5.02 ABIRATERONE ACETATE AND METHYLPREDNISOLONE Pack containing 120 tablets abiraterone (as acetate) 125 mg and 60 tablets methylprednisolone 4 mg, Yonsa® MPRED, Sun Pharma ANZ Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested an Authority Required listing for a composite pack (co-pack) comprising abiraterone acetate tablets in a fine particle formulation (SAA) and oral methylprednisolone (MPRED) tablets for the treatment of patients with metastatic castration resistant prostate cancer (mCRPC).

1.2 Listing was requested based on a cost-minimisation analysis versus the currently listed formulation of abiraterone acetate comparator (described as originator abiraterone acetate (OAA)) administered with the glucocorticoid prednisolone (Table 1).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients aged ≥ 18 years with mCRPC
Intervention	SAA 500 mg once daily with concomitant MPRED 4 mg BID
Comparator	OAA 1000 mg once daily with concomitant PRED 5 mg BID
Outcomes	Bioequivalence between SAA 500 mg and OAA 1000 mg Post-treatment testosterone and PSA levels
Clinical claim	SAA 500 mg is bioequivalent to OAA 1000 mg based on pharmacokinetics SAA 500 mg is clinically bioequivalent to OAA 1000 mg with respect to changes in testosterone and PSA levels SAA 500 mg has non-inferior safety to OAA 1000 mg

Source: Table 1.1, p2 of the submission. Abbreviations: BID = twice daily; mCRPC = metastatic castration resistant prostate cancer; MPRED = methylprednisolone; OAA = originator abiraterone acetate; PRED = prednisone; PSA = prostate specific antigen; SAA = SoluMatrixTM abiraterone acetate

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: The submission was made under the TGA/PBAC Parallel Process. The TGA Clinical Evaluation Report was available at the time of evaluation for PBAC consideration. The Delegate's Overview was provided with the Pre-PBAC Response. A final decision is expected in March 2022. Abiraterone in the proposed formulation is registered in the USA.

2.2 The PBAC noted following regulatory advice by the TGA in the Delegate's Overview:

- The sole efficacy study (STAAR) demonstrates a lack of inequivalence with OAA and SAA, rather than equivalent efficacy, given that the sample size was small (n=53) and run for too short a period to be definitive in the setting of prostate cancer. The PBAC

noted that SAA was considered by the TGA to be bioequivalent with OAA, with the same level of efficacy and safety, albeit at a lower dose than OAA.

- The TGA Delegate was of the mind to approve methylprednisolone 4 mg tablet, the glucocorticoid component of the composite pack. The TGA Delegate's Overview noted the dose equivalence of 5 mg prednisone to 4 mg methylprednisolone is well recognised and reported.
- Claims concerning administration of tablets without food in the PI. The Pre-PBAC Response noted that as SAA can be taken with or without food, this advice would remain in the PI, consistent with the US FDA label. The PBAC noted the TGA Delegate's Overview stated there was a less marked effect of food on SAA pharmacokinetics and this has not been examined head-to-head with OAA in data submitted in the TGA application.

Previous PBAC consideration

2.3 Abiraterone acetate (Zytiga®) was first listed on the PBS in 2013. This is the first consideration of a new formulation of abiraterone.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ABIRATERONE + METHLYPREDNISOLONE					
abiraterone acetate 125 mg tablet [120] (&) methylprednisolone 4 mg tablet [60], 1 pack	NEW	1	180	2	Yonsa MPRED

Restriction Summary New 1 *(based on 12353 – abiraterone)* **/ Treatment of Concept: New 2** *(based on 12352 – abiraterone as at 1 December 2021)*

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
	Indication: Castration resistant metastatic carcinoma of the prostate
	~~**Clinical criteria:**~~
	~~The treatment must be used in combination with a corticosteroid~~
	~~**AND**~~
	Clinical criteria:
	The treatment must not be used in combination with chemotherapy
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less
	AND
	Clinical criteria:
	~~Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug~~
	The treatment must cease as a PBS benefit where further disease progression occurs whilst being treated with this product
	AND
	Clinical criteria:
	~~Patient must not be undergoing treatment with this drug following treatment with any of: (i) darolutamide, (ii) enzalutamide; or~~
	~~Patient must have developed an intolerance to enzalutamide of a severity necessitating permanent treatment withdrawal~~
	Patient must only receive treatment with one novel hormonal drug per lifetime; or
	Patient must only receive treatment with a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation
	Caution: *The bioavailability on a mg to mg basis of abiraterone combination product and abiraterone single drug product is not equivalent. When changing between abiraterone products, exercise caution in explaining correct dosing directions to the patient.*
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative advice: *Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (ii) darolutamide, (iv) enzalutamide*
	Administrative Advice: Special Pricing Arrangements apply.

3.2 The sponsor proposed a special pricing arrangement (SPA) in line with the SPA that exists for the currently listed abiraterone formulation for which the published price is $3,280.86 (AEMP). The sponsor included the price of prednisone 5 mg tablets in the calculation of the price for the co-pack. The sponsor stated that the difference between the published price and the effective price would be provided as a rebate to the government.

3.3 The proposed restriction was the same as the current listing for abiraterone acetate. The PBAC noted that restriction flow-on changes to the PBS restrictions for abiraterone (as well as darolutamide and enzalutamide) to prevent the subsequent use of novel hormonal agents for the treatment of patients with non-metastatic castration resistant prostate cancer when recommending apalutamide at its November 2021 PBAC meeting (apalutamide, web outcome, November 2021 PBAC meeting). The PBAC noted these restriction flow-ons should also be applied to the requested listing (as per the apalutamide public summary document [PSD] from November 2021 meeting), which have been added above in addition to the current abiraterone PBS restriction.

3.4 The proposed PBS-schedule drug name and product pack descriptions were updated to match the 'medicinal product' and 'medicinal product pack' descriptions of the co-pack provided in the Australian Medicines Terminology (AMT) form.

3.5 The submission stated that because of the difference in administration between SAA and OAA, the products should not be considered interchangeable, and should not be considered eligible for brand substitution. The PBAC considered this to be appropriate.

3.6 The key factors presented in the submission for the rationale for PBS listing were to provide an alternative formulation of abiraterone for treatment of prostate cancer that can be administered without regard to food, and co-packaged together with a glucocorticoid, for patient convenience.

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

4 Population and disease

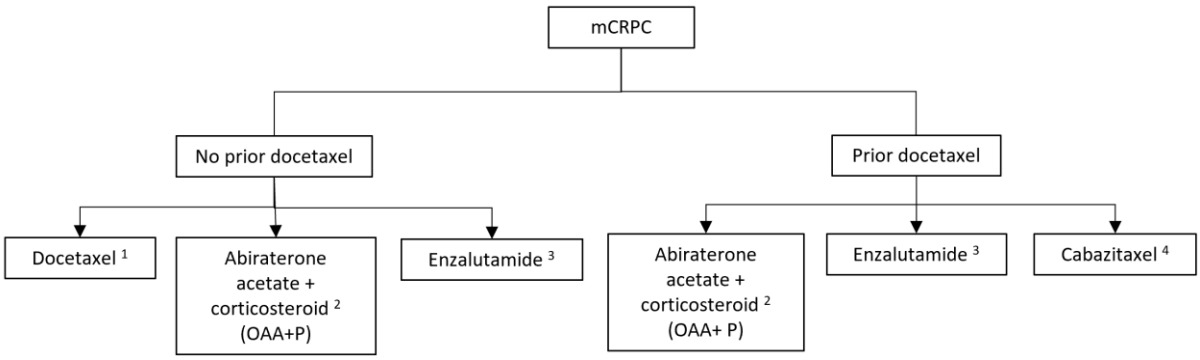
4.1 Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in Australian males. Due to the introduction of prostate specific antigen (PSA) testing, the majority of patients with prostate cancer are diagnosed at early stages with localised disease. Survival is high in patients with localised disease, with the 5-year survival reported to be 95.2% during 2011-2015. However, metastatic disease has a much poorer prognosis with the median survival for patients with mCRPC at 13 months.

4.2 The proposed PBS population for this submission was the same as the PBS patient population for which abiraterone is currently listed i.e. patients with castration-resistant metastatic carcinoma of the prostate. The definition of mCRPC in the clinical trial informing the submission (STAAR) was defined as disease progression despite

serum testosterone levels < 50 ng/dL with ongoing therapy with gonadotropin releasing hormone (GnRH) agonist/antagonist.

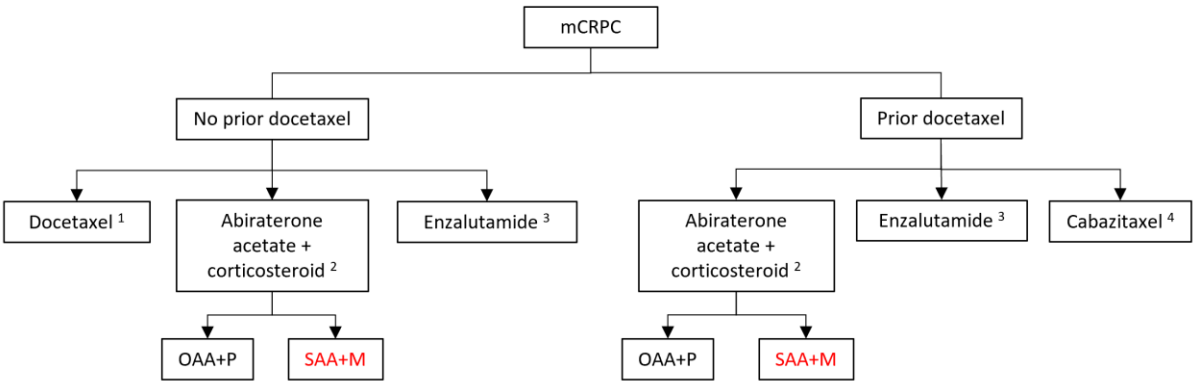
4.3 The submission proposed that the co-pack of SAA and MPRED would be an alternative to the currently listed abiraterone product given with prednisolone. The current and proposed treatment algorithms are shown below, based on current treatment guidelines and the existing PBS listings for products for treatment of metastatic prostate cancer.

Figure 1: Current treatment algorithm



Source: Figure 1.2.1, p 16 of the submission. Abbreviations: mCRPC = metastatic castration resistant prostate cancer; OAA+P = originator abiraterone acetate 1000 mg once daily + prednisone 5 mg twice daily. 1 Unrestricted listing. 2 Must not have received prior enzalutamide treatment OR must have developed intolerance to enzalutamide of a severity necessitating permanent withdrawal. 3 Must not have received prior abiraterone treatment OR must have developed intolerance to abiraterone of a severity necessitating permanent withdrawal. 4 Must have failed treatment with docetaxel due to resistance or intolerance

Figure 2: Proposed treatment algorithm



Source: Figure 1.2.2, p 16 of the submission. Abbreviations: mCRPC = metastatic castration resistant prostate cancer; OAA+P = originator abiraterone acetate 1000 mg once daily + prednisone 5 mg twice daily; SAA+M = SoluMatrix™ abiraterone acetate 500 mg once daily + methylprednisolone 4 mg twice daily. 1 Unrestricted listing. 2 Must not have received prior enzalutamide treatment OR must have developed intolerance to enzalutamide of a severity necessitating permanent withdrawal. 3 Must not have received prior abiraterone treatment OR must have developed intolerance to abiraterone of a severity necessitating permanent withdrawal. 4 Must have failed treatment with docetaxel due to resistance or intolerance.

4.4 Abiraterone is an irreversible inhibitor of CYP17 that reduces production of androgens. Methylprednisolone (MPRED) is a glucocorticoid. The submission stated that MPRED 4 mg is considered to have equivalent glucocorticoid effects to prednisone 5 mg.

5 Comparator

5.1 The submission nominated OAA given with prednisolone 5 mg tablets as the main comparator. The main arguments provided in support of this nomination were that the proposed formulation would be used as an alternative to the currently listed abiraterone product given with prednisolone.

5.2 There are currently other treatments available on the PBS for metastatic prostate cancer. For pricing purposes, the lowest cost comparator in metastatic prostate cancer should be considered as a pricing comparator for SAA. Further discussion is included below in the 'Economic analysis' section.

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 that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on:

- three pharmacokinetic studies comparing the SAA formulation with the OAA product in healthy subjects (Studies 102, 103, and 104)
- one randomized, open-label, active-controlled, multi-centre study comparing SAA plus methylprednisolone to OAA plus prednisone, in patients with metastatic castration-resistant prostate cancer (Study 201; STAAR); and
- three studies of OAA in patients with metastatic castration-resistant prostate cancer (Study 301, Study 302, and Sun et al., 2016).

6.4 None of the studies of SAA + MPRED measured survival so the submission used the bioequivalence studies of SAA vs OAA to bridge to the likely effect that SAA would have on survival. This is the basis of the claim of non-inferiority for efficacy and safety.

6.5 Details of the trials presented in the submission are provided in the table below. These trials were selected from a citation list of 62 publications representing 7 studies.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 102	Single-dose, four-way crossover, relative bioavailability study of SoluMatrix™ abiraterone acetate 125 mg, 500 mg and 625 mg and Zytiga® 1000 mg under fasted conditions in healthy male subjects. Goldwater et al. Comparison of a novel formulation of abiraterone acetate vs. the originator formulation in healthy male subjects: two randomized, open-label, crossover studies. Acharya et al. Open-label, phase I, pharmacokinetic studies of abiraterone acetate in healthy men.	17 April 2015 *Clin Pharmacokinet* 2017; 56: 803-813 *Cancer Chemother Pharmacol* 2012; 69 (6): 1583-1590..
Study 104	A two period, two treatment crossover relative bioavailability and bioequivalence study of SoluMatrix™ abiraterone acetate 500 mg with methylprednisolone (4 mg BID) dosed to steady state and Zytiga® 1000 mg with prednisone (5 mg BID) dosed to steady state under fasted conditions in healthy male subjects. Hussaini et al. Impact of an alternative steroid on the relative bioavailability and bioequivalence of a novel versus the originator formulation of abiraterone acetate.	18 September 2015 *Cancer Chemother Pharmacol* 2017; 80: 479-486.
Study 103	Single-dose, two-way crossover, food effect study of SoluMatrixTM abiraterone acetate 500 mg under fed and fasted conditions in healthy male subjects. Papangelou et al. (2017). The effect of food on the absorption of abiraterone acetate from a fine particle dosage form: a randomized crossover trial in healthy volunteers. Oncol Therapy 2017; 5: 161-170..	10 July 2015 *Oncol Therapy* 2017; 5: 161-170.
STAAR (Study 201)	A randomized, open-label, active-controlled, multi-center study to evaluate serum testosterone levels in patients with metastatic castration-resistant prostate cancer on SoluMatrix™ abiraterone acetate 500 mg (4 x 125 mg qd) with methylprednisolone (4 mg BID) as compared to Zytiga® 1,000 mg (4 x 250 mg qd) with prednisone (5 mg BID): The STAAR study. Stein et al. (2018). Randomized phase 2 therapeutic equivalence study of abiraterone acetate fine particle formulation vs. originator abiraterone acetate in patients with metastatic castration-resistant prostate cancer: The STAAR study.	NCT02737332, 24 July 2017 *Urol Oncol* 2018; 36 (2): 81.e9-81.e16. doi: 10.1016/j.urolonc.2017.10.018. Epub 2017 Nov 14.
Study 301 NCT00638690	de Bono et al. Abiraterone and increased survival in metastatic prostate cancer. Fizazi et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Mulders et al. Efficacy and safety of abiraterone acetate in an elderly patient subgroup (aged 75 and older) with metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy.	*New Engl J Med* 2011; 364 (21): 1995-2005. *Lancet Oncol* 2012; 13 (10): 983-992. *Eur Urol* 2014; 65 (5): 875-883.
Study 302 NCT00887198	Ryan et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. Ryan et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Rathkopf et al. Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302).	*New Engl J Med* 2013; 368 (2): 138-148. *Lancet* 2015; 16: 152-160. *Eur Urol* 2014; 66 (5): 815-825.

Trial ID	Protocol title/ Publication title	Publication citation
	Miller et al. The Phase 3 COU-AA-302 Study of Abiraterone Acetate Plus Prednisone in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: stratified Analysis Based on Pain, Prostate-specific Antigen, and Gleason Score.	*Eur Urol* 2018; 74 (1): 17-23
	Smith et al. Efficacy and Safety of Abiraterone Acetate in Elderly (75 Years or Older) Chemotherapy Naïve Patients with Metastatic Castration Resistant Prostate Cancer.	J *Urol* 2015; 194 (5): 1277-1284
Sun et al. (2016)	Sun et al. (2016). Abiraterone acetate for metastatic castration-resistant prostate cancer after docetaxel failure: A randomized, double-blind, placebo-controlled phase 3 bridging study.	*Int J Urol* 2016; 23: 404-411.
Systematic reviews and meta-analysis		
	Cao et al. CYP17 inhibitors improve the prognosis of metastatic castration-resistant prostate cancer patients: A meta-analysis of published trials.	*J Cancer Res Therap* 2020; 16 (5): 990-1001.
	Zhou et al. Abiraterone for treatment of metastatic castration-resistant prostate cancer: A systematic review and meta-analysis.	*Asian Pac J Cancer Prevent* 2014; 15 (3): 1313-1320.
	Shameem et al. Comparative analysis of the effectiveness of abiraterone before and after docetaxel in patients with metastatic castration-resistant prostate cancer.	*World J Clin Oncol* 2015; 6 (4): 64-72.
	Wang et al. Effectiveness and tolerability of targeted drugs for the treatment of metastatic castration-resistant prostate cancer: a network meta-analysis of randomized controlled trials.	*J Cancer Res Clin Oncol* 2018; 144 (9): 1751-1768.
	McCool et al. Systematic review and network meta-analysis of treatments for chemotherapy-naive patients with asymptomatic/mildly symptomatic metastatic castration-resistant prostate cancer.	*Value Health* 2018; 21 (10): 1259-1268

6.6 For the purposes of the PBAC consideration, the only relevant study was the STAAR study as it is a direct comparative trial of SAA with OAA, and it is in the target population for PBS listing. The outcome measures were appropriate for a bioequivalence study, however, survival outcomes were not measured. The PBAC decision to recommend listing of OAA was based on consideration of one study (Study 301) that measured survival (abiraterone, Public Summary Document, November 2011 PBAC meeting).

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

Table 3: Key features of the STAAR trial

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
SAA+MPRED vs OAA + prednisone.					
STAAR	53	R, OL 84 days	Low	Male patients aged ≥ 18 years, metastatic prostate adenocarcinoma, with disease progression ECOG PS 0 or 1	Serum testosterone, PSA levels, pharmacokinetic data, safety

Source: Table 2.2.3, p36 of the submission. Abbreviations; ECOG = Eastern Cooperative Oncology Group; MPRED = methylprednisolone; OAA = originator abiraterone acetate; OL = open label; PS = performance status; PSA = prostate specific antigen R = randomised; SAA = SoluMatrix™ abiraterone acetate

6.8 The overall risk of bias in the trial was low. Although it was an open label study, the endpoints were objective laboratory measures.

6.9 The differences between the trial setting and the Australian setting as provided in the submission is shown below. The assessment may be reasonable but is limited in certainty by the small sample size of the trial.

Table 4: Differences between the trial setting and the Australian setting

	STAAR		Australian setting	Conclusions
	SAA+M N = 24	OAA+P N = 29	Vatandoust *et al.* (2018) N = 1951	
Patient demographics				
Age, n (%) ≥ 70 years ≥ 75 years	 20 (83.3) 14 (58.3)	 19 (65.5) 15 (51.7)	 1951 (100) -	Largely consistent with Australian setting
Disease characteristics				
Gleason score, n (%) 2-6 < 7 7 (3+4) 7 (4+3) > 7 8-9 Not reported	 - 5 (20.8) 6 (25.0) 12 (50.0) - 1 (4.2)	 - 5 (17.2) 5 (17.2) 17 (58.6) - 2 (6.9)	 728 (39) - 477 (25) 330 (17) 326 (17) 27 (1)	Differences noted likely due to the exclusion of mCRPC from the Australian study
Treatment details *				
SAA dosing	500 mg once daily at least 1 hour before to 2 hours after a meal	NA	500 mg once daily with or without food	Inconsistent with Australian setting
OAA dosing	NA	1000 mg once daily at least 1 hour before to 2 hours after a meal	1000 mg once daily on an empty stomach at least 1 hour before or 2 hours after a meal	Consistent with Australian setting
Healthcare system				
Study sites	United States		South Australia, Australia	Largely consistent with Australian setting

Source: Table 2.7.1, p71 of the submission.
Abbreviations: NA = not applicable; OAA(+P) = originator abiraterone acetate 1000 mg once daily (+ prednisone 5 mg twice daily); SAA(+M) = SoluMatrix™ abiraterone acetate 500 mg once daily (+ methylprednisolone 4 mg twice daily)
* Obtained from the TGA PIs for the respective medicines

6.10 The submission stated that 'approximately 25 patients per group would provide 80% power to conclude bioequivalence of SAA+M to OAA+P on testosterone, with the assumptions of a coefficient of variation of 25%, an upper and lower limit of 80 to 125%, and an expected test-to-reference ratio of 1.05.' The evaluation noted this may be appropriate for bioequivalence assessment but is not an adequate sample size to support formal non-inferiority.

Comparative effectiveness

6.11 The results of the STAAR trial are presented in the table below.

Table 5: Results of the STAAR trial

Outcome	Measured on	N*	SAA	N*	OAA	LSM Difference (95%CI)
Serum Testosterone, ng/dL, Mean (SD)	Baseline Average Days 9 + 10# Day 28 Day 56 Day 84	24 24 21 23 22	7.35 (3.74) 0.33 (0.45) 0.23 (0.26) 1.75 (7.29) 0.96 (3.32)	29 28 27 24 22	7.95 (4.38) 0.29 (0.20) 0.25 (0.3) 0.25 (0.28) 0.24 (0.21)	-0.60 (-2.88, 1.68) 0.03 (-0.06, 0.13) 0.0 (-0.03, 0.02) 1.48 (-1.45, 4.41) 0.69 (-0.67, 2.04)
Percentage with Complete Testosterone Suppression (≤ 1.0 ng/dL), n (%)	Day 28 Day 56 Day 84	21 23 22	20 (95%) 21 (91%) 20 (91%)	27 24 22	25 (93%) 23 (96%) 22 (100%)	
PSA, ng/mL, LS Mean (LS SEM)	Baseline Day 28 Day 56 Day 84	24 24 23 23	51.8 (37.2) 22.4 (12.0) 24.4 (13.2) 27.8 (16.8)	29 27 26 26	113.6 (33.8) 37.5 (11.3) 40.8 (12.5) 46.6 (15.8)	-61.8 (-162.8, 39.2) -15.1 (-48.3, 18.1) -16.4 (-53.0, 20.2) -18.8 (-65.3, 27.7)
Percentage with ≥ 50% Reduction in PSA, n (%)	Day 28 Day 56 Day 84	24 23 23	16 (67%) 15 (65%) 15 (65%)	27 26 26	19 (70%) 17 (65%) 19 (79%)	

Source: 11-1, CSR p67, Table 11-2, CSR p67, CSR pp68-9, Table 11-4, CSR p70, Figure 11-3, CSR p73, Figure 11-4, CSR p74. LSM = least squares mean; SEM = standard error of the mean; PSA = prostate specific antigen; SAA = abiraterone acetate in fine particle formulation; OAA = originator abiraterone acetate

* N varies because of missing data.

Serum testosterone data were missing for 11 patients on Day 9 and for 12 patients on Day 10, and data for these patients are for one day only (CSR p69).

6.12 The assessment of bioequivalence was conducted by the TGA. From the clinical equivalence perspective, the small sample size results in uncertainty. For example, the serum testosterone concentrations at day 56 were 1.75 (7.29) ng/dL in the SAA treated group vs 0.25 (0.28) in the OAA treated group. The least squares mean difference was 1.48 (-1.45, 4.41), which was not statistically significant, but if the difference is in fact real, the evaluation noted that SAA may not be clinically equivalent or non-inferior to OAA.

Comparative harms

6.13 The adverse events as reported in the STAAR trial are shown below. As noted above, given the small size of the study, it was not possible to exclude potentially significant differences.

Table 6: Summary of key adverse events in the trials

	SAA N = 24	OAA N = 29
Total AEs, N	48	84
Patients with AEs, n (%)	18 (75.0%)	24 (82.8%)
Patients with Gastrointestinal AEs, n (%)	5 (20.8%)	5 (17.2%)
Patients with Hypertension, n (%)	1 (4.2%)	2 (6.9%)
Patients with Hypokalaemia, n (%)	0	1 (3.6%)
All Severe AEs, N	1 (elevated alanine aminotransferase)	1 (hyponatremia)

Source: Table 12-2, CSR pp83-4, Table 12-3, CSR pp86-7. AE = adverse event; SAA = abiraterone acetate in fine particle formulation; OAA = originator abiraterone acetate

Benefits/harms

6.14 As the claim was for non-inferiority, information on the benefits and harms was not presented in the evaluation.

Clinical claim

6.15 The submission described SAA + MPRED as non-inferior in terms of effectiveness and safety compared to OAA + prednisone.

6.16 The PBAC noted the following limitations of the clinical data:

- The PBAC noted the surrogate endpoints (serum testosterone, PSA levels, pharmacokinetic data) did not necessarily translate into improved overall survival.
- Given patients in both arms of STAAR were fasted, it was uncertain whether equivalence could be concluded between SAA (without regard to food) and OAA (fasted).
- The PBAC noted the TGA Delegate's Overview stated that the STAAR trial provided supportive evidence of efficacy only. Therefore, although the data for SAA appeared to be comparable to OAA, the PBAC considered that it was not possible to exclude potentially significant differences in terms of safety.

6.17 The PBAC noted the TGA Delegate's overview accepted the claim of bioequivalence for SAA and MPRED to OAA and prednisolone, respectively, which was consistent with the submission's claim of non-inferior comparative effectiveness and safety. However, the PBAC remained concerned about patient safety. The PBAC noted that the proposed co-pack was made up of components which were not individually listed on the PBS. The PBAC noted that the doses available for SAA and MPRED were different to those of OAA and prednisolone, which could cause confusion when patients transition from the individual products to the co-pack. Additionally, the PBAC was concerned that SAA + MPRED risked unnecessary proliferation of products and dose

forms on the PBS. Further discussion about PBAC's concerns about the co-pack in practice is included in the 'Quality Use of Medicines' section below.

Economic analysis

6.18 The submission presented a cost-minimisation analysis, using the published price of OAA, noting that a special pricing arrangement applies. The key assumptions and components of the cost-minimisation approach are summarised in the table below.

Table 7: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	SAA 500 mg in combination with methylprednisolone 4 mg bid is non-inferior to OAA 1,000 mg qd in combination with prednisone 5 mg bid in terms of efficacy.
Therapeutic claim: safety	SAA 500 mg qd in combination with methylprednisolone 4 mg bid is non-inferior to OAA 1,000 mg qd in combination with prednisone 5 mg bid in terms of safety.
Evidence base	Direct comparison of a pharmacokinetic studies (Study 102 and Study 104) as well as a randomised controlled trial investigating the comparative efficacy and safety of SAA+M versus OAA+P (STAAR)
Equi-effective doses	SAA 500 mg qd in combination with methylprednisolone 4 mg bid ≡ OAA 1,000 mg qd in combination with prednisone 5 mg bid
Direct medicine costs	The cost of treatment with SAA 500 mg qd in combination with methylprednisolone 4 mg bid and OAA 1,000 mg qd in combination with prednisone 5 mg bid.
Other costs or cost offsets	No other costs of cost offsets resulting from differences in prescribing, administration, medicine-specific monitoring, or management of adverse events are considered in the CMA

Source: Table 2.8.1, p 87 of the submission. Abbreviations: SAA = abiraterone acetate in fine particle formulation; OAA = originator abiraterone acetate; qd = once daily; bid = twice daily

6.19 The equi-effective daily doses were estimated as SAA 500 mg qd + methylprednisolone 4 mg bid is equivalent to OAA 1,000 mg qd + prednisone 5 mg bid, based on the pharmacokinetic studies and the STAAR study.

6.20 The submission included the cost of prednisone 5 mg tablets in the analysis, and no other costs or cost-offsets, which was reasonable. The results of the analysis, based on published prices, are shown below. Overall, the PBAC considered that the proposed price of SAA + MPRED should be no higher than the lowest cost comparator for metastatic prostate cancer.

Table 8: Results of the cost-minimisation analysis (published AEMP)

	SAA+M	OAA	Prednisone
AEMP for Max Qty	$3,283.57	$3,280.86	$2.71
Treatment days for Max Qty	30 [120/4; 60/2]	30 [120/4; 60/2]	30 [60/2]
Total medicine cost per day	$109.45 [$3,283.57/30]	$109.36 [$3,280.86/30]	$0.09 [$2.71/30]
Cost of treatment	$3,283.57 [$109.45 x 30]	$3,280.86 [$109.36 x 30]	$2.71 [$0.09 x 30]
Total cost of treatment	$3,283.57	$3,283.57 [$3,280.86 + $2.71]	
Difference in cost of treatment	$0		

Source: Table 3.2.2, p 91 of the submission. Abbreviations: SAA = abiraterone acetate in fine particle formulation; OAA = originator abiraterone acetate; max = maximum; qty = quantity, AEMP = approved ex-manufacturer price

Estimated PBS usage & financial implications

6.21 This submission was not considered by DUSC. The submission presented a market share approach to estimate use and financial impact. This was appropriate.

Table 9: Data sources and parameter values applied in the utilisation and financial estimates

	Value	Source
Prescriptions		
Predicted prescriptions for OAA	Prescriptions 2022: [redacted][1] 2023: [redacted][1] 2024: [redacted][2] 2025: [redacted][2] 2026: [redacted][2] 2027: [redacted][2]	**Observed data:** Services Australia PBS statistics for item numbers 2698B (250 mg, 120 tablets) and 11206T (500 mg, 60 tablets). **Extrapolation:** Linear trend analysis using the MS Excel build-in trend line function
Changes in utilisation		
Uptake of SAA+M (%)	Uptake 2022: [redacted]% 2023: [redacted]% 2024: [redacted]% 2025: [redacted]% 2026: [redacted]% 2027: [redacted]%	Sun Pharma assumption
Cost of medicines		
SAA+M combination pack SAA 125 mg, 120 tablets + M 4 mg x 60 tablets	Published AEMP: $3,283.57	Sun Pharma proposed
OAA 500 mg, 60 tablets 250 mg, 120 tablets	 Published AEMP: $3,280.86 Published AEMP: $3,280.86	Schedule of Pharmaceutical Benefits [PBS items 2698B and 11206T; October 2021]
Prednisone 5mg, 60 tablets	 Effective AEMP: $2.71	Schedule of Pharmaceutical Benefits [PBS item 1935W; October 2021]
Patient co-payments		
Beneficiary type distribution	General ordinary: 2% General safety net: 3% Concessional ordinary: 63% Concessional safety net: 32% RPBS ordinary: 65% RPBS safety net: 35%	Utilisation of OAA + prednisone [PBS items: 2698B, 11206T, 1935W]
Patient co-payments	General ordinary: $41.30 General safety net: $6.60 Concessional ordinary: $6.60 RPBS ordinary: $6.60	PBS website

Source: Table 4.1.1, p87-8 of the submission. Abbreviations: PBS = Pharmaceutical Benefits Scheme, AEMP = Approved Ex-Manufacturer Price, M = methylprednisolone, SAA = abiraterone acetate in fine particle formulation, OAA = originator abiraterone acetate

The redacted values correspond to the following ranges:

[1] *10,000 to < 20,000*

[2] *20,000 to < 30,000*

6.22 The estimated use and financial implications as presented in the submission are shown below. The predicted number of prescriptions in each year was based on the estimated annual percent change from the trendline analysis. The overall market for abiraterone is unlikely to expand substantially due to the listing of SAA + MPRED.

Table 10: Estimated use and financial implications (published DMPQ)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of OAA scripts dispensed	[redacted][1]	[redacted][1]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Number of prednisone scripts dispensed	[redacted][1]	[redacted][1]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
SAA+M market share	[redacted]%	[redacted]%	[redacted]%	4[redacted]%	[redacted]%	[redacted]%
Number of SAA+M scripts dispensed[a]	[redacted][2]	[redacted][2]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][1]
Estimated financial implications of SAA + MPRED						
Cost to the PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][7]	$[redacted][7]	$[redacted][8]	$[redacted][8]
Patient co-payments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Total cost to PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][7]	$[redacted][7]	$[redacted][8]	$[redacted][8]
Estimated financial implications of OAA + prednisone						
Cost to the PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][7]	$[redacted][7]	$[redacted][8]	$[redacted][9]
Patient co-payments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Total cost to PBS/RPBS	$[redacted][3]	$[redacted][4]	$[redacted][7]	$[redacted][7]	$[redacted][8]	$[redacted][9]
Net financial implications						
Cost to the PBS/RPBS	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Patient co-payments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Total cost to PBS/RPBS	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]

Source: Table 4.2.1, 4.2.2, 4.2.3 4.2.4, 4.2.5, 4.2.6, 4.4.1 pp 96-8, p104 of the submission. Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; OAA = originator abiraterone acetate; SAA+MPRED = abiraterone acetate in fine particle formulation in combination with methylprednisolone

Submission assumed no changes in the use of other resource items that impact the MBS or other Health budgets

[a] Assumes 12.18 scripts per year

The redacted values correspond to the following ranges:

[1] 10,000 to <20,000

[2] 500 <5,000

[3] $0 to <$10 million

[4] $10 million to <$20 million

[5] 20,000 to <30,000

[6] 5,000 to <10,000

[7] $20 million to <$30 million

[8] $30 million to <$40 million

[9] $40 million to <$50 million

6.23 The total cost to the PBS/RPBS of listing SAA + MPRED as presented in the submission was estimated to be $30 million to < $40 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing. The total net savings to the PBS/RPBS of listing SAA + MPRED as presented in the submission was estimated to be a net cost saving in Year 6, and a total net saving of a net cost saving in the first 6 years of listing. The submission noted the savings were due to the changes to co-payments. The

evaluation noted the reduction in co-payment resulting in listing of a co-pack is likely to result in a net cost to Government.

6.24 The submission presented sensitivity analyses to vary the extrapolations based on a 12-month moving average, extrapolated prescriptions (versus percent change from the previous year), extrapolation based on a logistic trendline and 5% use of OAA 250 mg. The results of these analyses show that the net financial implications for the Health budget are most sensitive to the trendline selection but the overall impact is small (<$100,000 variation per year).

Quality Use of Medicines

6.25 The PBAC discussed there were significant concerns regarding the quality use of SAA and MPRED in clinical practice. The PBAC considered the following were of high risk:

- Patient confusion between SAA and OAA given both products are called abiraterone but have different daily doses of 500 mg and 1000 mg, respectively
- Confusion regarding timing of oral prednisone (typically given 10 mg daily as per EviQ), contrasting with methylprednisolone 4 mg twice daily

The PBAC considered further information from the sponsor would be required to clarify how these risks would be mitigated.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of a composite pack (co-pack) comprising abiraterone acetate tablets in a fine particle formulation (SAA) and oral methylprednisolone (MPRED) tablets for the treatment of patients with metastatic castration resistant prostate cancer. The PBAC raised concerns regarding the quality use of the co-pack in practice, noting there would be a risk of confusion among patients due to differences in dosing of SAA and MPRED compared to the currently listed form of abiraterone (OAA) and prednisolone. The PBAC considered further information from the sponsor would be required to clarify how these risks would be mitigated.

7.2 The PBAC noted there were no consumer comments for this item and considered there was no clinical need for a co-pack of SAA and oral methylprednisolone given the availability of OAA and prednisolone.

7.3 The PBAC considered the nominated comparator OAA given with prednisolone 5 mg tablets was acceptable given these would likely be replaced by SAA + MPRED in practice, although considered that enzalutamide was also a relevant comparator.

7.4 The PBAC noted that the doses available for SAA and MPRED were different to that of OAA and prednisolone which could cause confusion when patients transition from the

individual products to the co-pack. The PBAC also noted concern that SAA risked unnecessary proliferation of products and dose forms. The PBAC considered further information from the sponsor would be required to clarify how these risks would be mitigated.

7.5 The PBAC noted the STAAR study was the most appropriate evidence as it was a direct comparative trial of SAA with OAA which also looked at the population proposed for PBS listing. However, the PBAC noted the study had limitations including the trial was based on surrogate endpoints (serum testosterone and PSA levels) which do not translate to improved overall survival. Additionally, the PBAC noted that TGA Delegate's Overview stated that the STAAR study provided supportive evidence of efficacy only. Therefore, although the data for SAA appeared to be comparable to OAA, the PBAC considered that it was not possible to exclude potentially significant differences in terms of safety.

7.6 Additionally, the PBAC noted the TGA Delegate's Overview was supportive of the registration of SAA + MPRED as a co-pack. The TGA Delegate's Overview noted that SAA is bioequivalent to OAA; and the dose equivalence of 5 mg prednisone to 4 mg methylprednisolone is well recognised and reported. However, the PBAC considered that, on balance, the patient safety issues noted in paragraph 7.4 outweighed the submission's claimed benefit of listing a co-pack which was patient convenience.

7.7 A resubmission may be lodged for consideration at any future PBAC meeting in accordance with lodgement timelines applicable to a standard re-entry pathway submission for that PBAC meeting.

7.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.