shows that at year 5, the revised estimated net cost to the PBS in the pre-PBAC response would be $60 - $100 million.

6.45 To manage uncertainties raised by DUSC with respect to the estimates of patient numbers, uptake rates and cost-offsets, the pre-PBAC response offered a [redacted]% rebate on PBS expenditure above the caps, based on the revised estimates in the table above.

6.46 The PBAC noted the revised financial estimates unreasonably exclude symptomatic patients.

6.47 The PBAC did not consider the [redacted]% rebate offered in the pre-PBAC response would adequately address the uncertainties raised by DUSC and the financial risk of use beyond that assessed for cost-effectiveness and outside of the restriction (use beyond disease progression, sequential use or retreatment, use in patients with WHO performance status greater than 1). The PBAC considered that risk-sharing arrangements should take account of the once in a lifetime use, 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 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,

with longer duration of therapies.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 7 PBAC Outcome

7.1 The PBAC deferred recommending an extended PBS listing for enzalutamide for the treatment of metastatic castrate-resistant prostate cancer (mCRPC) prior to docetaxel, on the basis of requiring: a more appropriate assumption of the duration of post-docetaxel treatments in the watchful waiting arm of the model, which requires a further price reduction to maintain an acceptable ICER; a broadening of the proposed restriction to include symptomatic patients; and 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.

7.2 The proposed PBS restriction limited treatment in the pre-docetaxel setting to asymptomatic patients, defined on the basis of a lack of opioid use for cancer pain. The PBAC considered this was unworkable and inappropriate. The PBAC noted the pre-PBAC response (p1) highlighted that treatment guidelines for first-line treatment of mCRPC differed for asymptomatic and symptomatic patients as outlined in the 2015 NCCN guidelines. However, the PBAC agreed with the ESC and DUSC that no strong clinical reasoning was provided for a PBS listing that excludes symptomatic patients, and that it would create inequity, particularly as the PBAC previously considered that some symptomatic patients may prefer to delay chemotherapy until after treatment with an oral agent. The PBAC recommended that the PBS restriction specify treatment in the pre-docetaxel setting without referring to symptoms, leaving clinicians to decide when treatment should be initiated.

7.3 The PBAC agreed with the request to retain the current 'once in a lifetime' criteria in the PBS restriction which would mean the use of enzalutamide prior to chemotherapy would preclude treatment with enzalutamide or abiraterone after chemotherapy. The post-docetaxel restrictions for abiraterone and enzalutamide would need to be updated to make this clear. Any proposal for retreatment with these agents would require new data.

7.4 The PBAC agreed with the ESC that watchful waiting (or active surveillance) was the appropriate comparator for this submission.

7.5 The PBAC noted the secondary and exploratory (post-hoc) outcomes in PREVAIL supported maintaining better quality of life for longer with earlier enzalutamide treatment in mCRPC. The PBAC noted that significant increases in additional time: before initiation of cytotoxic chemotherapy; before onset of cancer pain; and to discontinuation of initial therapy were observed in patients treated with enzalutamide versus placebo (watchful waiting) in the PREVAIL trial. The PBAC considered that the claim of superior (albeit modest) comparative effectiveness in relation to quality of life outcomes was reasonable.

7.6 The PBAC agreed with the ESC that time to initiation of cytotoxic chemotherapy may not adequately capture the benefits of earlier enzalutamide treatment in asymptomatic patients, which would include delaying skeletal events and bone pain. This may overestimate the cost-effectiveness of enzalutamide by using the outcome

with the largest duration of benefit, as shown in Table 4 above, thereby overestimating time spent in the first health state of the model. However, the PBAC considered the outcome was a reasonable endpoint in this instance, given the proposed reversal of the sequence of treatments from a cytotoxic chemotherapy (docetaxel) followed by an oral androgen receptor signalling inhibitor (enzalutamide) was not expected to give patients substantial survival benefit but would provide meaningful improvements in quality of life by avoiding cytotoxic chemotherapy for longer.

7.7 The PBAC noted the patient population in the PREVAIL trial included asymptomatic and mildly symptomatic patients only. The PBAC considered the benefits in delaying cytotoxic chemotherapy would apply to symptomatic patients considered suitable for enzalutamide in a pre-docetaxel setting.

7.8 The PBAC noted that a statistically significantly greater proportion of patients treated with enzalutamide compared to placebo in PREVAIL experienced adverse events. However, the PBAC considered that the harms from enzalutamide treatment manageable.

7.9 The PBAC noted the ICER was driven by the cost-offsets from treatments in the post-docetaxel setting in the watchful waiting arm, which had inappropriately been assumed to continue until death. The PBAC noted the revised base case provided in the pre-PBAC response but considered the 14 months of post-docetaxel treatment was not adequately justified and is likely to be an overestimate, based on the June 2016 DUSC review of prostate cancer medicines.

7.10 The PBAC accepted the 10-year time horizon in the model and the total cost of chemotherapy naïve treatment with enzalutamide using the outcome of time to discontinuation of study drug, as provided in the pre-PBAC response.

7.11 The PBAC accepted the ICER for mCRPC in the pre-docetaxel setting should not exceed the $45,000/QALY gained - $75,000/QALY gained presented in this resubmission, noting a similar ICER was accepted for listing cabazitaxel in the post-docetaxel setting. The model would need to be adjusted for an average time on post-docetaxel therapies in line with the DUSC review with a further price reduction to ensure the ICER remains acceptable.

7.12 The PBAC noted the financial estimates are predicated on the duration of therapy in both the pre- and post-docetaxel settings as estimated by the economic model. The estimates for the pre-docetaxel setting need to be updated to include symptomatic patients, revisions regarding duration of therapies, and the revised price. The caps on total expenditure for both the settings would need to be merged or the existing caps for the post-docetaxel setting be reduced in accordance with the cost-offsets arising in this setting, and the rebates further negotiated, as discussed in paragraph 6.47.

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

**Outcome:**
Deferred

## 8 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.

## 9 Sponsor's Comment

The sponsor had no comment.