Metastatic prostate cancer: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To compare the predicted versus actual use of cabazitaxel, abiraterone and enzalutamide for metastatic castration resistant prostate cancer.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

- Cabazitaxel: 1 August 2012
- Abiraterone: 1 August 2013
- Enzalutamide: 1 December 2014

Data Source / methodology

Data was extracted from the Department of Human Services (DHS) prescription database for all PBS listings for the treatment of metastatic castration resistant prostate cancer and all PBS listings for docetaxel identified as being for the treatment of prostate cancer based on the date of supply to the patient. Data was extracted for the period January 2000 to March 2016, inclusive. Only records for males were included. The analyses include the number of prescriptions dispensed, number of patients treated, and the length of time on treatment. An assessment of therapies used prior to commencing cabazitaxel, abiraterone or enzalutamide was also undertaken.

Key Findings

- The total number of patients receiving a medicine subsidised for use in the post-docetaxel metastatic castration resistant prostate cancer (mCRPC) setting had increased substantially from 1,418 patients in 2013 to 4,165 patients in 2015. The number of patients treated was higher than predicted.
- The prescribing practices for these medicines is evolving. The therapy received by patients has changed when comparing patients who initiate a PBS listing for mCRPC in 2013 versus 2015. Not all of the patterns of use met the current PBS restrictions.
- When reviewing the therapies received for patients initiating treatment after the entry of enzalutamide to the market:
  - around one-quarter (24%) of patients were first initiated on either abiraterone or enzalutamide without the prior use of docetaxel;

- around 10% of patients received a supply of cabazitaxel after abiraterone or enzalutamide; and
- 11% of patients transitioned from one oral drug to another (either abiraterone or enzalutamide).

Purpose and scope

The purpose of this report is to compare the predicted versus actual use of cabazitaxel, abiraterone and enzalutamide for the treatment of metastatic castration resistant prostate cancer (mCRPC).

At its February 2015 meeting, DUSC requested that the routine 24 month review of cabazitaxel utilisation be deferred until at least 24 months of data for abiraterone was available. Cabazitaxel has now been available on the PBS for more three years and abiraterone for more than two years. Enzalutamide is also included in this review as it has been available for over a year. As eligibility for cabazitaxel, abiraterone and enzalutamide supplied through the PBS requires a patient to have failed treatment with docetaxel due to resistance or intolerance (or since 1 November 2014 predicted to be unsuitable) utilisation of docetaxel is also presented.

Background

Pharmacology

Cabazitaxel and docetaxel are antineoplastic agents which work by stopping cells from growing and multiplying.[1],[2]

Abiraterone is an androgen biosynthesis inhibitor that selectively inhibits 17α-hydroxylase/C17,20-lyase (CYP17), an enzyme expressed in and required for androgen biosynthesis in testicular, adrenal and in prostatic tumour tissues.[3]

Enzalutamide is an androgen receptor signalling inhibitor that blocks the androgen receptor signalling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors, and consequently inhibits the nuclear translocation of these receptors and inhibits the binding of androgen receptor to DNA.[4]

Therapeutic Goods Administration (TGA) approved indications

Docetaxel is indicated for treatment of patients with androgen independent (hormone refractory) prostate cancer. It is also indicated for metastatic breast cancer, adjuvant treatment of breast cancer, non-small cell lung cancer, ovarian cancer and head and neck cancer.

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[1] Jevtana® (cabazitaxel) Australian Consumer Medicine Information. Macquarie Park, NSW: sanofi-aventis australia pty ltd. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-CMI-03785-3&d=2016050416114622483

[2] Docetaxel Australian Consumer Medicine Information. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=CMI&q=docetaxel&r=https://www.ebs.tga.gov.au/

[3] Zytiga® (abiraterone) Australian approved product information. Sydney: Janssen-Cilag Pty Ltd. Approved 1 March 2012, Most recent amendment 12 November 2015.

[4] Xtandi® (enzalutamide) Australian approved product information. Sydney: Astellas Pharma Australia Pty Ltd. Approved 1 July 2014, Most recent amendment 14 April 2016.

Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen.

Abiraterone is indicated with prednisone or prednisolone for the treatment of patients with metastatic advanced prostate cancer (castration resistant prostate cancer, mCRPC):

- who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT). This indication is not PBS subsidised.
- who have received prior chemotherapy containing a taxane.

Enzalutamide is indicated for the treatment of patients with mCRPC:

- following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated. This indication is not PBS subsidised.
- who have previously received docetaxel.

Dosage and administration

Table 1: Dosage and administration of medicines for metastatic prostate cancer

Drug	Recommended dose and frequency of administration
CABAZITAXEL	25 mg/m^2 administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone (or prednisolone) 10 mg administered daily throughout cabazitaxel treatment.
ABIRATERONE ACETATE	1 g (four 250 mg tablets) swallowed whole as a single daily dose that must not be taken with food. Abiraterone is used with low-dose prednisone or prednisolone. The recommended dosage of prednisone or prednisolone is 10 mg daily.
ENZALUTAMIDE	160 mg (four 40 mg capsules) swallowed whole as a single oral daily dose with or without food.
DOCETAXEL	75 mg/m2 administered as a one hour infusion every three weeks. Prednisone or prednisolone 5 mg orally twice daily is administered continuously, commencing day 1 and continuing through each cycle.

Source: Product Information

Further details are available in the Product Information (PI) and Consumer Medicine Information (CMI) available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

Clinical situation

Metastatic castration resistant prostate cancer (mCRPC) is 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 clinical algorithm for the treatment of metastatic prostate cancer is evolving. When PBAC considered the existing listings, the previous treatment guidelines for mCRPC recommended first-line therapy with docetaxel, provided chemotherapy is suitable, followed by enzalutamide, abiraterone or

cabazitaxel after failure with docetaxel therapy. More recent guidelines for first-line treatment of mCRPC issued by the National Comprehensive Cancer Network®(NCCN® 2015) recommend docetaxel with prednisolone where symptoms are present or enzalutamide or abiraterone with prednisolone when the cancer is not causing symptoms. First-line immunotherapy, such as Sipuleucel-T, is also recommended when the cancer is causing few or no symptoms. For second-line therapy after abiraterone or enzalutamide, the NCCN® (2015) recommends further treatment with these agents or docetaxel with prednisolone. Other recommended treatment options include immunotherapy and secondary hormone therapy with antiandrogens, ketoconazole, corticosteroids or diethylstilbestrol (DES). After first-line therapy with docetaxel, the NCCN® (2015) suggests the following treatment options: enzalutamide; abiraterone with prednisolone; cabazitaxel with prednisolone; docetaxel rechallenge; mitozantrone; immunotherapy (Sipuleucel-T); and secondary hormone therapy (antiandrogens, ketoconazole, corticosteroids or DES).

PBS listing details (as at March 2016)

Table 2: PBS listing of IV medicines

Item	Name, form & strength, pack size	Max. amount	Rpts	DPMA	Brand name and manufacturer
4376H (Public)	CABAZITAXEL Concentrated injection 60 mg (as acetone solvate) in 1.5 mL, with diluent	55 mg	5	$5,897.41	Jevtana® sanofi-aventis Australia Pty Ltd
7236W (Private)				$6,016.41	
10148D (Public)	DOCETAXEL Various strengths and vial sizes	250 mg	5	$132.52	DBL Docetaxel® Hospira Pty Limited Docetaxel Sandoz® Sandoz Pty Ltd Oncotaxel® Amneal Pharmaceuticals Pty Ltd

Source: the PBS website.

Table 3: PBS listing of oral medicines

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
2698B	ABIRATERONE abiraterone acetate 250 mg tablet	120	2	$3,600.41	Zytiga® Janssen-Cilag Pty Ltd
10174L	ENZALUTAMIDE enzalutamide 40 mg capsule	112	2	$3,700.17	Xtandi® Astellas Pharma Australia Pty Ltd

Source: the PBS website. Special pricing arrangements apply.

Table 4: Abridged Restrictions (as at 1 April 2016)

Medicine	Abridged PBS restriction
Docetaxel	The PBS listing of docetaxel is unrestricted.
Cabazitaxel	Authority Required (STREAMLINED) for castration resistant metastatic carcinoma of the prostate. The treatment: - must be in combination with prednisone or prednisolone, - must not be used in combination with abiraterone Additionally, the patient: - must have failed treatment with docetaxel due to resistance or intolerance, - must have a WHO performance status of 2 or less, and - must not receive PBS-subsidised cabazitaxel if progressive disease develops while on cabazitaxel.
Abiraterone	Authority Required for castration resistant metastatic carcinoma of the prostate. The treatment: - must be in combination with prednisone or prednisolone, and - must not be used in combination with chemotherapy Additionally, the patient: - must have failed treatment with docetaxel due to resistance or intolerance; OR must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel, - must have a WHO performance status of 2 or less, - must not receive PBS-subsidised abiraterone if progressive disease develops while on abiraterone, - must not have received prior treatment with enzalutamide; OR must have developed intolerance to enzalutamide of a severity necessitating permanent treatment withdrawal.
Enzalutamide	Authority Required castration resistant metastatic carcinoma of the prostate. The treatment must not be used in combination with chemotherapy, and the patient: - must have failed treatment with docetaxel due to resistance or intolerance; OR must be unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel, - must have a WHO performance status of 2 or less, - must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug, - must not have received prior treatment with abiraterone; OR must have developed intolerance to abiraterone of a severity necessitating permanent treatment withdrawal.

Source: the PBS website.

For full details of the current PBS listing refer to the PBS website.

Table 5: Date of first PBS listing and changes to listing for mCRPC medicines

Drug	Date	PBS listing or change to listing
Docetaxel	1 November 2007	Listed for mCRPC as Authority Required
Cabazitaxel	1 August 2012	Listed as Authority Required for Private Hospital use and Authority required (STREAMLINED) for Public Hospital use
Docetaxel	1 December 2011	Listing changed from Authority Required to Authority required (STREAMLINED) when the Efficient Funding of Chemotherapy measure was introduced
Abiraterone	1 August 2013	Listed as Authority Required
Docetaxel	1 November 2014	Listing changed from Authority required (STREAMLINED) to unrestricted
Abiraterone	1 November 2014	Deletion of note that "Patients who have received PBS-subsidised abiraterone or cabazitaxel are not eligible for PBS-subsidised docetaxel"
Abiraterone	1 December 2014	Clinical criteria amended to include patients unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel
Enzalutamide	1 December 2014	Listed as Authority Required
Cabazitaxel	1 February 2015	Listing for use in Private Hospitals changed from Authority Required to Authority required (STREAMLINED)

Source: the PBS website.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

Docetaxel

The PBAC (July 2007) recommended the listing of docetaxel on the PBS as an authority required benefit for the treatment of androgen independent (hormone refractory) metastatic carcinoma of the prostate in a patient with a Karnofsky performance-status score of at least 60%. It was recommended that docetaxel must be used as first-line chemotherapy and administered in three weekly cycles with a maximum of 10 cycles of treatment.

The PBAC (July 2014) considered a request from the Department to change the listing for docetaxel from Authority required (STREAMLINED) listings to unrestricted benefit listings for all its listed indications following the substantial price reductions for this drug since the PBAC's original recommendations for its listings.

The PBAC recommended amending the listings for all docetaxel to unrestricted benefit listings. This listing change came into effect from 1 November 2014.

Cabazitaxel

Cabazitaxel was rejected by the PBAC at its July 2011 and November 2011 meetings on the basis of a high and uncertain cost-effectiveness ratio. In terms of utilisation, the PBAC considered that it was highly likely that lower doses would be required in clinical practice due to toxicity and therefore considerable wastage would result from only a 60mg vial

being available. The PBAC also considered that uptake of cabazitaxel was overestimated because the significant adverse events for many patients will limit the suitability of this treatment.

For further details refer to the Public Summary Document from the July 2011 PBAC meeting.

Cabazitaxel was subsequently recommended at the March 2012 PBAC meeting for treatment of hormone refractory metastatic carcinoma of the prostate in patients previously treated with a docetaxel containing regimen on the basis of acceptable cost-effectiveness compared with mitozantrone.

Abiraterone

Abiraterone was considered by the PBAC at its November 2011, March 2012, July 2012, November 2012 and July 2014 meetings. At its July 2012 meeting, the PBAC recommended listing abiraterone 250 mg tablets on the PBS as an Authority Required listing for the treatment, in combination with prednisone or prednisolone, of mCRPC in a patient who has failed treatment with docetaxel on a cost-minimisation basis with cabazitaxel and cost-effectiveness basis when compared with best supportive care.

The PBAC recalled its concerns from March 2012, that there would be considerable risk of use of abiraterone in patients prior to using docetaxel (given the current absence of evidence of health gain of abiraterone further up the treatment algorithm) as well as a risk that patients may be treated with both abiraterone and cabazitaxel either sequentially or in combination. To manage these risks, the PBAC reaffirmed its decision that abiraterone should be included in the same risk-sharing arrangement as cabazitaxel, with estimates of use based on a shared subsidisation cap specified for the existing risk-sharing arrangement for cabazitaxel adjusted for the additional price advantage for oral versus I.V. treatment and considering the differences in length of treatment for these agents. The PBAC considered that the re-submission's assumption of a 75% market uptake for abiraterone was subject to much uncertainty.

For further details refer to the Public Summary Document from the July 2012 PBAC meeting.

At the July 2014 meeting, the PBAC noted comments from clinicians that for a small number of patients the current abiraterone restriction, requiring failure of, or intolerance to, docetaxel is a hurdle in gaining access to treatment where a single administration of docetaxel would inevitably demonstrate the patient was intolerant to docetaxel. PBAC considered a solution may be to amend the current restriction to allow PBS subsidised abiraterone where a patient is considered “unsuitable for docetaxel treatment on the basis of demonstrated or predicted intolerance to docetaxel”. PBAC considered this to be a minor change that may provide access to a small number of patients who are currently disadvantaged by the requirement to demonstrate intolerance. The proposed amendment of the restriction would not expand the market and would be adequately dealt with under existing risk share arrangements.

Enzalutamide

At its July 2014 meeting, the PBAC recommended an Authority required listing for enzalutamide for the treatment of mCRPC after treatment failure with docetaxel, on a cost-minimisation basis with abiraterone. The equi-effective doses are enzalutamide 160 mg and abiraterone 1000 mg. The PBAC accepted that abiraterone was the appropriate comparator given the intended place of enzalutamide in the current treatment of metastatic prostate cancer. The PBAC noted that there are now a number of new effective agents for metastatic prostate cancer and therefore the treatment algorithm may continue to evolve over the short-medium term.

The PBAC considered that given the lack of evidence of efficacy of enzalutamide in patients who have previously received abiraterone, a note should be included in the restrictions to prevent subsidised use in this patient population.

The PBAC noted the submission and pre-PBAC response expressed concerns that the current risk share arrangement for cabazitaxel and abiraterone underestimates the patient pool in the post-docetaxel setting. The PBAC did not consider that the submission had provided evidence to support this claim, and recommended that enzalutamide join the same risk share as abiraterone.

For further details refer to the Public Summary Document from the July 2014 PBAC meeting.

Abiraterone and Enzalutamide Prior to Treatment with Docetaxel

The PBAC considered submissions for abiraterone (July 2014) and enzalutamide (November 2015) to allow treatment of patients who have progressed following treatment with androgen deprivation therapy (ADT) but have not yet received treatment with docetaxel.

The submission for abiraterone was rejected because:

- "watchful waiting" was not considered an appropriate comparator for establishing cost-effectiveness in this setting;
- the post-hoc subgroup analysis for defining the PBS eligible population was inadequately justified;
- the ICERs for both the post-hoc sub group and particularly the more appropriate ITT population were unacceptably high; and
- the total PBS cost of treatment with abiraterone shifting from post-docetaxel to post-ADT was uncertain.

For further details refer to the Public Summary Document from the July 2014 PBAC meeting.

The submission for enzalutamide was rejected because it was focused on a claim of survival advantage, which was small and uncertain, rather than on outcomes that clinicians and patients considered to be of most value.

For further details refer to the Public Summary Document from the November 2015 PBAC meeting.

Approach taken to estimate utilisation

Cabazitaxel and abiraterone (Based on model agreed with Sponsor of abiraterone)

The initial eligible population for the 2012 calendar year was estimated by averaging the number of patients supplied with docetaxel for mCRPC.

To derive a growth rate for the eligible population, the number of deaths attributed to prostate cancer was firstly estimated by applying the mortality rate for prostate cancer to the ABS projected male population by age group. The number of hormone resistant prostate cancer patients was then estimated by dividing the number of prostate cancer deaths by an assumption for the number of patients who die from the disease (90%). Year-on-year growth in the eligible population was then derived as presented in Tables 6 and 7 (model step B).

Based on the opinion of advisory board members and other key opinion leaders it was assumed that 50% of the eligible population would be candidates for chemotherapy with the remainder being ineligible for chemotherapy. The derivation of the number of patients eligible for first-line PBS therapy for these groups are presented separately in Tables 6 and 7, respectively.

Table 6: Derivation of the chemotherapy-eligible population

	Model step	2012	2013	2014	2015	2016	2017	2018
Sponsor estimate	A	[redacted]						
Population growth rate	B	-	103%	104%	104%	104%	104%	103%
Eligible population	C = A x B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion eligible for chemotherapy	D	50%	50%	50%	50%	50%	50%	50%
Number eligible for chemotherapy	E = C x D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion chemotherapy-eligible willing to be treated	F	96%	96%	96%	96%	96%	96%	96%
Number chemotherapy-eligible willing to be treated	G = E x F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion chemotherapy-eligible who are treated	H	55%	95%	100%	100%	100%	100%	100%
Estimated eligible population	**I**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7. Derivation of the chemotherapy-ineligible population

	Model step	2012	2013	2014	2015	2016	2017	2018
Sponsor estimate	A	[redacted]						
Population growth rate	B	-	103%	104%	104%	104%	104%	103%
Eligible population	C = A x B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion ineligible for chemotherapy	D	50%	50%	50%	50%	50%	50%	50%
Number ineligible for	E = C x D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Model step	2012	2013	2014	2015	2016	2017	2018
chemotherapy								
Proportion chemotherapy-ineligible willing to be treated	F	90%	90%	90%	90%	90%	90%	90%
Number chemotherapy-ineligible willing to be treated	G = E x F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion chemotherapy-ineligible who are treated	H	0%	100%	100%	100%	100%	100%	100%
Estimated eligible population	**I**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In estimating the number of patients treated with cabazitaxel and abiraterone, it was assumed that [redacted] chemotherapy-ineligible patients treated would receive abiraterone and [redacted] of chemotherapy-eligible patients treated would receive abiraterone (Table 8).

The mean number of cycles was applied to the number of patients to estimate the number of prescriptions for cabazitaxel. The same approach was used for abiraterone. The estimated utilisation of cabazitaxel and abiraterone is shown in Table 8.

Table 8: Estimated utilisation for cabazitaxel and abiraterone

	Model step	2013	2014	2015	2016	2017	2018
Chemotherapy-eligible patients							
Number of eligible (treated) patients	A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate for abiraterone	B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate for cabazitaxel	C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated with abiraterone	D=A x B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated with cabazitaxel	E = A x C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy-ineligible patients							
Number of eligible patients	F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate for abiraterone	G	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number treated with abiraterone	H = F x G	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated treated populations							
Cabazitaxel	I = E	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	J = D + H	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of prescriptions							
Mean annual prescriptions for cabazitaxel	K	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean annual prescriptions for abiraterone	L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prescriptions for cabazitaxel	M = I x K	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prescriptions for abiraterone	N = J x L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: The growth rate in the treated population was based on ABS population growth.

Enzalutamide

The modelled number of eligible patients is described in Table 9.

Table 9: Estimated utilisation for enzalutamide

	2014	2015	2016	2017	2018
AIHW cancer incidence projections					
Number of patients eligible for docetaxel					
Enzalutamide market update					
2014 cabazitaxel market share					
2014 abiraterone market share					
Substitution for cabazitaxel					
Substitution for abiraterone					
Number of patients treated with enzalutamide					
Length of therapy (scripts)					
Number of enzalutamide prescriptions					

The main issues noted by DUSC included the following:

- The base case estimates assumed that use of enzalutamide would be entirely offset by a reduction in the use of abiraterone and cabazitaxel. This may underestimate the financial implications to the government upon listing enzalutamide due to:
    - The potential for enzalutamide to be used subsequent to, rather than only as a substitute for abiraterone (and cabazitaxel) (i.e. an increased market in the post-docetaxel setting);
    - The potential for concomitant use of enzalutamide and abiraterone, rather than only as a substitute for abiraterone;
    - The extent of the population with an "unmet clinical need", i.e. those unable to take abiraterone or cabazitaxel or prednisone/prednisolone (which is required for treatment with abiraterone or cabazitaxel). This had been neither quantified nor accounted for in the current estimates.
- Using an epidemiological approach, the prevalent patient population had been estimated from the modelled incidence rate (derived from answers provided in a commissioned survey) and using a mortality rate that may or may not have been relevant to the Australian context and may not have accounted for factors that may drive prevalence (e.g. age, improved diagnosis, effective therapies). This may have over- or under- estimated the potential number of patients eligible for treatment.
- The potential for use beyond the restriction: (i) use in 'sicker' patients (i.e. WHO >2); (ii) use beyond disease progression; and (iii) use in earlier stages of disease (i.e. replacing other anti-androgens) and in light of the Phase 3 PREVAIL study.

Methods

All data analyses were undertaken using SAS Enterprise Guide version 7.1.

Data was extracted from the Department of Human Services (DHS) prescription database for all PBS listings for the treatment of prostate cancer and all PBS listings for docetaxel

based on the date of supply to the patient. The data differs from that available from the DHS (Medicare) PBS statistics website which is based on the date of processing and is only for subsidised R/PBS prescriptions (under patient co-payment not included). The PBS item codes used for data extraction are summarised in Appendix A. Data was extracted from January 2000 to the most current available data (March 2016, inclusive). Only records for males were included.

For the patient level analyses and counts of patients supplied cabazitaxel, abiraterone or enzalutamide, PBS & RPBS (R/PBS) prescription data were extracted from the DHS Prescription database for scripts supplied from August 2012, the date corresponding to the first listing of cabazitaxel. The number of prevalent patients was determined by counting the number of people supplied at least one PBS prescription using person specific numbers (non-identifying) in the data for the specified time periods. Patient initiation was defined as the date of supply of the first PBS or RPBS prescription.

Data extraction of records for the supply of docetaxel for patient identified as having prostate cancer

The PBS listing of docetaxel changed from Authority Required (STREAMLINED) to unrestricted on 1 November 2014. There was an absence of adequate data to verify directly the supply of docetaxel for prostate cancer. As such, the supply of docetaxel for the treatment of prostate cancer was estimated based on whether a patient had received another PBS listed drug for the treatment of prostate cancer.

A patient was identified as having prostate cancer if they had ever received a supply of any PBS listing for prostate cancer from January 2000 to March 2016. The PBS item codes used for this analysis are provided in Appendix A. Claim records for docetaxel which were likely for the treatment of prostate cancer were extracted by matching patient identifiers from the above analysis. Only records classified as male were included in the data extraction.

Analysis of drugs received prior to initiation on cabazitaxel, abiraterone or enzalutamide

Patients first initiating to therapy on cabazitaxel, abiraterone or enzalutamide were identified for each listing year. For each yearly initiating cohort, the number of patients receiving a prior supply of docetaxel, cabazitaxel, abiraterone or enzalutamide was derived.

Drug sequence analysis

All records for the supply of docetaxel (categorised as dispensed for the treatment of prostate cancer described above), cabazitaxel, abiraterone and enzalutamide from 1 January 2012 to 31 March 2016 were extracted.

The sequence in the use of docetaxel, cabazitaxel, abiraterone or enzalutamide was examined for the following initiating cohorts:

- patients initiating treatment with docetaxel or cabazitaxel between 1 January to 31 July 2013 (i.e. within the seven months prior to the listing of abiraterone from 1 August 2013); and

- patients initiating treatment with docetaxel, cabazitaxel, abiraterone or enzalutamide between 1 January to 31 March 2015 (i.e. after the listing of enzalutamide).

For each initiating cohort, unique patient counts were derived for each sequence of treatment.

Potential coadministration was assessed by identifying records where a patient was supplied a different drug within 7 days of the last supply and a future supply differed to the last drug that the patient had transitioned to. A small proportion (0.1%) of records was identified as having potential coadministration and it was assumed that this would have a negligible impact on the drug sequence analyses.

Analysis of the supply of docetaxel prior to initiation on abiraterone before 1 December 2014

The clinical criteria in the restrictions for oral therapy (abiraterone and enzalutamide) were amended from 1 December 2014 to include patients unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel. The number of supplies of prior docetaxel was examined in patients who initiated on abiraterone in the 12 months before the restriction change (i.e. 1 December 2012 to 30 November 2013). For this initiating cohort, unique patient counts were derived for patients categorised as having no prior supply, one supply or receiving multiple supplies of docetaxel before initiation to abiraterone.

Enzalutamide was not included in this analysis as it first listed from 1 December 2014.

Length of treatment analyses for cabazitaxel, abiraterone and enzalutamide

The length of treatment with cabazitaxel and abiraterone was examined. As enzalutamide was a more recent listing from December 2014 with limited longitudinal data, it was not included in this analysis.

To exclude a potential bias from the inclusion of treatment experienced or grandfathered patients, any patient initiating cabazitaxel or abiraterone within the first two months of their listing were excluded. Cabazitaxel was listed on 1 August 2012, therefore patients who initiated between 1 August 2012 and 30 September 2012 were excluded. The length of treatment for cabazitaxel was analysed for patients who initiated cabazitaxel between 1 October 2012 to 31 March 2013 inclusive. Abiraterone was listed 1 August 2013, therefore patients who initiated between 1 August 2013 and 30 September 2013 were excluded. The length of treatment for abiraterone was analysed for patients who initiated abiraterone from 1 October 2013 to 31 March 2014 inclusive.

The highest median time to re-supply was 29 days. It was assumed that a patient had discontinued therapy if there was no re-supply within a period of three times the median time to re-supply (i.e. 87 days). A patient was assumed to be continuing treatment if the time from their last supply was less than 87 days from the data cut-off date (31 March 2016) and they were censored from the treatment duration analyses. Kaplan-Meier plots were constructed to calculate the duration of therapy.

The mean and median number of prescriptions supplied for cabazitaxel and abiraterone were also derived for the initiating cohorts for these drugs described above. This analysis was based on the date of supply.

Results

Analysis of drug utilisation

Number of prevalent patients

Table 10 and Figure 1 present the number of prevalent patients receiving either cabazitaxel, abiraterone or enzalutamide by calendar year and by quarter, respectively. The total number of patients receiving a medicine subsidised for use in the post-docetaxel mCRPC setting has increased substantially from 2013 to 2015.

Table 10: Number of prevalent patients supplied cabazitaxel, abiraterone or enzalutamide by calendar year

	2012	2013	2014	2015
Total – all listings	203[a]	1,418	2,527	4,165

Source: DHS Supplied Prescriptions database, extracted April 2016. The figures are unique counts for patients who received at least one supply of cabazitaxel, abiraterone or enzalutamide within a given calendar year.
[a] Part year figure as cabazitaxel first listed on 1 August 2012.

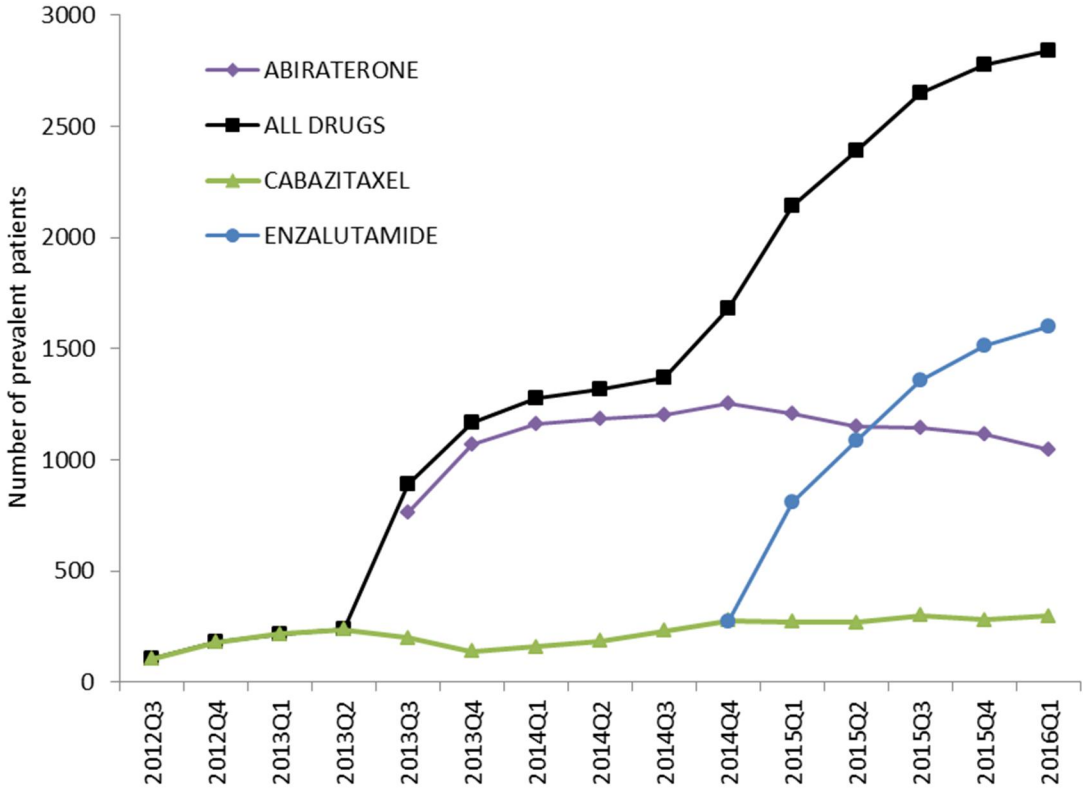

Figure 1: Total number of prevalent patients by quarter

Source: DHS Supplied Prescriptions database, extracted April 2016.

Number of incident patients

Table 11 and Figure 2 present the number of patients receiving their first episode of PBS therapy with either cabazitaxel, abiraterone or enzalutamide by calendar year and by quarter, respectively.

Table 11: Number of incident patients

	2012	2013	2014	2015
Abiraterone	-	999	1,326	981
Cabazitaxel[1]	203	293	67	84
Enzalutamide	-	-	177	1,623
Total	**203**	**1,292**	**1,570**	**2,688**

Source: DHS Supplied Prescriptions database, extracted April 2016. Based on the date of supply.
[1] Part year figure as cabazitaxel first listed on 1 August 2012.

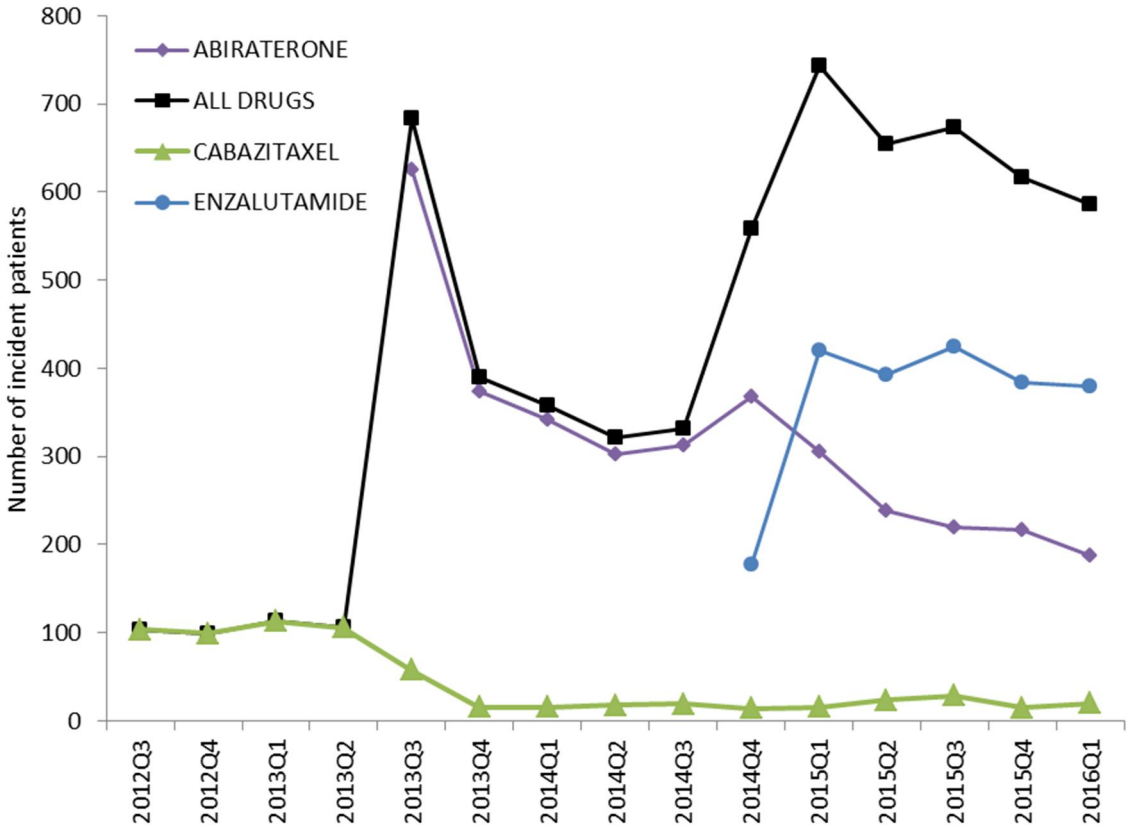

Figure 2: Total number of incident patients by quarter
Source: DHS Supplied Prescriptions database, extracted April 2016. Based on the date of supply.

The utilisation of cabazitaxel and abiraterone was relatively stable between Quarter 3 2013 and Quarter 3 2014 (Figure 2). During this time, 95% of patients were first initiated to abiraterone compared with 5% for cabazitaxel.

There was strong year-on-year growth in the uptake of cabazitaxel, abiraterone and enzalutamide (Table 12). However, since 2013 there was declining growth the number of patients receiving docetaxel prior to cabazitaxel, abiraterone or enzalutamide (Table 12).

Table 12: Growth in the prevalent population supplied cabazitaxel, abiraterone or enzalutamide compared to growth in the prior use of docetaxel

	2012	2013	2014	2015
Patients supplied docetaxel first initiating to one of cabazitaxel, abiraterone or enzalutamide				
Number of patients	195 [a]	1,184	1,205	1,030
Year-on-year growth	-	83.5%	1.7%	-17.0%
Prevalent patients supplied with cabazitaxel, abiraterone or enzalutamide				
Number of patients	203 [a]	1,418	2,527	4,165
Year-on-year growth	-	85.7%	43.9%	39.3%

Source: DHS Supplied Prescriptions database, extracted April 2016.
[a] Part year figure as cabazitaxel first listed on 1 August 2012.

Number of first-time initiations to cabazitaxel, abiraterone or enzalutamide

First initiations to cabazitaxel and abiraterone were relatively stable since the second quarter of 2015 (Figure 3). Over the first quarter from its first listing, there were a high number of initiations to enzalutamide (Figure 3). Since the first quarter of 2015 the number of initiations to enzalutamide has declined (Figure 3).

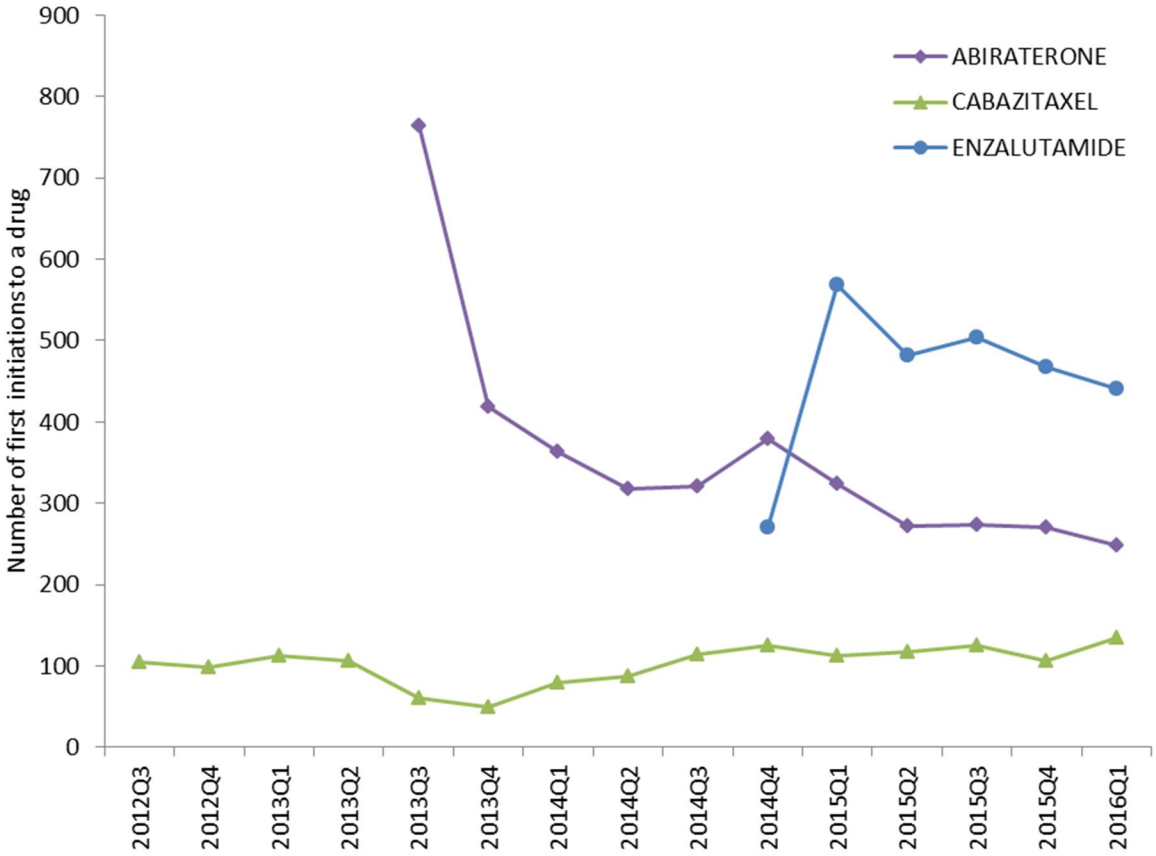

Figure 3: Number of first initiations to drug by quarter
Source: DHS Supplied Prescriptions database, extracted April 2016. Based on the date of supply. Note that a patient could be initiated on more than one different drug within a quarter.

Utilisation of therapies prior to a first initiation to cabazitaxel, abiraterone and enzalutamide

Tables 13 to 15 present analyses of prior therapy received by patients initiating on cabazitaxel, abiraterone or enzalutamide in a given year, respectively.

Table 13: Number of patients initiating to cabazitaxel by calendar year and prior therapies used before initiation to cabazitaxel

Drug	2012	2013	2014	2015
Cabazitaxel	203	330	406	463
Prior use of docetaxel	195	326	402	447
Prior use of abiraterone	-	37	339	302
Prior use of enzalutamide	-	-	2	110

Source: DHS Supplied Prescriptions database, extracted April 2016.

Table 14: Number of patients initiating to abiraterone by calendar year and prior therapies used before initiation to abiraterone

Drug	2013	2014	2015
Abiraterone	1,183	1,382	1,140
Prior use of docetaxel	1,070	1,112	480
Prior use of cabazitaxel	184	56	22
Prior use of enzalutamide	-	-	140

Source: DHS Supplied Prescriptions database, extracted April 2016.

Table 15: Number of patients initiating to enzalutamide by calendar year and prior therapies used before initiation to enzalutamide

Drug	2014	2015
Enzalutamide	270	2,022
Prior use of docetaxel	147	838
Prior use of abiraterone	84	359
Prior use of cabazitaxel	25	129

Source: DHS Supplied Prescriptions database, extracted April 2016.

Since the change in the clinical criteria from 1 December 2014 in the restrictions for abiraterone and enzalutamide to include patients unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel, an increasing number of patients were first initiated on abiraterone or enzalutamide without the prior use of docetaxel (Tables 14 and 15).

An analysis was undertaken of the utilisation of docetaxel prior to commencing treatment with the first oral agent listed, abiraterone, between November 2013 and October 2014, i.e. 12 months prior to change in the restriction criteria from 1 December 2014. For this initiating cohort, 12% did not receive a prior supply of PBS docetaxel and 7.6% received only one supply of PBS docetaxel (Table 16). The proportion of patients receiving only one supply of docetaxel (7.6%) may represent the small population that the PBAC (July 2014) considered would be intolerant to this drug.

Table 16: Number of prior supplies of docetaxel for patients initiating abiraterone between 1 November 2013 to 31 October 2014

Number of prior supplies of docetaxel	n	Proportion (%)
None	157	12.2%
One only	98	7.6%
Multiple	1,030	80.2%
Total	1,285	100.0%

Source: DHS Supplied Prescriptions database, extracted April 2016.

Transitions between drugs

The sequence of therapy was examined for two cohorts:

- Patients initiating treatment with docetaxel or cabazitaxel between 1 January to 31 July 2013 (i.e. within the seven months prior to the listing of abiraterone from 1 August 2013); and
- Patients initiating treatment with docetaxel, cabazitaxel, abiraterone or enzalutamide between 1 January to 31 March 2015 (i.e. after the listing of enzalutamide).

For patients initiating therapy before the listing of abiraterone, the majority commenced on docetaxel before receiving abiraterone or cabazitaxel (Table 17). Of the 842 initiators, 187 patients (22%) received cabazitaxel after being supplied abiraterone or enzalutamide.

Table 17: Summary of drug sequences for patients after initiating on their first episode of docetaxel or cabazitaxel between 1 January to July 2013 (n=842)

Drug sequence	n	Proportion
DOCETAXEL	309	36.7%
DOCETAXEL -> ABIRATERONE	260	30.8%
DOCETAXEL -> ABIRATERONE -> CABAZITAXEL	158	18.7%
DOCETAXEL -> ABIRATERONE -> ENZALUTAMIDE	34	4.0%
DOCETAXEL -> CABAZITAXEL -> ABIRATERONE	28	3.3%
DOCETAXEL -> ABIRATERONE -> CABAZITAXEL -> ENZALUTAMIDE	22	2.6%
Other: DOCETAXEL -> CABAZITAXEL DOCETAXEL -> ENZALUTAMIDE DOCETAXEL -> ABIRATERONE -> ENZALUTAMIDE -> CABAZITAXEL DOCETAXEL -> CABAZITAXEL -> ABIRATERONE -> ENZALUTAMIDE DOCETAXEL -> CABAZITAXEL -> ENZALUTAMIDE CABAZITAXEL -> ABIRATERONE DOCETAXEL -> ENZALUTAMIDE -> CABAZITAXEL CABAZITAXEL	31	3.9%

Source: DHS Supplied Prescriptions database, extracted April 2016.

Table 18 summarises the sequence of therapy received by 3,772 patients first episode of therapy after 1 December 2014 following the listing of enzalutamide and change to the restrictions for abiraterone and enzalutamide to include patients unsuitable for docetaxel treatment on the basis of predicted intolerance to docetaxel. Seventy-five percent of patients received a prior supply of docetaxel before transitioning to abiraterone, enzalutamide or cabazitaxel (Table 18). Around one-quarter (24%) of patients were first initiated on either abiraterone or enzalutamide (Table 18). There were 419 patients (11%) who transitioned from one oral drug to another (either abiraterone or enzalutamide). Abiraterone and enzalutamide are generally well tolerated drugs, for example the proportion of patients who discontinued abiraterone treatment in Trial COU-AA-301 due to drug-related adverse events was 4.8%.

Cabazitaxel was used after an oral agent (abiraterone or enzalutamide) in around 10% of patients (Table 18). The PBAC (March 2012) previously considered that there should be no use of cabazitaxel after failure with abiraterone therapy. The restriction wording for cabazitaxel may need to be clarified to specify that it should not be used in combination with or following abiraterone or enzalutamide.

Table 18: Summary of drug sequences for patients initiating on docetaxel, cabazitaxel, abiraterone or enzalutamide between 1 January to March 2015 (n=3,772)

Drug sequence	n	Proportion
DOCETAXEL	899	23.8%
DOCETAXEL -> ABIRATERONE	821	21.8%
ABIRATERONE	401	10.6%
DOCETAXEL -> ENZALUTAMIDE	349	9.3%
ENZALUTAMIDE	285	7.6%
DOCETAXEL -> ABIRATERONE -> CABAZITAXEL	284	7.5%
DOCETAXEL -> ABIRATERONE -> ENZALUTAMIDE	145	3.8%
DOCETAXEL -> ENZALUTAMIDE -> CABAZITAXEL	87	2.3%
Other: ABIRATERONE -> DOCETAXEL ABIRATERONE -> ENZALUTAMIDE ENZALUTAMIDE -> ABIRATERONE DOCETAXEL -> ENZALUTAMIDE -> ABIRATERONE DOCETAXEL -> CABAZITAXEL DOCETAXEL -> ABIRATERONE -> CABAZITAXEL -> ENZALUTAMIDE ENZALUTAMIDE -> DOCETAXEL DOCETAXEL -> CABAZITAXEL -> ENZALUTAMIDE DOCETAXEL -> ABIRATERONE -> ENZALUTAMIDE -> CABAZITAXEL DOCETAXEL -> CABAZITAXEL -> ABIRATERONE ABIRATERONE -> DOCETAXEL -> CABAZITAXEL DOCETAXEL -> ENZALUTAMIDE -> ABIRATERONE -> CABAZITAXEL ENZALUTAMIDE -> DOCETAXEL -> CABAZITAXEL ABIRATERONE -> CABAZITAXEL ABIRATERONE -> DOCETAXEL -> ENZALUTAMIDE ABIRATERONE -> ENZALUTAMIDE -> DOCETAXEL ENZALUTAMIDE -> DOCETAXEL -> ABIRATERONE DOCETAXEL -> CABAZITAXEL -> ABIRATERONE -> ENZALUTAMIDE DOCETAXEL -> CABAZITAXEL -> ENZALUTAMIDE -> ABIRATERONE ENZALUTAMIDE -> ABIRATERONE -> DOCETAXEL ABIRATERONE -> CABAZITAXEL -> ENZALUTAMIDE ABIRATERONE -> DOCETAXEL -> ENZALUTAMIDE -> CABAZITAXEL ABIRATERONE -> ENZALUTAMIDE -> DOCETAXEL -> CABAZITAXEL CABAZITAXEL CABAZITAXEL -> ABIRATERONE CABAZITAXEL -> ABIRATERONE -> ENZALUTAMIDE DOCETAXEL -> ENZALUTAMIDE -> CABAZITAXEL -> ABIRATERONE	501	13.3%

Drug sequence	n	Proportion
ENZALUTAMIDE -> CABAZITAXEL		

Source: DHS Supplied Prescriptions database, extracted April 2016.

Duration of therapy

The duration of therapy was examined for cabazitaxel and abiraterone. This was not done for enzalutamide as it was a relatively recent listing (from December 2014) with limited longitudinal data. The mean and median duration of treatment with cabazitaxel and abiraterone is presented in Table 19.

Table 19: Treatment duration for cabazitaxel and abiraterone, excluding treatment breaks

	Number of initiators	Mean (years)	Median (years)	Lower 95%CI (years)	Upper 95%CI (years)
Cabazitaxel	3,242 [a]	0.45	0.34	0.29	0.36
Abiraterone	1,353 [b]	0.76	0.56	0.49	0.58

[a] Includes patients who initiated cabazitaxel between October 2012 and March 2013.
[b] Includes patients who initiated abiraterone between October 2013 and March 2014.

For the patients initiating on cabazitaxel and abiraterone included in the duration of therapy analysis above, a summary of the number of prescriptions received by these cohorts is presented in Table 20. The mean number of scripts for each drug was higher than predicted (10.9 vs. [redacted] scripts for cabazitaxel and 9.5 vs. [redacted] scripts for abiraterone).

Possible factors influencing duration of use of abiraterone could include continued use beyond disease progression or use in earlier lines of therapy. The higher than expected number of prescriptions for cabazitaxel may be due to no other treatment options being available to the initiating cohort at the time.

Table 20: Number of prescriptions for cabazitaxel and abiraterone

Drug	Number of patients	Median	Mean	Min	Max
Cabazitaxel [a]	2,304	8	10.9	1	55
Abiraterone [b]	9,232	8	9.5	1	42

[a] Includes patients who initiated cabazitaxel between October 2012 and March 2013.
[b] Includes patients who initiated abiraterone between October 2013 and March 2014.

Analysis of expenditure

Table 21: Number of prescriptions and benefits paid for cabazitaxel, abiraterone and enzalutamide

	2012	2013	2014	2015
Cabazitaxel				
Total prescriptions	731	2225	2467	3110
Total benefits	$4,360,373	$13,281,636	$14,805,301	$18,650,884
Patient contributions	$2,934	$8,749	$9,187	$13,905
Net cost to Government	$4,357,439	$13,272,887	$14,796,114	$18,636,979
Abiraterone				
Total prescriptions	-	4192	11841	11533
Total benefits	-	$15,190,125	$42,977,963	$41,907,802
Patient contributions	-	$32,319	$105,836	$103,503
Net cost to Government	-	$15,157,806	$42,872,127	$41,804,300
Enzalutamide				
Total prescriptions	-	-	357	11546
Total benefits	-	-	$1,332,606	$43,027,220
Patient contributions	-	-	$2,548	$104,345
Net cost to Government	-	-	$1,330,058	$42,922,875
Overall market utilisation				
Total prescriptions	731	6417	14665	26189
Total benefits	$ 4,360,373	$ 28,471,761	$59,115,870	$ 103,585,906
Patient contributions	$2,934	$41,068	$117,570	$221,752
Net cost to Government	$4,357,439	$28,430,693	$58,998,300	$103,364,154

Source: DHS Supplied Prescriptions database, extracted April 2016.
Figures are based on the date of supply and the published prices for the medicines. Special Pricing Arrangements apply for each of these medicines.

Analysis of actual versus predicted utilisation

Cabazitaxel and abiraterone

Table 22: Predicted vs. Actual comparison for cabazitaxel and abiraterone

		2013	2014	2015
Predicted treated patients	Cabazitaxel	[redacted]	[redacted]	[redacted]
	Abiraterone	[redacted]	[redacted]	[redacted]
Actual treated patients	Cabazitaxel	438	494	630
	Abiraterone	1,182	2,194	2,039
Difference in predicted versus actual treated patients	Cabazitaxel	[redacted]	[redacted]	[redacted]
	Abiraterone	[redacted]	[redacted]	[redacted]
Predicted number of prescriptions	Cabazitaxel	[redacted]	[redacted]	[redacted]
	Abiraterone	[redacted]	[redacted]	[redacted]
Actual number of prescriptions	Cabazitaxel	2225	2467	3110
	Abiraterone	4192	11841	11533
Difference in predicted versus actual number of prescriptions	Cabazitaxel	[redacted]	[redacted]	[redacted]
	Abiraterone	[redacted]	[redacted]	[redacted]
Predicted Net drug cost to the PBS and RPBS excluding patient co-payments	Cabazitaxel	[redacted]	[redacted]	[redacted]
	Abiraterone	[redacted]	[redacted]	[redacted]
Actual Net drug cost to the PBS and RPBS excluding patient co-payments	Cabazitaxel	$13,272,887	$14,796,114	$18,636,979
	Abiraterone	$15,157,806	$42,872,127	$41,804,300
Difference in predicted versus actual net expenditure	Cabazitaxel	[redacted]	[redacted]	[redacted]
	Abiraterone	[redacted]	[redacted]	[redacted]

Note: All expenditure figures are for date of supply and are based on published prices and are net of patient co-payments. Abiraterone has a special pricing arrangement and government expenditure may be less than presented here.
The actual figures were sourced from the Department of Human Services PBS Prescriptions Database accessed February 2016.

In its consideration of cabazitaxel, the PBAC raised that wastage could occur with the availability of only the 60 mg vial as lower doses may be used in practice. Table 23 shows that the median quantity of dispensed cabazitaxel was consistently lower than the mean anticipated dose of [redacted]mg and the vial quantity of 60mg.

Table 23: Quantity of cabazitaxel supplied per prescription

Calendar year	Number of prescriptions	Mean (mg)	Median (mg)	Lower quartile (mg)	Upper quartile (mg)
2012	731	41.5	40	36	50
2013	2,225	41.4	40	36	48
2014	2,467	41.6	40	38	49
2015	3,110	41.8	40	38	50

Source: DHS Supplied Prescriptions database, extracted April 2016.

Enzalutamide

Table 24: Predicted vs. Actual comparison for enzalutamide

		2015
Treated patients	Predicted	[redacted]
	Actual	2,255
	Difference	[redacted]
Number of prescriptions	Predicted	[redacted]
	Actual	11,423
	Difference	[redacted]
Net drug cost to the PBS and RPBS excluding patient co-payments	Predicted	[redacted]
	Actual	$42,463,786
	Difference	[redacted]

Note: All expenditure figures are for date of supply and are based on published prices and are net of patient co-payments. Abiraterone has a special pricing arrangement and government expenditure may be less than presented here.
The actual figures were sourced from the Department of Human Services PBS Prescriptions Database accessed February 2016. These figures are based on the date of prescription supply.

DUSC consideration

DUSC noted the ChemoHormonal Therapy versus Androgen Ablation Randomised trial (CHAARTED) trial demonstrated the clinical efficacy of docetaxel in earlier lines of therapy when taken in combination with androgen deprivation therapy. DUSC considered the place in therapy of docetaxel may have changed following the publication of these results, and its change from an Authority Required (Streamlined) listing to unrestricted listing on 1 November 2014.

DUSC recalled the submission related to the listing of enzalutamide claimed its use would substitute for abiraterone. DUSC noted the growth in the number of treated patients following the introduction of both abiraterone and enzalutamide, indicating that enzalutamide had added to the market rather than substituting for abiraterone and its use in first-line may be greater than anticipated.

DUSC noted the PBS restrictions do not allow sequential treatment with the oral treatments. However, if a patient develops intolerance of a severity necessitating permanent treatment withdrawal with either abiraterone or enzalutamide, the patient is permitted to switch to the other medicine.

DUSC noted the drug sequence analysis of the time period 1 January to 1 March 2015, after enzalutamide was listed, showed 11% of patients transitioned between oral treatments. DUSC recalled in the trial 5% of patients developed intolerance to an oral treatment and needed to be switched. DUSC considered a proportion of the 11% of patients who transitioned between oral treatments is legitimate use after patients develop intolerance, but the remainder is likely to be sequential use following progression on one treatment.

DUSC noted that of the 842 initiators in cohort 1, who initiated treatment between 1 January and 31 July 2013 prior to the listing of abiraterone, 22% received cabazitaxel after being supplied abiraterone or enzalutamide. DUSC commented that although this drug transition is not specifically precluded by the PBS restriction, the cost-effectiveness of this practice had not been considered by the PBAC and was considered to be use beyond that intended.

DUSC noted the drug sequence analysis of the time period 1 January to 1 March 2015, after enzalutamide was listed, showed 24% of patients initiated on an oral treatment. DUSC recalled PBAC had considered submissions from the sponsors of abiraterone and enzalutamide for use in patients without prior to docetaxel, and these submissions were rejected. DUSC considered that there is considerable risk that enzalutamide and abiraterone may be used in this place in therapy outside of the current PBS restrictions.

DUSC noted the restriction of abiraterone changed from December 2014 to allow treatment of patients with predicted intolerance to docetaxel. DUSC questioned how clinicians would interpret and apply a prediction of intolerance in practice. The DUSC analysis stated that the "proportion of patients receiving only one supply of docetaxel (7.6%) may represent the small population that the PBAC (July 2014) considered would be intolerant to this drug." DUSC noted that at the time of the recommendation PBAC said there would be a small patient population genuinely predicted to be intolerant.

DUSC noted the treatment algorithm for metastatic prostate cancer is changing rapidly. Some pathways are likely legitimate patients for whom treatment is cost effective, but some use is not. Rather than moving from androgen deprivation therapy (ADT) to docetaxel to oral treatments, patients now may receive docetaxel with ADT, are more likely to switch between oral treatments, and are more likely to be treated with an oral therapy prior to docetaxel than was originally estimated. Some of this use may be due to genuine predicted intolerance to docetaxel or genuine intolerance to treatment with oral therapies, but some use is likely to be outside of the PBS eligibility criteria.

DUSC Actions

The report was referred to the Pharmaceutical Benefits Advisory Committee.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

sanofi-aventis Australia Pty Ltd:
The sponsor had no comment.

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

Astellas Pharma Australia Pty Ltd:
The sponsor had no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical

Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendix A - PBS item codes used to identify patients supplied with docetaxel who may have had prostate cancer

Drug	ATC4 Name	PBS item code	Form and strength
Abiraterone	Other hormone antagonists and related agents	2698B	Tablet containing abiraterone acetate 250 mg
Bicalutamide	Anti-androgens	8094B	Tablet 50 mg
Cabazitaxel	Taxanes	4376H	Concentrated injection 60 mg (as acetone solvate) in 1.5 mL, with diluent
Cabazitaxel	Taxanes	7236W	Concentrated injection 60 mg (as acetone solvate) in 1.5 mL, with diluent
Cyproterone	Anti-androgens	1270W	Tablet containing cyproterone acetate 50 mg
Cyproterone	Anti-androgens	8019C	Tablet containing cyproterone acetate 100 mg
Degarelix	Other hormone antagonists and related agents	2784M	Powder for injection 80 mg (as acetate), injection set
Degarelix	Other hormone antagonists and related agents	2785N	Powder for injection 120 mg (as acetate), 2, injection set
Degarelix	Other hormone antagonists and related agents	5455D	Powder for injection 80 mg (as acetate), injection set
Degarelix	Other hormone antagonists and related agents	5456E	Powder for injection 120 mg (as acetate), 2, injection set
Denosumab	Other drugs affecting bone structure and mineralization	5110Y	Injection 120 mg in 1.7 mL
Docetaxel	Taxanes	5149B	Powder for I.V. infusion 20 mg with solvent
Docetaxel	Taxanes	5156J	Powder for I.V. infusion 80 mg with solvent
Docetaxel	Taxanes	5274N	Solution concentrate for I.V. infusion 140 mg in 7 mL
Docetaxel	Taxanes	5463M	Solution concentrate for I.V. infusion 20 mg in 1 mL
Docetaxel	Taxanes	5464N	Solution concentrate for I.V. infusion 80 mg in 4 mL
Docetaxel	Taxanes	5486R	Solution concentrate for I.V. infusion 20 mg in 2 mL
Docetaxel	Taxanes	5487T	Solution concentrate for I.V. infusion 80 mg in 8 mL
Docetaxel	Taxanes	5585Y	Solution concentrate for I.V. infusion 160 mg in 16 mL
Docetaxel	Taxanes	5591G	Powder for I.V. infusion 20 mg with solvent
Docetaxel	Taxanes	5592H	Powder for I.V. infusion 80 mg with solvent
Docetaxel	Taxanes	5809R	Solution concentrate for I.V. infusion 140 mg in 7 mL
Docetaxel	Taxanes	5855E	Solution concentrate for I.V. infusion 20 mg in 1 mL

Drug	ATC4 Name	PBS item code	Form and strength
Docetaxel	Taxanes	5856F	Solution concentrate for I.V. infusion 80 mg in 4 mL
Docetaxel	Taxanes	5860K	Solution concentrate for I.V. infusion 20 mg in 2 mL
Docetaxel	Taxanes	5861L	Solution concentrate for I.V. infusion 80 mg in 8 mL
Docetaxel	Taxanes	5862M	Solution concentrate for I.V. infusion 160 mg in 16 mL
Docetaxel	Taxanes	5921P	Injection set containing 1 single use vial concentrate for I.V. infusion 20 mg (anhydrous) in 0.5 mL with solvent
Docetaxel	Taxanes	5922Q	Injection set containing 1 single use vial concentrate for I.V. infusion 80 mg (anhydrous) in 2 mL with solvent
Docetaxel	Taxanes	7285K	Solution concentrate for I.V. infusion 160 mg in 16 mL
Docetaxel	Taxanes	8071T	Injection set containing 1 single use vial concentrate for I.V. infusion 20 mg (anhydrous) in 0.5 mL with solvent
Docetaxel	Taxanes	8074Y	Injection set containing 1 single use vial concentrate for I.V. infusion 80 mg (anhydrous) in 2 mL with solvent
Docetaxel	Taxanes	8967Y	Solution concentrate for I.V. infusion 160 mg in 16 mL
Enzalutamide	Anti-androgens	10174L	Capsule 40 mg
Flutamide	Anti-androgens	1417N	Tablet 250 mg
Goserelin	Gonadotropin releasing hormone analogues	1454M	Subcutaneous implant 3.6 mg (as acetate) in pre-filled injection syringe
Goserelin	Gonadotropin releasing hormone analogues	8093Y	Subcutaneous implant (long acting) 10.8 mg (as acetate) in pre-filled injection syringe
Goserelin and bicalutamide	Gonadotropin releasing hormone analogues	9064C	Pack containing 1 subcutaneous implant containing goserelin 3.6 mg (as acetate) in pre-filled injection syringe and 28 tablets bicalutamide 50 mg
Goserelin and bicalutamide	Gonadotropin releasing hormone analogues	9065D	Pack containing 1 subcutaneous implant containing goserelin 10.8 mg (as acetate) in pre-filled injection syringe and 28 tablets bicalutamide 50 mg
Goserelin and bicalutamide	Gonadotropin releasing hormone analogues	9066E	Pack containing 1 subcutaneous implant containing goserelin 10.8 mg (as acetate) in pre-filled injection syringe and 84 tablets bicalutamide 50 mg
Leuprorelin	Gonadotropin releasing hormone analogues	8707G	Suspension for subcutaneous injection (modified release) containing leuprorelin acetate 7.5 mg, injection set

Drug	ATC4 Name	PBS item code	Form and strength
Leuprorelin	Gonadotropin releasing hormone analogues	8708H	Suspension for subcutaneous injection (modified release) containing leuprorelin acetate 22.5 mg, injection set
Leuprorelin	Gonadotropin releasing hormone analogues	8709J	Suspension for subcutaneous injection (modified release) containing leuprorelin acetate 30 mg, injection set
Leuprorelin	Gonadotropin releasing hormone analogues	8859G	Suspension for subcutaneous injection (modified release) containing leuprorelin acetate 45 mg, injection set
Leuprorelin	Gonadotropin releasing hormone analogues	8875D	I.M. injection (modified release), powder for injection containing leuprorelin acetate 7.5 mg with diluent in pre-filled dual-chamber syringe
Leuprorelin	Gonadotropin releasing hormone analogues	8876E	I.M. injection (modified release), powder for injection containing leuprorelin acetate 22.5 mg with diluent in pre-filled dual-chamber syringe
Leuprorelin	Gonadotropin releasing hormone analogues	8877F	I.M. injection (modified release), powder for injection containing leuprorelin acetate 30 mg with diluent in pre-filled dual-chamber syringe
Leuprorelin	Gonadotropin releasing hormone analogues	10656W	I.M. injection (modified release), powder for injection containing leuprorelin acetate 45 mg with diluent in pre-filled dual-chamber syringe
Leuprorelin acetate	Gonadotropin releasing hormone analogues	1565J	I.M. injection (modified release), set containing 1 vial powder for injection 7.5 mg, 1 ampoule diluent 2 mL and 1 syringe with 2 needles
Leuprorelin acetate	Gonadotropin releasing hormone analogues	8211E	I.M. injection (modified release), set containing 1 vial powder for injection 22.5 mg, 1 ampoule diluent 2 mL and 1 syringe with 2 needles
Leuprorelin acetate	Gonadotropin releasing hormone analogues	8484M	I.M. injection (modified release), set containing 1 vial powder for injection 30 mg, 1 ampoule diluent 2 mL and 1 syringe with 2 needles
Nilutamide	Anti-androgens	8131Y	Tablet 150 mg
Triptorelin	Gonadotropin releasing hormone analogues	5297T	Powder for I.M. injection (prolonged release) 22.5 mg (as embonate) with solvent, syringe and needles
Triptorelin	Gonadotropin releasing hormone analogues	9378N	Powder for I.M. injection (prolonged release) 3.75 mg (as embonate) with solvent, syringe and needles
Triptorelin	Gonadotropin releasing hormone analogues	9379P	Powder for I.M. injection (prolonged release) 11.25 mg (as embonate) with solvent, syringe and needles