

**3.01 ABIRATERONE ACETATE,  
Tablet 250 mg, 500 mg  
Zytiga<sup>®</sup>,  
Janssen-Cilag Pty Ltd**

**ENZALUTAMIDE  
Capsule, 40 mg  
Xtandi<sup>®</sup>,  
Astellas Pharma Australia Pty Ltd**

**Purpose of Item**

- 1.1 The Secretariat sought advice on amending the existing listings for abiraterone and enzalutamide for the treatment of metastatic castration-resistant prostate cancer (mCRPC) by removing the requirement for patients to have failed prior docetaxel or to have a predicted intolerance to docetaxel ('pre-docetaxel').
- 1.2 Allowing use of abiraterone and enzalutamide in the pre-docetaxel mCRPC setting would better align with the use of these drugs in clinical practice. PBS data considered in the context of the major November 2020 enzalutamide submission (see Public Summary Document (PSD) of the November 2020 PBAC meeting, item 7.01, paragraph 5.6) indicated that the majority of use is in patients who have not received prior treatment with docetaxel.

**2 Background**

***Registration status***

- 2.1 Enzalutamide is registered for the treatment of patients with:
  - non-metastatic castration-resistant prostate cancer (mCRPC);
  - mCRPC following failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet indicated; and
  - mCRPC who have previously received docetaxel.

- 2.2 Abiraterone is registered for use in combination with prednisone or prednisolone for the treatment of patients with:
- newly diagnosed high-risk metastatic hormone sensitive prostate cancer in combination with ADT;
  - mCRPC who are asymptomatic or mildly symptomatic after failure of ADT; and
  - mCRPC who have received prior chemotherapy containing a taxane.

### ***Current PBS listings***

- 2.3 Abiraterone and enzalutamide are listed on the PBS for the treatment of patients with mCRPC whose disease has progressed following treatment with docetaxel, or who have a predicted intolerance to docetaxel.
- 2.4 At the July 2014 PBAC meeting enzalutamide was recommended for listing with the above indication on a cost-minimisation basis with abiraterone (paragraph 7.1, enzalutamide PSD, July 2014).

### ***Previous PBAC consideration***

- 2.5 Abiraterone was previously considered for use pre-docetaxel at the July 2014 PBAC meeting. It was not recommended because the comparator was inappropriate, the sub-group analysis was not considered the most relevant patient group for PBS eligibility, the ICER was too high and the total PBS cost of treatment with abiraterone shifting from post-docetaxel to post-ADT was uncertain (paragraph 7.1, abiraterone, PSD, July 2014).
- 2.6 Enzalutamide was previously considered by the PBAC for the treatment of mCRPC in patients who have not received prior docetaxel in November 2015 (not recommended), March 2017 (deferred) and July 2017 (deferred).
- 2.7 In July 2017, the PBAC deferred making a recommendation 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 were required regarding the proposed price of enzalutamide, the proposed financial caps, and the size of the patient population to ensure that the incremental cost-effectiveness ratio (ICER) was acceptable (paragraph 5.1, enzalutamide, PSD, July 2017).

## **3 Proposed listing**

- 3.1 Noting that both apalutamide and enzalutamide are TGA indicated for use in mCRPC patients who have failed ADT, revised PBS restrictions which remove the requirement for prior docetaxel would be in line with both how these drugs are being used in clinical practice and their TGA indications. The Secretariat proposed the amendments to the existing restrictions as outlined below (suggested deletions are in strikethrough).

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ENZALUTAMIDE					
enzalutamide 40 mg capsule, 112	10174L	1	112	2	Xtandi
<b>Category/Program:</b> GENERAL – General Schedule (GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online)					
<b>PBS indication:</b> Castration resistant metastatic carcinoma of the prostate					
<b>Clinical criteria:</b> The treatment must not be used in combination with chemotherapy					
<b>AND</b>					
<b>Clinical criteria:</b> <del>Patient must have failed treatment with docetaxel due to resistance or intolerance; or</del> <del>Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel</del>					
<b>AND</b>					
<b>Clinical criteria:</b> Patient must have a WHO performance status of 2 or less					
<b>AND</b>					
<b>Clinical criteria:</b> Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug					
<b>AND</b>					
<b>Clinical criteria:</b> Patient must not have received prior treatment with abiraterone; or Patient must have developed intolerance to abiraterone of a severity necessitating permanent treatment withdrawal.					
<b>Administrative advice:</b> Special Pricing Arrangements apply					
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised					
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised					

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ABIRATERONE					
abiraterone acetate 500 mg tablet, 60	11206T	1	60	2	Zytiga
abiraterone acetate 250 mg tablet, 120	2698B	1	120	2	Zytiga
<b>Category/Program:</b> GENERAL – General Schedule (GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required					
<b>PBS indication:</b> Castration resistant metastatic carcinoma of the prostate					
<b>Clinical criteria:</b> The treatment must be used in combination with a corticosteroid					
<b>AND</b>					
<b>Clinical criteria:</b> The treatment must not be used in combination with chemotherapy					
<b>AND</b>					
<b>Clinical criteria:</b> <del>Patient must have failed treatment with docetaxel due to resistance or intolerance; or</del> <del>Patient must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel</del>					
<b>AND</b>					
<b>Clinical criteria:</b> Patient must have a WHO performance status of 2 or less					
<b>AND</b>					
<b>Clinical criteria:</b>					

Patient must not receive PBS-subsidised treatment abiraterone if progressive disease develops while on abiraterone
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not have received prior treatment with enzalutamide; or
Patient must have developed intolerance to enzalutamide of a severity necessitating permanent treatment withdrawal.
<b>Administrative advice:</b> Special Pricing Arrangements apply
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised

- 3.2 The intent, which remains unchanged, is that a patient could only receive either enzalutamide or abiraterone once per lifetime.

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

## 4 Current considerations

### ***Estimated PBS usage***

- 4.1 Data provided by the DUSC Secretariat, (which was provided to the sponsors of abiraterone, cabazitaxel and enzalutamide in September 2020 for the years 2013 to 2019), indicated that the majority of use of abiraterone and enzalutamide was in patients who had not received prior treatment with docetaxel (69% of patients in

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2020). It should be noted that some of the use of docetaxel may have been in the castrate-sensitive setting.

**Table 1: DUSC Secretariat analysis of abiraterone, enzalutamide and cabazitaxel use, 2014 to 2020\***

	2014	2015	2016	2017	2018	2019	2020
<b>Number of prevalent patients supplied with abiraterone and enzalutamide**</b>							
Abiraterone	2,196	2,053	1,842	2,083	2,236	2,410	2,495
Enzalutamide	271	2,272	3,065	3,563	4,081	4,295	4,445
Cabazitaxel	495	635	762	771	835	990	1,010
Total	2,528	4,169	4,890	5,671	6,360	6,919	7,950
<b>Number of patients first initiating on abiraterone or enzalutamide***</b>							
<b>Abiraterone</b>							
Without prior docetaxel use, n(%)	269 (20)	661 (60)	637 (65)	782 (65)	815 (70)	876 (72)	824 (69)
With prior docetaxel use, n(%)	1,057 (80)	457 (40)	339 (35)	418 (35)	360 (30)	347 (28)	373 (31)
Total	1,326	1,118	976	1,200	1,175	1,223	1,197
<b>Enzalutamide</b>							
Without prior docetaxel use, n(%)	109 (62)	1,110 (68)	1,115 (68)	1,238 (70)	1,262 (68)	1,237 (69)	1,325 (69)
With prior docetaxel use, n(%)	68 (38)	515 (32)	521 (32)	534 (30)	580 (32)	547 (31)	596 (31)
Total	177	1,625	1,636	1,772	1,842	1,784	1,921

\* PBS data was extracted from the Services Australia Prescription database for the period 1 January 2000 to 31 December 2020 based on the date of supply. Patients were classified as having been supplied abiraterone, cabazitaxel or enzalutamide after a prior supply of docetaxel or supplied a mCRPC drug without a prior PBS supply of docetaxel (based on previous 5 years).

\*\* As patient may use more than one drug, sum of prevalent including all drugs is more than the unique count for any drug.

\*\*\* Figures are for first ever initiation on either abiraterone or enzalutamide. That is, this analysis identifies dispensing of first ever PBS treatment after docetaxel, or first ever drug supplied after no prior record of supply of docetaxel.

Source: DUSC Secretariat

DUSC = Drug Utilisation Sub-Committee

- 4.2 As shown in Table 1, the number of patients first initiating on abiraterone or enzalutamide has been relatively stable since 2017, whereas the number of prevalent patients has increased. This may reflect increasing durations of therapy.
- 4.3 The treatment algorithm for CRPC is evolving due to the availability of more sensitive screening (prostate-specific membrane antigen (PSMA) PET scanning) that can detect micro metastases that are not seen with conventional imaging.
- 4.4 There is clinical data to support the earlier use of enzalutamide, including in patients with micro metastases. The PROSPER trial (N = 1,401) compared enzalutamide with placebo (both in combination with ADT) in patients with mCRPC. In the overall population enrolled in PROSPER, enzalutamide was associated with a statistically significant increase in overall survival (OS) compared with placebo. The hazard ratio was 0.73 (95% confidence interval (CI): 0.61, 0.89) at the third interim analysis,<sup>1</sup> with 42% (196/465) of patients from the placebo arm having received subsequent enzalutamide.<sup>2</sup> While patients in this study were non-metastatic by conventional imaging, it is likely that a substantial proportion would have had micro metastases on

<sup>1</sup> Sternberg et al, Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer; N Engl J Med 2020; 382:2197-2206. Accessed at: <https://www.nejm.org/doi/full/10.1056/NEJMoa2003892>

<sup>2</sup> Based on Table 1 of Sternberg et al, noting 19% of patients crossed-over to enzalutamide, while others received it as a subsequent post-progression therapy.

PSMA-PET. A study by Fendler et al 2019 retrospectively assessed the extent of disease detected by PSMA-PET in a cohort (N = 200) of high-risk patients with CRPC who were selected to be similar to those included in PROSPER. 55% of the study population had distant metastatic disease despite having no signs of distant metastases on conventional imaging.<sup>3</sup>

- 4.5 In their pre-PBAC response, the sponsor for abiraterone noted that the COU-302 trial provided clinical evidence supporting earlier use of abiraterone prior to docetaxel.<sup>4</sup>
- 4.6 The price of abiraterone and enzalutamide have reduced substantially due to negotiated administrative price reductions since the previous considerations for a revised listing.
- 4.7 There is expected to be no financial impact as amending the restrictions will align them with current clinical practice. The majority of patients are currently supplied abiraterone or enzalutamide without a PBS claim record of a prior supply of docetaxel. For the remaining patients, the use of abiraterone or enzalutamide prior to docetaxel is expected to replace the use of these agents post-docetaxel (noting patients would only be eligible to receive one of enzalutamide or abiraterone once per lifetime). Given the high use of abiraterone or enzalutamide prior to docetaxel in current practice, amending the restriction was considered also likely to have minimal impact on the use of docetaxel or the duration of treatment with abiraterone or enzalutamide.

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

## **5 PBAC Outcome**

- 5.1 The PBAC recommended amending the listings of abiraterone and enzalutamide to allow their use in patients with metastatic castration-resistant prostate cancer (mCRPC) prior to receiving docetaxel. The PBAC considered that removal of the requirement for patients to have either received prior docetaxel or to have a predicted intolerance to docetaxel would better align the restrictions for abiraterone and enzalutamide with how these drugs are being used in clinical practice and with their TGA indications.
- 5.2 The PBAC noted that data provided by the DUSC Secretariat indicated that in 2020 69% of use of abiraterone and enzalutamide was in patients who had not received a prior supply of docetaxel.
- 5.3 The PBAC recalled that it had previously considered both abiraterone (in July 2014) and enzalutamide (in November 2015, March 2017 and July 2017, with the March 2017 submission remaining deferred this meeting) for use in patients prior to


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<sup>3</sup> Fendler et al, Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer; Clin Cancer Res December 2019 (25) (24) 7448-7454; Accessed at: <https://clincancerres.aacrjournals.org/content/25/24/7448>

<sup>4</sup> Ryan et al, Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy; N Engl J Med 2013; 368:138-148

docetaxel. The PBAC also noted the results from the PROSPER trial and the Fendler et al 2019 study. The PBAC considered that the clinical benefit of abiraterone and enzalutamide prior to docetaxel had been established.

- 5.4 The PBAC noted that the prices of abiraterone and enzalutamide had reduced significantly since their previous considerations for this indication due to negotiated administrative priced reductions. The PBAC considered that both drugs would now likely be cost effective without prior use of docetaxel.

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- 5.6 Given the high use of abiraterone and enzalutamide without a prior supply of docetaxel, the PBAC considered that there would be no financial implications of the restriction change. The PBAC considered that any additional use of abiraterone and enzalutamide prior to docetaxel would, in the majority of cases, replace use post docetaxel, as patients are only eligible to receive abiraterone or enzalutamide once per lifetime. The PBAC considered that the amendments to the abiraterone and enzalutamide restrictions would also have minimal impact on the use of docetaxel and the duration of treatment with abiraterone and enzalutamide.
- 5.7 The PBAC considered that the proposed changes to the existing clinical criteria of the abiraterone and enzalutamide restrictions, to allow use without prior docetaxel were appropriate.
- 5.8 The PBAC noted that the availability of more sensitive screening, such as prostate-specific membrane antigen (PSMA) PET scans, has resulted in patients previously classified as having non-metastatic castration resistant prostate cancer (m0CRPC) on conventional imaging being classified as having metastatic disease. Hence, these patients are eligible to receive abiraterone or enzalutamide through the PBS. The PBAC further considered that if sensitive screening tests are used, the majority of patients with a rapidly rising PSA are likely to be diagnosed with, or will soon progress to, mCRPC. Given this, the PBAC foreshadowed that it would like to consider revising the abiraterone and enzalutamide listings further, such that the requirement for the disease to be classified as metastatic is removed. The PBAC considered the once per

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lifetime requirement should remain. The PBAC noted that this change to the listing was likely to result in patients being treated earlier, as well as increase the number of patients treated. The PBAC requested that the Department seek comment from the sponsors regarding this proposed listing change (the removal of the word ‘metastatic’ from the PBS indication) and the associated financial impact for consideration at the July 2021 PBAC meeting.

**Outcome:**

Recommended

## 6 Recommended listing

6.1 *Amend the existing enzalutamide listing, without any price change to the existing price, and subject to sponsor agreement, as follows:*

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ENZALUTAMIDE					
enzalutamide 40 mg capsule, 112	10174L	1	112	2	Xtandi
<b>Amend Restriction Summary 4670 / ToC: 4670: Authority Required</b> (as of 1 March 2021)					
<b>Category/Program:</b> GENERAL – General Schedule (GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia					
<b>Severity:</b> Castration resistant metastatic					
<b>Condition:</b> Carcinoma of the prostate					
<b>PBS indication:</b> Castration resistant metastatic carcinoma of the prostate					
<b>Clinical criteria:</b>					
The treatment must not be used in combination with chemotherapy					
<b>AND</b>					
<b>Clinical criteria:</b>					
<del>Patient must have failed treatment with docetaxel due to resistance or intolerance; or</del>					
<del>Patient must be unsuitable for docetaxel treatment of the basis of predicted intolerance to docetaxel</del>					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have a WHO performance status of 2 or less					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must not have received prior treatment with abiraterone; or					
Patient must have developed intolerance to abiraterone of a severity necessitating permanent treatment withdrawal.					
<b>Administrative advice:</b> Special Pricing Arrangements apply					
<b>Administrative advice:</b> No increase in the maximum quantity or number of units may be authorised					
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised					
<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					

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6.2 Amend the existing abiraterone listings, without any price change to the existing price and subject to sponsor agreement, as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ABIRATERONE					
abiraterone acetate 500 mg tablet, 60	11206T	1	60	2	Zytiga
abiraterone acetate 250 mg tablet, 120	2698B	1	120	2	Zytiga
<b>Amend Restriction Summary 6944 / ToC: 6944: Authority Required</b> (as at 1 March 2021)					
<b>Category/Program:</b> GENERAL – General Schedule (GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia					
<b>PBS indication:</b> Castration resistant metastatic carcinoma of the prostate					
<b>Clinical criteria:</b>					
The treatment must be used in combination with a corticosteroid					
<b>AND</b>					
<b>Clinical criteria:</b>					
The treatment must not be used in combination with chemotherapy					
<b>AND</b>					
<b>Clinical criteria:</b>					
<del>Patient must have failed treatment with docetaxel due to resistance or intolerance; or</del>					
<del>Patient must be unsuitable for docetaxel treatment of the basis of predicted intolerance to docetaxel.</del>					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have a WHO performance status of 2 or less					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must not receive PBS-subsidised treatment abiraterone if progressive disease develops while on abiraterone					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must not have received prior treatment with enzalutamide; or					
Patient must have developed intolerance to enzalutamide of a severity necessitating permanent treatment withdrawal.					
<b>Administrative advice:</b> Special Pricing Arrangements apply					
<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## 7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **8 Sponsors' Comments:**

Astellas Pharma Australia Pty Ltd: The PBAC's decision to remove the requirement to use docetaxel first is going to be welcomed by the clinical and patient community.

Janssen-Cilag Pty Ltd: The sponsor had no comment.