

6.01 ABIRATERONE AND METHYLPREDNISOLONE

**Pack containing 120 tablets abiraterone (as acetate)
125 mg and 30 tablets methylprednisolone 4 mg,
Yonsa Mpred[®],
Sun Pharma ANZ Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested Authority Required (telephone) listing for the composite pack comprising abiraterone acetate, a novel hormonal agent (NHA), in a fine particle formulation (SoluMatrixTM) together with 30 methylprednisolone (MPRED) tablets, herein SAA+MPRED, for the treatment of metastatic hormone sensitive prostate cancer (mHSPC)¹.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus apalutamide, with the sponsor seeking the same indication and listing conditions as apalutamide. At the July 2022 meeting, the PBAC recommended apalutamide for mHSPC, regardless of disease volume or suitability for docetaxel (paragraph 7.1, apalutamide Public Summary Document (PSD) July 2022 PBAC meeting).
- 1.3 There was no available clinical evidence for SAA+MPRED in combination with androgen deprivation therapy (ADT) in patients with mHSPC. All clinical evidence presented for SAA+MPRED in the submission were derived from randomised controlled trials (RCTs) of the originator brand of abiraterone acetate (OAA) administered at a dose of 1,000 mg orally once daily plus prednisone or prednisolone (P) at a dose of 5 mg orally once daily in combination with ADT (OAA+P + ADT). This was justified on the basis that the PBAC had accepted the bioequivalence of the formulations (see Previous PBAC consideration section).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with mHSPC
Intervention	SAA 500 mg (4 x 125 mg tablets) orally once daily plus MPRED 4 mg orally once daily plus ADT (SAA+MPRED + ADT)
Comparator	Apalutamide 240 mg (4 x 60 mg tablets) orally once daily plus ADT (APA + ADT)
Outcomes	rPFS, OS and time to initiation of cytotoxic chemotherapy
Clinical claim	SAA+MPRED + ADT is non-inferior to APA + ADT with respect to efficacy but inferior with respect to safety

Source: Table 1.1-1, p 4 of the submission

ADT = androgen deprivation therapy; APA = apalutamide; mHSPC = metastatic hormone sensitive prostate cancer; MPRED = methylprednisolone; SAA = SoluMatrixTM abiraterone acetate; rPFS = radiographic progression free survival; OS = overall survival

¹ Note that mHSPC and metastatic castration-sensitive prostate cancer (mCSPC) are used interchangeably in the literature and PBAC submissions. The term mHSPC was used to be consistent with the recommended PBS listing of apalutamide in this indication.

2 Background

Registration status

- 2.1 SAA+MPRED was registered by the TGA on 29 March 2022 for the following indications:
- newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC) in combination with ADT;
 - patients with metastatic advanced prostate cancer (castration-resistant prostate cancer, mCRPC) who are asymptomatic or mildly symptomatic after failure of ADT; and
 - patients with mCRPC who have received prior chemotherapy containing a taxane.
- 2.2 These are identical indications to that of OAA.

Previous PBAC consideration

- 2.3 This was the first submission for SAA+MPRED for mHSPC. SAA+MPRED was recommended for mCRPC, based on bioequivalence between SAA 500 mg + MPRED 4 mg twice daily and OAA administered at a dose of 1,000 mg orally once daily plus prednisone or prednisolone (P) at a dose of 5 mg orally twice daily (OAA+P). Both are administered in combination with androgen deprivation therapy (ADT) (paragraph 7.2, SAA + MPRED PSD, November 2022 PBAC meeting).
- 2.4 The PBAC has recommended other NHAs in this setting, including apalutamide (July 2022), enzalutamide (March 2023) and darolutamide (May 2023). Apalutamide was listed on the PBS on 1 June 2023.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	DMPQ for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Abiraterone acetate 125 mg fine particle formulation tablet and methylprednisolone 4 mg tablet composite pack	\$	1	120 (SAA) and 30 (MPRED)	5	YONSA MPRED™
Category / Program: General Schedule					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Administrative Advice: - No increase in the maximum quantity or number of units may be authorised. - No increase in the maximum number of repeats may be authorised. - 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.					
Condition: Metastatic castration sensitive					
Indication: Carcinoma of the prostate					
Clinical criteria: The treatment must be/have been initiated within 6 months of treatment initiation with androgen deprivation therapy; AND Treatment must be used in combination with androgen deprivation therapy; AND Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); OR Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation; AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug					
Treatment criteria: Patients must be undergoing concurrent androgen deprivation therapy					
Administrative Advice: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide.					

Source: Table 4.1-1 and Table 4.1-2, p 15 -16 of the submission

DPMQ = dispensed price for maximum quantity; MPRED = methylprednisolone; SAA = SoluMatrix™ abiraterone acetate

- 3.1 The submission proposed listing of a new medicinal product pack that has 30 methylprednisolone tablets of the existing medicinal product 'abiraterone (& methylprednisolone'. The existing PBS-listed medicinal product pack has 60 methylprednisolone tablets.
- 3.2 An identical restriction to that recommended by the PBAC for apalutamide for mHSPC was sought.
- 3.3 The pre-PBAC response requested a grandfather restriction for patients who have been self-funding mHSPC treatment with abiraterone. The Secretariat noted that a separate grandfather restriction was not required as the current restriction allows for patients who have previously been receiving treatment to transfer to PBS-funded treatment as long as they had commenced treatment with SAA+MPRED within 6

months of commencing ADT. The Secretariat further noted that to exempt ‘grandfathered’ patients from a recency limit of having initiated ADT whilst requiring the rest of the population to have commenced ADT within 6 months was inequitable and not the intent of ‘grandfather’ restrictions.

- 3.4 As the effective approved ex-manufacturer price (AEMP) for apalutamide was unknown to the sponsor, the cost minimisation approach between SAA+MPRED and apalutamide was based on the published AEMP of apalutamide.
- 3.5 The submission stated that the Sponsor expects to join the same risk sharing arrangement (RSA) as apalutamide upon listing.

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

4 Population and disease

- 4.1 mHSPC is a stage of advanced prostate cancer when the cancer has spread past the prostate, but the tumour is sensitive/responds to ADT. Metastatic prostate cancer is incurable, all patients with mHSPC will eventually progress to mCRPC. The goal of treatment is to delay progression to mCRPC and prolong survival. ADT lowers serum testosterone to castration levels and is an integral part of the initial treatment of men with mHSPC. Recent evidence also supports the use of additional systemic therapies including docetaxel (a chemotherapeutic agent) and NHAs (abiraterone, enzalutamide, darolutamide and apalutamide) in combination with ADT for initial therapy of men with advanced disease. These combination therapies have now become a preferred approach for men with locally advanced HSPC and both non-metastatic and metastatic castration-resistant disease (ASCO 2021² and NCCN 2022³).

² Virgo, Katherine S., et al. 2021. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: ASCO guideline update." *Journal of Clinical Oncology*, 39(11):1274-1305.

³ Schaeffer, Edward M., et al. 2022. NCCN Guidelines® Insights: Prostate Cancer, Version 1.2023: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*, 20(12):1288-1298.

- 4.2 Results from a growing list of published network meta-analyses (Sathianathen 2020⁴, Marchioni 2019⁵, Chen 2020⁶, Wang 2021⁷, Wenzel 2021⁸, Mori 2021⁹, Mutlu 2021¹⁰) suggest the different dual therapies (i.e., an NHA + ADT) do not differ significantly with respect to overall survival (OS). All are more effective than ADT alone and all NHA plus ADT combinations were associated with significantly fewer side effects compared to docetaxel plus ADT.
- 4.3 It was noted that the TGA registration for SAA+MPRED (and similarly for OAA+P) are for patients with high-risk mHSPC. Patients with high-risk mHSPC were defined as having at least two of the three high-risk factors associated with poor prognosis: a) Gleason score of ≥ 8 , b) presence of ≥ 3 lesions on bone scan, and c) presence of measurable visceral (excluding lymph node disease) metastasis. This was based on the results of the LATITUDE trial which enrolled only high-risk newly diagnosed mHSPC patients. However, trial evidence for OAA is also available in patients with low-risk disease (from STAMPEDE) and both trials had recruited patients with low and high volume disease. It was noted that most guidelines (ESMO 2020¹¹, NICE 2019 and EAU 2021) broadly consider apalutamide, darolutamide, abiraterone, enzalutamide or docetaxel plus ADT to be treatment options irrespective of disease volume or risk.

Triple therapy

- 4.4 Evidence is also emerging for the use of triple therapy consisting of a NHA plus ADT plus docetaxel. OAA+P and darolutamide have demonstrated evidence of benefit when used as triple therapies. The PEACE-1 trial demonstrated that OAA+P + ADT + docetaxel was beneficial in terms of OS compared to ADT + docetaxel. In the subgroup

⁴ Sathianathen NJ, Koschel S, Thangasamy IA, et al., 2020. Indirect Comparisons of Efficacy between Combination Approaches in Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. *Eur Urol*, 77(3):365-372.

⁵ Marchioni M, Di Nicola M, Primiceri G, et al., 2020. New Antiandrogen Compounds Compared to Docetaxel for Metastatic Hormone Sensitive Prostate Cancer: Results from a Network Meta-Analysis. *J Urol*, 203(4):751-759.

⁶ Chen J, Ni Y, Sun G, et al., 2020. Comparison of Current Systemic Combination Therapies for Metastatic Hormone-Sensitive Prostate Cancer and Selection of Candidates for Optimal Treatment: A Systematic Review and Bayesian Network Meta-Analysis. *Frontiers in Oncology*, 10:519388.

⁷ Wang L, Paller CJ, Hong H, et al., 2021. Comparison of Systemic Treatments for Metastatic Castration-Sensitive Prostate Cancer: A Systematic Review and Network Meta-analysis. *JAMA Oncol.*, 7(3):412-420.

⁸ Wenzel M, Nocera L, Collà Ruvolo C, et al., 2021. Overall survival and adverse events after treatment with darolutamide vs. apalutamide vs. enzalutamide for high-risk non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis. *Prostate Cancer Prostatic Dis*, 25(2):139-148.

⁹ Mori K, Mostafaei H, Sari Motlagh R, et al., 2021. Systemic therapies for metastatic hormone-sensitive prostate cancer: network meta-analysis. *BJU International*, 129(4):423-433.

¹⁰ Mutlu H and Bozcuk H. The optimal upfront therapy in metastatic hormone-sensitive prostate cancer: A network meta-analysis. *Journal of Cancer Research and Therapeutics* (online ahead of print, accessed 5 August 2021). DOI: 10.4103/jcrt.JCRT_23_20

¹¹ Parker, Chris, et al. 2020. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 31(9):1119-1134.

receiving triple therapy (abiraterone + ADT + docetaxel), median OS was not reached compared to 4.4 years (53 months) for those receiving ADT + docetaxel, with hazard ratio for death of 0.75 (95% CI: 0.59, 0.95) (i.e., lower HR indicates improved survival). The PBAC has previously considered evidence for darolutamide when used as triple therapy, with the ARASENS¹² trial showing a benefit for darolutamide + ADT + docetaxel compared to ADT + docetaxel in terms of OS (HR = 0.68; 95% CI: 0.57, 0.80). In contrast, there is currently no evidence available (or forthcoming) for the use of apalutamide in triple therapy; whereas the ENZAMET¹³ trial demonstrated no additional benefit for enzalutamide when added to ADT + docetaxel. However, there were key differences between ENZAMET compared to PEACE-1 and ARASENS that may have contributed to the difference in results.

Choice of therapy

- 4.5 Guidance is still emerging in relation to the choice of dual versus triple therapy in mHSPC, with the latest National Comprehensive Cancer Network (NCCN) guidelines encouraging triple therapy with the addition of either darolutamide or abiraterone to ADT + docetaxel for patients with high volume disease who are fit for chemotherapy (NCCN 2022). However, other international guidelines, such as ESMO and ASCO, are yet to update their recommendations. It was noted that the TGA approved indications for apalutamide, enzalutamide and abiraterone (OAA or SAA + MPRED) do not mention specific combination therapies for mHSPC and thus, would allow use as either dual or triple therapy for mHSPC. Only darolutamide is specifically indicated for use in combination with docetaxel in mHSPC.
- 4.6 Other considerations for patients include (i) the potential toxicities associated with abiraterone (hypokalaemia, hypertension, oedema, hepatotoxicity), enzalutamide (oedema, fatigue, hypertension, hyperglycaemia, seizures), apalutamide (rash, diarrhoea, arthralgias), darolutamide (fatigue, skin rash, hepatotoxicity, arthralgias and myalgia, cardiotoxicity) and docetaxel (myelosuppression, febrile infections, nail changes, neuropathy); and (ii) the expected duration of treatment (until disease progression if tolerated for abiraterone, apalutamide, enzalutamide and darolutamide versus 18 weeks for docetaxel).
- 4.7 On a related point, patient preference for NHAs over docetaxel has been consistently observed in prostate cancer. The PBS listings of enzalutamide and abiraterone for mCRPC were originally restricted to patients who had failed treatment with docetaxel OR were unsuitable for docetaxel on the basis of predicted intolerance. Despite the restrictions, data provided by the DUSC Secretariat indicated that in 2020, 69% of use of abiraterone and enzalutamide was in patients who had not received a prior supply

¹² Smith MR, Hussain M, Saad F, et al., 2022. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *New England Journal of Medicine*, 386(12):1132-1142.

¹³ Davis ID, Martin AJ, Stockler MR, et al., 2019. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *New England Journal of Medicine*, 381(2):121-31.

of docetaxel. This prompted the PBAC to review the PBS listings of enzalutamide and abiraterone, ultimately recommending the listings be amended to allow use of enzalutamide and abiraterone prior to docetaxel. The PBAC considered this would better align the restrictions for abiraterone and enzalutamide with how these drugs are being used in clinical practice and with their TGA indications (paragraphs 5.1 and 5.2, abiraterone enzalutamide PSD March 2021 PBAC meeting).

- 4.8 The submission's clinical algorithms depicting current and proposed clinical management in mHSPC were simplistic showing only ADT + docetaxel and apalutamide + ADT as current management options, with the addition of SAA+MPRED + ADT in the proposed management algorithm. Thus, the algorithms omitted the potential use of abiraterone in triple therapy (given the positive trial evidence) and near market comparators such as enzalutamide and darolutamide that have recently been considered by the PBAC.
- 4.9 Given the one NHA per lifetime rule on the PBS, for patients who do not respond to treatment with an NHA in the mHSPC setting treatment options in the mCRPC setting would include docetaxel, cabazitaxel or olaparib (in those with positive BRCA variance). Therefore, the PBS listing of SAA+MPRED, as with the potential listing of other NHAs in the mHSPC setting, would have the effect of shifting NHA use earlier in the treatment pathway, pushing docetaxel further down the pathway. The overall impact of this shift on OS was not considered by the submission. However, based on PBS data in mCRPC, the majority (70.8%) of patients do not receive any further active treatments upon ceasing treatment with enzalutamide or abiraterone in mCRPC (paragraph 5.2, olaparib PSD March 2021 PBAC meeting), indicating that the vast majority of patients either decided to forgo further treatments or were no longer fit enough for docetaxel treatment post NHA.

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

5 Comparator

- 5.1 The submission nominated apalutamide (in combination with ADT) as the main comparator. The main rationale for the nomination was that apalutamide had received a positive PBAC recommendation for use in patients with mHSPC in July 2022. The ESC considered that this was reasonable. Given the PBAC has also considered enzalutamide and darolutamide for mHSPC, they could also be considered near market comparators.
- 5.2 The ESC considered for the purpose of Section 101(3B) of the *National Health Act 1953*, that SAA+MPRED was an alternative therapy to apalutamide, enzalutamide and darolutamide for the treatment of mHSPC, and that SAA+MPRED does not provide a significant improvement in efficacy over these drugs. The ESC advised that the price of SAA+MPRED should therefore be not higher than the price of apalutamide, enzalutamide or darolutamide based on the daily cost at recommended doses (SAA

500 mg plus MPRED 4 mg daily is equi-effective to apalutamide 240 mg daily, enzalutamide 160 mg daily and darolutamide 1,200 mg daily).

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from The Medical Oncology Group of Australia (MOGA) via the Consumer Comments facility on the PBS website. The MOGA expressed its strong support for the abiraterone and methylprednisolone submission, categorising it as one of the therapies of “highest priority for PBS listing”. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for abiraterone and methylprednisolone, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹⁴.

Clinical trials

6.3 There was no available clinical evidence for SAA+MPRED + ADT in patients with mHSPC. All clinical evidence presented for SAA+MPRED + ADT in the submission was derived from published RCTs of OAA+P in combination with ADT (OAA+P + ADT). This was reasonable as the PBAC had previously considered the “claim of non-inferior effectiveness and safety of Yonsa MPRED (SAA+MPRED) to OAA+P was reasonable” (paragraph 7.2, SAA + MPRED PSD November 2022 PBAC meeting). The submission presented the same randomised pharmacokinetic evidence from the March 2022 and November 2022 mCRPC submissions to support the claim of bioequivalence of SAA+MPRED to OAA+P. These studies were previously considered and accepted by the PBAC to demonstrate bioequivalence of the formulations.

6.4 As there was no direct comparative evidence available between OAA+P + ADT and apalutamide + ADT, the submission was based on an indirect comparison (Bucher method) which relied on evidence from two RCTs for OAA+P + ADT (STAMPEDE and LATITUDE) and one RCT for apalutamide + ADT (TITAN). ADT (or placebo + ADT) was the common reference.

6.5 A claim of non-inferior efficacy was made on the basis of an absence of statistically significant differences between OAA+P + ADT versus apalutamide + ADT for the

¹⁴ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

outcomes of OS, radiographic progression-free survival (rPFS), and time to initiation of cytotoxic chemotherapy.

- 6.6 A claim of inferior safety was based on the finding that statistically significantly more patients treated with OAA+P + ADT experienced a Grade \geq 3 adverse events (AE) compared to apalutamide + ADT. The clinical trials presented in the submission are shown in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
STAMPEDE NCT00268476	James, de Bono, Spears, Clarke, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy	N Engl J Med, 2017, 377, 338-351
	Hoyle, Ali, James, Cook, Parker, et al. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer	Eur Urol, 2019, 76, 719-728
	James, Clarke, Cook, Ali, Hoyle, et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476).	Int J Cancer, 2022, 151, 422-434
LATITUDE NCT01715285	Fizazi., Tran, Fein, Matsubara, Rodriguez-Antolin, Alekseev, et al. Abiraterone plus Prednisone in Metastatic, Castration sensitive Prostate Cancer.	N Engl J Med, 2019, 377, 352-360
	Chi, Protheroe, Rodríguez-Antolín, Facchini, et al, 2018. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial.	Lancet Oncol, 2018, 194-206
	Fizazi, Tran, Fein, Matsubara, Rodriguez-Antolin, Alekseev, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial.	Lancet Oncol, 2019, 20, 686-700
TITAN NCT02489318	Chi, Agarwal, Bjartell, Chung, de Santana Gomes, Given, Álvaro Soto et al. Apalutamide for metastatic, castration-sensitive prostate cancer.	Engl J Med, 2019, 381, 13-24
	Agarwal, McQuarrie, Bjartell, Chowdhury, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study.	The Lancet Oncology, 2019; 20(11):1518-30.
	Chi, Chowdhury, Bjartell, Chung, de Santana Gomes, Given, Agarwal. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study.	Journal of Clinical Oncology, 2021, 39(20), 2294-2303

Source: Table 2.2-3, pp 39-40 of the submission

- 6.7 The key features of the RCTs are summarised in Table 3. All trials reported low rates of loss to follow up and were analysed on an intention to treat (ITT) basis. LATITUDE and TITAN were considered to have a low risk of bias as both RCTs were double blind. STAMPEDE was considered to have an unclear to high risk of bias due to its open label design. Even though the primary outcome of OS in STAMPEDE was an objective outcome measure, bias could have arisen from clinicians knowing the treatment assignment. Although STAMPEDE included a mixed patient population (advanced prostate cancer and mHSPC), the submission presented information from the prespecified subgroup of mHSPC patients treated with OAA+P + ADT versus ADT alone.

6.8 Treatment allocations were unblinded after the first interim analysis after a median follow up of 30.4 months in LATITUDE (data-cut off (DCO) Oct 2016) and 22.7 months in TITAN (DCO Nov 2018). In both trials, patients were permitted to crossover from placebo to active treatment after unblinding, with 12% and 40% of patients switching treatment in LATITUDE and TITAN respectively).

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
OAA+P + ADT vs. ADT alone						
STAMPEDE (NCT00268476)	1,003	R, OL 73 months*	High ¹	Prespecified subgroup: mHSPC patients naïve to NHAs (95% newly diagnosed).	OS, failure free survival	NA
LATITUDE (NCT01715285)	1,199	R, DB 51.8 months*	Low	High-risk mHSPC patients naïve to NHAs (100% newly diagnosed)	rPFS, OS, time to initiation of cytotoxic chemotherapy and AEs	NA
APA + ADT vs. ADT alone						
TITAN (NCT02489318)	1,052	R, DB 44 months*	Low	mHSPC patients naïve to NHAs (81% newly diagnosed)	rPFS, OS, time to initiation of cytotoxic chemotherapy and AEs	NA

Source: constructed during the evaluation based on information provided by the submission in Section 2 and Appendix 4-8.

ADT = androgen deprivation therapy; AE = adverse event; APA = apalutamide; DB = double blind; mHSPC = metastatic hormone sensitive prostate cancer; NA = not applicable, NHA = novel hormonal agent; OAA = originator brand of abiraterone acetate; OL = open label; OS = overall survival; P = prednisone/prednisolone; R = randomised; rPFS = radiographic progression-free survival

* At the last data cut, see Table A2.4.3 for earlier data cuts.

1 STAMEPE was an open label trial, in which patients and clinicians were aware of treatment assignment.

6.9 The submission noted differences between the trials affecting transitivity, including that LATITUDE enrolled patients who were at high-risk (99.9% of patients) and most had high volume disease (80% of patients). In comparison, 47% of patients in STAMPEDE and 55% of patients in TITAN had high-risk disease. In STAMPEDE and TITAN, 55% and 63% of patients had high volume disease, respectively. This resulted in LATITUDE patients experiencing higher rates of rPFS, death and a faster time to initiation of chemotherapy, regardless of assignment to treatment (i.e., OAA+P + ADT vs. placebo + ADT). Another potential source of bias was the greater proportion of patients with newly diagnosed mHSPC in LATITUDE and STAMPEDE (100% and 95% respectively) versus TITAN (85%). Given patients with metastatic disease following localised prostate cancer tend to have improved outcomes compared to de novo metastatic disease^{15, 16}, this may have biased results in favour of TITAN.

¹⁵ Gravis G, Boher JM, Joly F, et al., 2016. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur. Urol. 70(2), pp.256–262.

¹⁶ Lv M, Zhang X, Shen Y, Wang F, et al. Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. Medicine (Baltimore). 2017 Apr;96(17):e6799.

Comparative effectiveness

6.10 Table 4 and Figure 1 summarise the results of OS, rPFS, and time to initiation of cytotoxic chemotherapy from STAMPEDE, LATITUDE and TITAN and the results of the ITCs. The main results were based on outcomes reported from the final DCOs from each of the included trials. For completeness ITCs using results from earlier DCOs were also estimated during the evaluation and were consistent with results based on final DCOs.

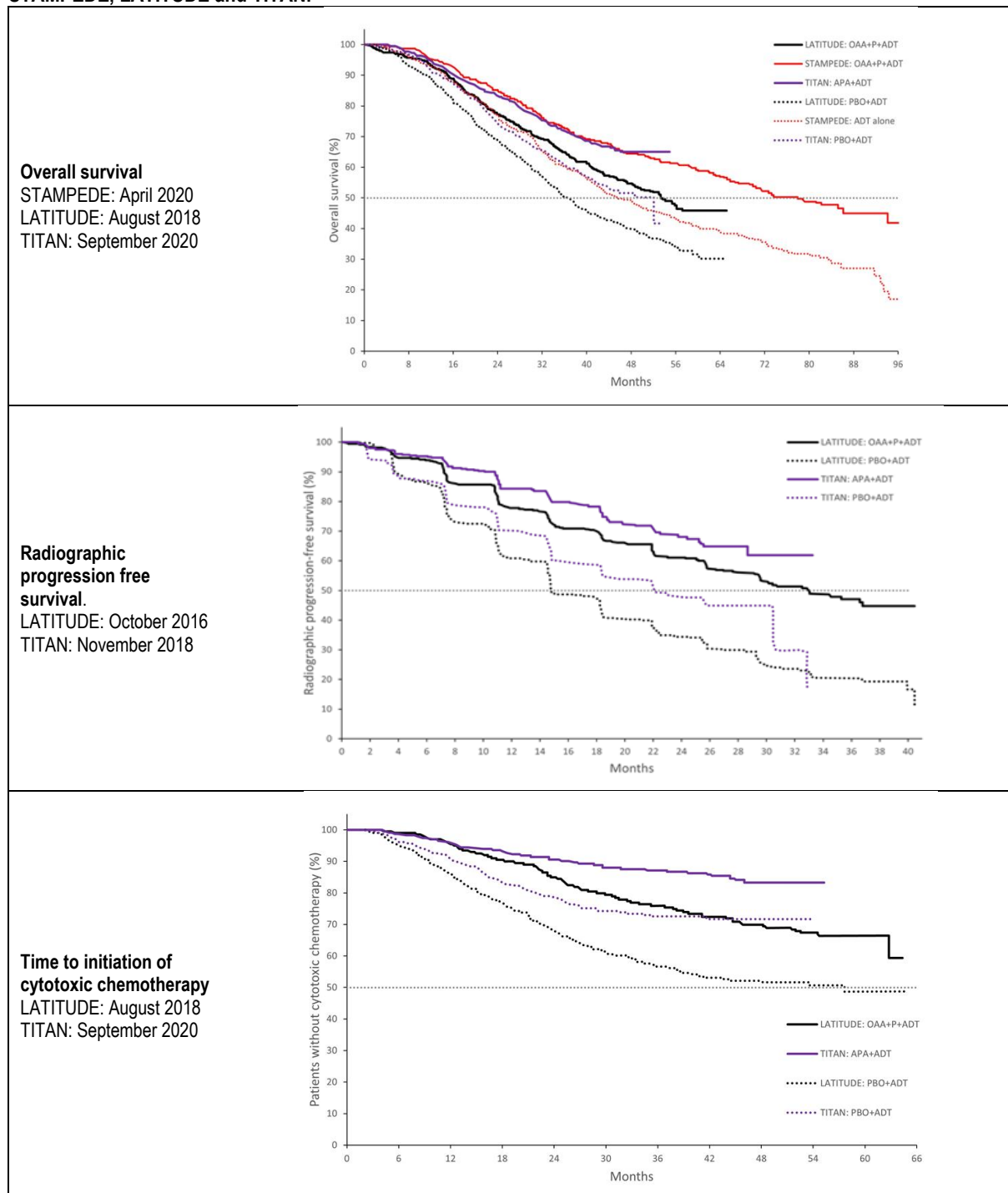
Table 4: ITC results for OS, rPFS and time to initiation of cytotoxic chemotherapy

Outcome	STAMPEDE (mHSPC subgroup)		LATITUDE		TITAN	
	OAA+P + ADT	ADT alone	OAA+P + ADT	PBO + ADT	APA + ADT	PBO + ADT
Overall survival (OS):						
Final analysis DCO	April 2020		August 2018		September 2020	
Median follow up	73 months		51.8 months		44 months	
Events, n/N (%)	244/501 (49)	329/502 (66)	275/597 (46)	343/602 (57)	170/525 (32.4)	235/527 (45)
Median, months (IQR)	79 (33, NE)	46 (25, 92)	53.3 (48.2, NE)	36.5 (33.5, 40.0)	NE (NE, NE)	52.2 (41.9, NE)
HR (95% CI), p-value	0.60 (0.50, 0.71); p <0.0001		0.66 (0.56, 0.78); p <0.0001		0.65 (0.53, 0.79); p <0.0001	
Meta-analysis	0.63 (0.56, 0.71); p <0.0001 ($I^2=0\%$, $\pi^2=0$, $p=0.44$)				NR	
ITC: STAMPEDE + LATITUDE vs TITAN	0.97 (0.77, 1.22)					
Radiographic progression free survival (rPFS)						
Interim analysis DCO	February 2017		October 2016		November 2018	
Median follow up	42 months		30.4 months		22.7 months	
Events, n/N (%)	NR	NR	239/597 (40)	354/602 (59)	134/525 (26)	231/527 (44)
Median, months (IQR)	NR	NR	33	14.8	NE	22.1 (18.5, 32.9)
HR (95% CI), p-value	NR		0.47 (0.39, 0.55); p <0.001		0.48 (0.39, 0.60); p <0.001	
ITC: LATITUDE vs TITAN	0.98 (0.74, 1.29)					
Time to initiation of cytotoxic chemotherapy						
Final analysis DCO	April 2020		August 2018		September 2020	
Median follow up	73 months		51.8 months		44 months	
Events, n/N (%)	NR	NR	150/597 (25)	218/602 (36)	69/525 (13)	126/527 (24)
Median, months (IQR)	NR	NR	NE (62.6, NE)	57.6 (38.2, NE)	NE (NE, NE)	NE (NE, NE)
HR (95% CI), p-value	NR		0.51 (0.41, 0.63); p <0.0001		0.47 (0.35, 0.63); p <0.0001	
ITC: LATITUDE vs TITAN	1.09 (0.75, 1.56)					

Source: Table 2.5-7, Table 2.5-8, Table 2.5-9, Table 2.5-11, Table 2.5-13, Table 2.5,14, Table 2.5-15, pp 83-95 of the submission; Table 2.6.-2, Table 2.6-4, Table 2.6-5, Table 2.6-7, pp 119-122 of the submission

ADT = androgen deprivation therapy; APA = apalutamide; CI = confidence interval; DCO = data cut off, HR = hazard ratio; ITC = indirect treatment comparison; IQR = inter-quartile range; ITT = Intention-to-treat; NE = not estimable; NR = not reported; OAA = originator brand of abiraterone acetate; OS = overall survival; P = prednisone/prednisolone; PBO = placebo; rPFS = radiographic progression free survival

Figure 1: Overlaid Kaplan-Meier curves of rPFS, OS and time to initiation of cytotoxic chemotherapy from STAMPEDE, LATITUDE and TITAN.



Source: Figure 2.6-3 to Figure 2.6.5, p123-128 of the submission
 ADT = androgen deprivation therapy; APA = apalutamide; OAA = originator brand of abiraterone acetate; OS = overall survival; P = prednisone/prednisolone; PBO = placebo; rPFS = radiographic progression free survival

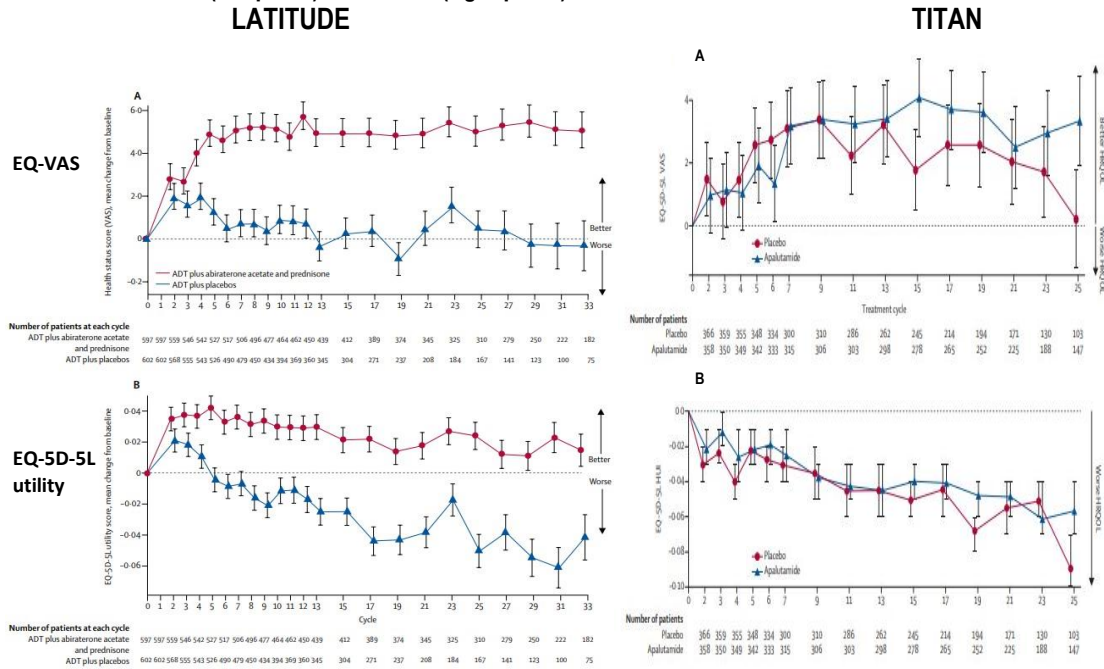
6.11 For OS, the results presented in Table 4 and Figure 1 show that both OAA+P + ADT (STAMPEDE and LATITUDE) and apalutamide + ADT (TITAN) were associated with

statistically significant reductions in the risk of death versus ADT alone. The meta-analysis of STAMPEDE and LATITUDE estimated a HR of 0.63 (95% CI: 0.56, 0.71), which was similar to the HR of 0.65 (95% CI: 0.53, 0.79) from TITAN for intervention versus control. The results of the ITC between OAA+P + ADT and apalutamide + ADT found no statistically significant differences between the two treatments (HR = 0.97; 95% CI: 0.77, 1.22). The overlaid Kaplan-Meier curves also illustrated clear separation of OS curves for the intervention and control arms in all three included trials. While the intervention and control arms of STAMPEDE and TITAN were similar, the Kaplan Meier curves for both treatment (OAA+P + ADT) and control (placebo + ADT) in LATITUDE were lower (whilst maintaining similar separation between the treatment and control arms as other trials), indicating that patients in LATITUDE experienced faster progression to death, likely due to higher baseline risk given all patients had high-risk mHSPC.

- 6.12 rPFS was only reported in LATITUDE and TITAN, and the results from these trials showed that treatment with both OAA+P + ADT (LATITUDE) and apalutamide + ADT (TITAN) resulted in a statistically significant reduction in rPFS versus ADT + placebo (HR = 0.47; 95% CI: 0.39, 0.55) and HR = 0.48; 95% CI: 0.39, 0.60, respectively). The results of the ITC demonstrated no significant differences between the two treatments (HR = 0.97; 95% CI: 0.77, 1.22). The overlaid rPFS Kaplan-Meier curves illustrated that patients in LATITUDE were more likely to experience rPFS at any point in time versus those in TITAN, likely attributable to their high-risk status.
- 6.13 For time to initiation of cytotoxic chemotherapy, both OAA+P + ADT (HR = 0.51; 95% CI: 0.41, 0.63) and apalutamide + ADT (HR = 0.47; 95% CI: 0.35, 0.63) treatments resulted in statistically significantly slower time to initiation of cytotoxic chemotherapy versus ADT + placebo. The ITC demonstrated no significant differences between the treatments (HR = 1.09; 95% CI: 0.75, 1.56). The overlaid Kaplan-Meier curves illustrated overall higher risks for initiation of cytotoxic for patients in LATITUDE versus those enrolled in TITAN.
- 6.14 The submission also presented a subgroup analysis of high vs. low-risk patients in STAMPEDE to support the validity of the OS results from STAMPEDE and LATITUDE being used in a meta-analysis and to illustrate that disease risk is not a treatment modifier for OAA+P + ADT. Overall, the subgroup analysis results from STAMPEDE showed that OAA+P + ADT was statistically significantly superior to ADT in terms of OS in both high (HR = 0.54; 95% CI: 0.41, 0.70) and low-risk (HR = 0.66; 95% CI: 0.44, 0.98) patients, with a marginally larger effect in the high-risk group at interim analysis. At final analysis both HRs were 0.54. However, higher-risk patients were more likely to die than low-risk patients at any point regardless of the treatment assigned. This would suggest the absolute gain in terms of death avoided due to OAA+P + ADT may differ depending on the risk status of the patient population. It should be noted that death rate in the control arm of STAMPEDE was greatest in high-risk patients (interim DCO: low-risk = 24% vs. high-risk = 61%; final DCO: low-risk = 54% vs. high-risk = 77%).

6.15 Figure 2 illustrates results for EQ-5D-5L from LATITUDE and TITAN. Health-related quality of life (HRQoL) was measured using the EQ-5D-5L as an exploratory outcome in LATITUDE in October 2016 DCO and as a post-hoc analysis in TITAN in November 2018 DCO.

Figure 2: Repeated-measures analysis of the mean change from baseline in the EQ-5D-5L (A) VAS and (B) utility score in LATITUDE (left panel) and TITAN (right panel)



Source: Figure 2.5-10 to 2.5.11, p97-98 of the submission

ADT = androgen deprivation therapy; HRQoL = health-related quality of life; HUI = health utility index; SEM = standard error of the mean; VAS = visual analogue scale

6.16 The results from LATITUDE (see left panel) illustrated that those treated with OAA+P + ADT generally experienced an improvement in HRQoL; whereas those treated with placebo + ADT experienced no change on the visual analogue scale (VAS) or a decline in utility scores. The results from TITAN (see right panel) showed a much smaller difference in VAS and utilities between patients in the intervention arm versus patients in the control arm, with the mean change from baseline for both measures marginally higher for patients treated with apalutamide + ADT than those treated with placebo + ADT. In both LATITUDE and TITAN, utility scores declined over time irrespective of treatment assigned.

Comparative harms

6.17 The results of the safety analysis (OAA+P + ADT vs placebo + ADT) at both the interim (October 2016) and final analysis (August 2018) from LATITUDE are presented in Table 5. The submission also presented data from STAMPEDE although only limited results were available from the trial publications for the mHSPC subgroup. Results from TITAN were previously considered by the PBAC as part of the apalutamide submissions for mHSPC.

6.18 It is important to note that drug exposure period differed across treatment arms in LATITUDE, patients in the OAA+P + ADT arm had a longer exposure period (median treatment duration 25.8 months) versus patients in the control arm (14.4 months). However, neither the submission nor the trial publication reported AEs adjusted for lengths of exposure.

Table 5: Summary of cumulative incidence of adverse events in LATITUDE at the interim and final analysis

LATITUDE Adverse event (AE)	Interim analysis (Oct 2016) Median follow up 30.4 months			Final analysis (August 2018) ^A Median follow up 51.8 months		
	OAA+P+ADT n/N (%)	PBO+ADT n/N (%)	Risk Difference (95% CI)	OAA+P+ADT n/N (%)	PBO+ADT n/N (%)	Risk Difference (95% CI)
Median treatment duration	24 months	14 months	-	25.8 months	14.4 months	-
Any AE	558/597 (93)	557/602 (93)	0.01 (-0.02; 0.04)	569/597 (95)	561/602 (93)	0.02 (-0.01; 0.05)
Grade 3 or 4 AE	374/597 (63)	287/602 (48)	0.15 (0.09; 0.21)	403/597 (68)	299/602 (50)	0.18 (0.12; 0.23)
Any SAE	165/597 (28)	146/602 (24)	0.03 (-0.02; 0.08)	192/597 (32)	151/602 (25)	0.07 (0.02; 0.12)
Grade 3 or 4 SAE	NR	NR	-	160/597 (27)	120/602 (20)	0.07 (0.02; 0.12)
Treatment-related SAE	NR	NR	-	30/597 (5)	13/602 (2)	0.03 (0.01; 0.05)
Discontinuation due to AE	73/597 (12)	61/602 (10)	0.02 (-0.01; 0.06)	93/597 (16)	63/602 (10)	0.05 (0.01; 0.09)
AE leading to dose modification or interruption	191/597 (32)	102/602 (17)	0.15 (0.10; 0.20)	209/597 (35)	108/602 (18)	0.17 (0.12; 0.22)
AE leading to death	28/597 (5)	24/602 (4)	0.01 (-0.02; 0.03)	38/597 (6)	25/602 (4)	0.02 (-0.00; 0.05)
Hypertension	219/597 (37)	133/602 (22)	0.15 (0.09; 0.20)	243/597 (41)	144/602 (24)	0.17 (0.12; 0.22)
Grade ≥ 3 hypertension	121/597 (20)	60/602 (10)	0.10 (0.06; 0.14)	131/597 (22)	63/602 (10)	0.11 (0.07; 0.16)
Hypokalaemia	122/597 (20)	22/602 (4)	0.17 (0.13; 0.20)	143/597 (24)	23/602 (4)	0.20 (0.16; 0.24)
Grade ≥ 3 hypokalaemia	62/597 (10)	8/602 (1)	0.09 (0.06; 0.12)	70/597 (12)	10/602 (2)	0.10 (0.07; 0.13)
Hepatotoxicity	NR	NR	-	146/597 (24)	109/602 (18)	0.06 (0.02; 0.11)
Grade ≥ 3 hepatotoxicity	NR	NR	-	53/597 (9)	21/602 (3)	0.05 (0.03; 0.08)
ALT increased	98/597 (16)	77/602 (13)	0.04 (-0.00; 0.08)	101/597 (17)	77/602 (13)	0.04 (0.00; 0.08)
Grade ≥ 3 ALT increased	33/597 (6)	8/602 (1)	0.04 (0.02; 0.06)	34/597 (6)	8/602 (1)	0.04 (0.02; 0.06)
Hyperglycaemia	75/597 (13)	68/602 (11)	0.01 (-0.02; 0.05)	83/597 (14)	73/602 (12)	0.02 (-0.02; 0.06)
Grade ≥ 3 hyperglycaemia	27/597 (5)	18/602 (3)	0.02 (-0.01; 0.04)	31/597 (5)	22/602 (4)	0.02 (-0.01; 0.04)
AST increased	87/597 (15)	68/602 (11)	0.03 (-0.01; 0.07)	92/597 (15)	68/602 (11)	0.04 (0.00; 0.08)
Grade ≥ 3 AST increased	26/597 (4)	9/602 (1)	0.03 (0.01; 0.05)	27/597 (5)	9/602 (1)	0.03 (0.01; 0.05)
Bone pain	74/597 (12)	88/602 (15)	-0.02 (-0.06; 0.02)	83/597 (14)	93/602 (15)	-0.02 (-0.06; 0.03)
Grade ≥ 3 bone pain	20/597 (3)	17/602 (3)	0.01 (-0.01; 0.02)	25/597 (4)	17/602 (3)	-0.01 (-0.01; 0.03)
Any cardiac disorder	74/597 (12)	47/602 (8)	0.05 (0.01; 0.08)	95/597 (16)	52/602 (9)	0.07 (0.04; 0.11)
Grade ≥ 3 cardiac disorder	20/597 (3)	6/602 (1)	0.02 (0.01; 0.04)	23/597 (4)	6/602 (1)	0.03 (0.01; 0.05)
Atrial fibrillation	8/597 (1)	2/602 (<1)	0.01 (-0.00; 0.02)	10/597 (2)	2/602 (<1)	0.01 (0.00; 0.02)
Grade ≥ 3 atrial fibrillation	2/597 (<1)	1/602 (<1)	0.00 (-0.00; 0.01)	2/597 (<1)	1/602 (<1)	0.00 (-0.00; 0.01)
Anaemia	54/597 (9)	85/602 (14)	-0.05 (-0.09; -0.01)	62/597 (10)	90/602(15)	-0.05(-0.08, -0.01)
Grade ≥ 3 anaemia	15/597 (3)	27/602 (4)	-0.02 (-0.04; 0.00)	17/597 (3)	26/602 (4)	-0.01 (-0.04; 0.01)
Back pain	110/597 (18)	123/602 (20)	-0.02 (-0.06; 0.02)	123/597 (21)	128/602 (21)	-0.01 (-0.05; 0.04)
Grade ≥ 3 back pain	14/597 (2)	19/602 (3)	-0.01 (-0.03; 0.01)	15/597 (3)	21/602 (3)	-0.01 (-0.03; 0.01)
Fatigue	77/597 (13)	86/602 (14)	-0.01 (-0.05; 0.02)	84/597 (14)	90/602 (15)	-0.01 (-0.05; 0.03)
Grade ≥ 3 fatigue	10/597 (2)	14/602 (2)	-0.01 (-0.02; 0.01)	11/597 (2)	14/602 (2)	-0.01 (-0.02; 0.01)
Spinal-cord compression	14/597 (2)	12/602 (2)	0.00 (-0.01; 0.02)	14/597(2)	12/602 (2)	0.004 (-0.02; 0.02)
Grade ≥ 3 SCC	12/597 (2)	10/602 (2)	0.00 (-0.01; 0.02)	12/597 (2)	10/602 (2)	0.003 (-0.01; 0.02)
Fluid retention or oedema	NR	NR	-	81/597 (14)	71/602 (12)	0.02 (-0.02; 0.06)
Grade ≥ 3 fluid retention or oedema	NR	NR	-	5/597 (1)	6/602 (1)	-0.00 (-0.01; 0.01)
Osteoporosis, incl fractures	NR	NR	-	43/597 (7)	27/602 (4)	0.03 (0.00; 0.05)

LATITUDE	Interim analysis (Oct 2016) Median follow up 30.4 months			Final analysis (August 2018) [^] Median follow up 51.8 months		
	OAA+P+ADT n/N (%)	PBO+ADT n/N (%)	Risk Difference (95% CI)	OAA+P+ADT n/N (%)	PBO+ADT n/N (%)	Risk Difference (95% CI)
Grade ≥ 3 osteoporosis, including fractures	NR	NR	-	9/597 (2)	14/602 (2)	-0.01 (-0.02; 0.01)
Cataract	NR	NR	-	22/597 (4)	8/602 (1)	0.02 (0.01; 0.04)
Grade ≥ 3 cataract	NR	NR	-	8/597 (1)	1/602 (<1)	0.01 (0.00; 0.02)

Source: Table 2.5-20 to Table 2.5-22, p103-108 of the submission, trial publications, Fizazi 2017, Table 2 and Fizazi 2019 Tables 4 and 5. ADT = androgen deprivation therapy; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; DCO = data cut-off; OAA = originator brand of abiraterone acetate; P = prednisone/prednisolone; PBO = placebo; SAE = serious adverse event, SCC = spinal cord compression.

[^] 72 patients (12%) in the control arm had also switched to OAA+P+ADT after the interim DCO, results for patients post switching are not reproduced, but are available in the trial publication (Fazazi 2019).

- 6.19 Overall, compared to placebo + ADT, patients treated with OAA+P + ADT reported significantly higher rates of the following AEs across the two analysis periods: Grade 3-4 AE, an AE leading to dose modification or interruption, hypertension (including Grade ≥ 3 hypertension), hypokalaemia (including Grade ≥ 3 hypokalaemia), hepatotoxicity, including increases in Grade ≥ 3 AST and ALT, any cardiac disorder (including Grade ≥ 3 cardiac disorder), atrial fibrillation, osteoporosis including fractures and cataracts. There was, however, a reduction in the reported number of anaemic events. Many of the AEs for OAA+P + ADT may be attributed to the effect of mineralocorticoid excess due to the effect of OAA on adrenal suppression and the required concomitant long-term oral corticosteroid administration with OAA.
- 6.20 The submission also presented an ITC for safety outcomes between OAA+P + ADT and apalutamide + ADT using data from LATITUDE (OAA+P + ADT vs. placebo + ADT) and TITAN (apalutamide + ADT vs. placebo + ADT) (see Table 6 below). The results of the ITCs showed that patients treated with OAA+P + ADT were significantly more likely to experience Grade 3-4 AEs (RD = 0.14; 95% CI: 0.06, 0.22) and Grade ≥ 3 hypertension (RD = 0.11; 95% CI: 0.06; 0.16) but fewer Grade ≥3 rash (RD = -0.05; 95% CI: -0.08; -0.02) than patients treated with apalutamide + ADT.
- 6.21 The submission's ITC was incomplete as many AEs observed more frequently in patients treated with OAA+P + ADT versus placebo + ADT in LATITUDE were omitted, including hypokalaemia (including Grade ≥ 3 hypokalaemia), increases in Grade ≥ 3 AST and ALT, any cardiac disorder (including Grade ≥ 3 cardiac disorder), atrial fibrillation, and potentially irreversible side effects of long-term mineral corticosteroid use such as hepatotoxicity, osteoporosis (including fractures) and cataracts. The pre-PBAC response stated that it was not possible to conduct ITCs for all AEs of special interest as a number were not reported in the TITAN publication.

Benefits/harms

- 6.22 A summary of the comparative harms for OAA+P + ADT versus apalutamide + ADT, based on the results of the ITC and using placebo + ADT as a common reference, is presented in Table 6 below. A summary of comparative benefits is not presented

given the submission made a claim of non-inferior efficacy for SAA+MPRED versus apalutamide.

Table 6: Summary of comparative harms for OAA+P + ADT vs APA + ADT

	OAA+P + ADT/ APA + ADT n/N	PBO + ADT n/N	Event rate/100 patients*		Risk Difference (95% CI)
			OAA+P + ADT/ APA + ADT	PBO + ADT	
Grade 3-4 adverse event (final analysis)					
LATITUDE: OAA+P+ADT vs PBO+ADT	403/597	299/602	68	50	0.18 (0.12; 0.23)
TITAN: APA+ADT vs PBO+ADT	259/524	220/527	49.9	41.7	0.08 (0.02; 0.14)
Indirect comparison: OAA+P + ADT vs. APA + ADT					0.10 (0.02; 0.18)
Grade ≥ 3 Hypertension (interim analysis)					
LATITUDE: OAA+P+ADT vs PBO+ADT	121/597	60/602	20	10	0.10 (0.06; 0.14)
TITAN: APA+ADT vs PBO+ADT	44/525	48/527	8.4	9.1	-0.01 (-0.04; 0.03)
Indirect comparison: OAA+P + ADT vs. APA + ADT					0.11 (0.06; 0.16)
Grade ≥ 3 Rash^A (interim analysis)					
LATITUDE: OAA+P+ADT vs PBO+ADT	0/597	1/602	0	0.2	-0.00 (-0.01; 0.00)
TITAN: APA+ADT vs PBO+ADT	33/524	5/527	6.3	0.9	0.05 (0.03; 0.08)
Indirect comparison: OAA+P + ADT vs. APA + ADT					-0.05 (-0.08; -0.02)

Source: 2.6-9, p 135-136 of the submission

ADT = androgen deprivation therapy; APA = apalutamide; CI = confidence interval; ITC = indirect treatment comparison; OAA = originator brand of abiraterone acetate; P = prednisone/prednisolone; PBO = placebo

^A In TITAN, this was defined as skin rash and included rash, maculo-papular rash, conjunctivitis, dermatitis, stomatitis, pruritic rash, urticaria, papular rash, skin exfoliation, blister, mouth ulceration, drug eruption, erythema multiforme, exfoliative rash, toxic skin eruption, papule, skin reaction, butterfly rash, generalized exfoliative dermatitis, genital rash, erythematous rash, macular rash, systemic lupus

6.23 On the basis of indirect evidence presented by the submission, for every 100 patients treated with SAA+MPRED + ADT (proxied by data for OAA+P + ADT) over a median follow up period of 51.8 months, in comparison with apalutamide + ADT (median follow-up of 44 months):

- Approximately 10 additional patients would experience a Grade 3-4 adverse event.
- Approximately 11 additional patients would experience Grade ≥ 3 hypertension.
- Approximately 5 fewer patients would experience Grade ≥ 3 rash.

Clinical claim

6.24 Based on i) indirectly comparable evidence presented for OAA+P + ADT and apalutamide + ADT via ADT as common comparator, and ii) assuming bioequivalence of OAA+P + ADT and SAA+MPRED + ADT, the submission described SAA+MPRED + ADT as non-inferior in terms of effectiveness compared with apalutamide + ADT and inferior in terms of safety. The ESC considered that these claims were reasonable. The results of ITCs showed that OAA+P + ADT vs. apalutamide + ADT were generally comparable for the efficacy outcomes: rPFS, OS and time to initiation of cytotoxic chemotherapy. The results of ITCs for safety outcomes showed that patients treated with OAA+P + ADT had significantly higher rates of Grade 3-4 AEs and Grade ≥ 3 hypertension versus apalutamide + ADT but fewer Grade ≥ 3 rash.

6.25 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.26 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.27 The submission presented a CMA to compare costs of treatment with SAA+MPRED to apalutamide (see Table 7).

6.28 Based on the established bioequivalence to OAA+P the submission proposed SAA 500 mg + MPRED 4 mg daily to be equi-effective to apalutamide 240 mg once daily.

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

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on the clinical evidence, SAA 500 mg in combination with MPRED 4 mg is non-inferior to APA 240 mg.
Therapeutic claim: safety	Based on the clinical evidence, SAA 500 mg in combination with MPRED 4 mg is inferior to APA 240 mg.
Evidence base	The assessment of comparative efficacy and safety is informed by the indirect comparison of the OAA+P + ADT LATITUDE and STAMPEDE trials and the APA + ADT TITAN trials. The direct comparison of Studies 102 and 104 demonstrate that SAA is bioequivalent to OAA which supports the use of the OAA+P + ADT LATITUDE and STAMPEDE trials to inform the assessment of comparative efficacy and safety
Equi-effective doses	SAA 500 mg once daily in combination with MPRED 4 mg once daily = APA 240 mg once daily
Direct medicine costs	The cost of treatment with SAA 500 mg once daily in combination MPRED 4 mg daily and APA 240 mg once daily
Other costs or cost offsets	Additional costs resulting from differences in medicine-specific monitoring costs (i.e., hypokalaemia, ALT, AST, and bilirubin tests) and management of AEs of grade ≥ 3 (i.e., hypertension).

Source: Table 3.1-1, 149 of the submission

ADT = androgen deprivation therapy; AE = adverse event; ALT = alanine aminotransferase; APA = apalutamide; AST = aspartate aminotransferase; MPRED = methylprednisolone; OAA = originator brand of abiraterone acetate; P = prednisone/prednisolone; SAA = SoluMatrix™ abiraterone acetate

6.29 The CMA was conducted over a two-year time horizon to capture differences in resource use and costs of monitoring and managing additional side effects associated with SAA+MPRED versus apalutamide. The ESC considered that the use of a two-year time horizon likely favoured SAA+MPRED, as the median duration of treatment in the trial exceeded 2-years (STAMPEDE = 29 months, LATITUDE = 25.8 months and TITAN = 39.3 months). Therefore, the mean duration of treatment with a NHA + ADT is likely to exceeded 24 months. The pre-PBAC response reiterated that although the duration of treatment would likely exceed 24 months, the application of a two-year time horizon was reasonable and that revisions to the CMA (see paragraphs 6.30 and 6.31) captured the longer term AEs associated with SAA+MPRED.

6.30 The only AE included in the submission’s CMA was the management of patients with hypertension Grade ≥ 3 which it considered would require hospitalisation. Cost of managing other AEs of interest for SAA+MPRED, particularly those associated with mineralocorticoid excess (i.e., hypokalaemia including Grade ≥ 3 hypokalaemia), and metabolic effects including increases in Grade ≥ 3 AST and ALT, any cardiac disorder (including Grade ≥ 3 cardiac disorder), atrial fibrillation, and potentially irreversible side effects such as hepatotoxicity, osteoporosis (including fractures) and cataracts were omitted. Thus, the CMA likely favoured SAA+MPRED. In the modelled economic

evaluations of apalutamide considered by the PBAC at the November 2021 and July 2022 PBAC meetings, one off costs for the management of AEs of special interest for apalutamide (e.g., rash, fractures, ischaemic heart disease) and those with a reported higher incidence in TITAN (November 2021 submission only) had been included. The ESC considered that it would have been appropriate to include the costs of additional AEs related to mineralocorticoid excess and long term corticosteroid use associated with SAA+MPRED use such as osteoporosis and cataracts. The pre-PBAC response provided a revised CMA which included costs associated with hypokalaemia, osteoporosis and cataracts.

- 6.31 For Grade ≥ 3 hypertension, the submission estimated an exposure adjusted incidence rate based on the median durations of treatment as reported at the interim analysis for OAA+P in LATITUDE (24 months) and apalutamide in TITAN (20.5 months). The estimated exposure adjusted Grade ≥ 3 hypertension rates of 10.13% per patient year for SAA+MPRED and 4.91% per patient year for patients treated with apalutamide resulted in rates of 20.27% and 9.81% for SAA+MPRED and apalutamide respectively over the two-year time horizon of the CMA. The unit cost of the hospitalisation was derived from the NHCDC AR-DRG, Public Sector, Round 24 (2019-2020) as a weighted average cost for the AR-DRG codes, F67A and F67B, resulting in an estimated cost of \$2,824.91. For hypokalaemia, osteoporosis and cataracts the pre-PBAC response also applied rates from the LATITUDE and TITAN trials adjusted over the two year time horizon (hypokalaemia: SAA+MPRED = 20.44% vs apalutamide = 0%; osteoporosis: SAA+MPRED = 6.7% vs apalutamide 0%; and cataracts: SAA+MPRED 3.43% vs apalutamide 0%). Hypokalaemia and cataracts were assumed to require hospitalisation for management and resolution, with costs derived from the NHCDC AR-DRG, Public Sector, Round 24 (2019-2020). Treatment of osteoporosis was assumed to require treatment with alendronate 70 mg once weekly and, for the proportion of patients who developed osteoporosis, the duration of treatment was aligned with the two-year time horizon of the analysis.
- 6.32 The submission stated that treatment with SAA+MPRED requires regular monitoring for hypertension, hypokalaemia, fluid retention and hepatotoxicity, with additional tests required for serum potassium, serum transaminases (i.e., ALT, AST), and bilirubin prior to treatment, every 2 weeks for 3 months then monthly thereafter. These were appropriately costed in the CMA based on MBS items costs (66509 for 4 tests and 66506 for 3 tests).
- 6.33 It was noted other monitoring such as blood glucose monitoring may be required for diabetic patients treated with SAA+MPRED. For patients reinitiating treatment with SAA+MPRED after temporary cessation for hepatotoxicity, more frequent liver laboratory tests would also be required.
- 6.34 The submission noted while treatment with apalutamide for the treatment of mHSPC has an effective price, it was unknown to the sponsor, therefore published AEMP for apalutamide was used. Table 8 shows the results of the CMA.

Table 8: Results of the cost-minimisation approach

Component	SAA+MPRED	APA
Cost of medicine		
Submission's proposed AEMP per script	\$	\$3,553.42
Dose duration – 2 years (24 months)	\$	\$86,523
Cost of managing Grade ≥ 3 hypertension		
Total cost per a patient over 2-year period	\$573	\$277
Cost of monitoring patients on medicine		
Blood tests associated with treatment	\$432	\$0
TOTAL COST	\$	\$86,800.03
Pre-PBAC revised CMA		
Cost of medicine		
Proposed AEMP per script	\$	\$3,553.30
Dose duration – 2 years (24 months)	\$	\$86,522.86
Cost of managing Grade ≥ 3 hypertension		
Total cost per a patient over 2-year period	\$57.55	\$277.18
Cost of managing:		
Hypokalaemia	\$763.55	\$0
Osteoporosis	\$28.20	\$0
Cataracts	\$98.06	\$0
Cost of monitoring patients on medicine		
Blood tests associated with treatment	\$432.20	\$0
TOTAL COST	\$	\$86,800.03

Source: Table 3.4-4, 156 of the submission

AEMP = approved ex-manufacturer price; APA = apalutamide; MPRED = methylprednisolone; SAA = SoluMatrix™ abiraterone acetate.

6.35 The submission estimated that based on an assumed AEMP for apalutamide of \$3,555.42 and the submission's assumptions of additional costs associated with SAA+MPRED treatment, SAA+MPRED would achieve cost minimisation at an AEMP of \$|. The revised CMA presented in the pre-PBAC response resulted in an AEMP of SAA+MPRED of \$|.

SAA+MPRED cost/patient/year: \$ [REDACTED] (assuming full compliance)

Table 9: Drug cost per patient for proposed and comparator drugs

	OAA+P Trial dose [^] and duration	SAA+MPRED CMA	SAA+MPRED Financial estimates	Apalutamide Trial dose and duration	Apalutamide CMA	Apalutamide Financial estimates
Dose	OAA 1000 mg + P 5 mg daily	SAA 500 mg + MPRED 4 mg daily	SAA 500 mg + MPRED 4 mg daily	APA 240 mg daily	APA 240 mg daily	APA 240 mg daily
Median duration*	25.8 months (LATITUDE) and 29 months (STAMPEDE)	24 months total duration was used in the CMA	52 weeks	25.8 months (TITAN)	24 months total duration was used in the CMA	52 weeks
Compliance	100%	100%	95.88%	100%	100%	95.88%
Cost/patient/month ^a	\$3,684.70 ^b	\$ ^c	\$ ^b	\$3,714.58 ^b	\$3,553.42 ^c	\$3,714.58 ^b
Cost/patient/year	\$44,861	\$	\$ ^d	\$45,225 ^e	\$43,262 ^f	\$43,362 ^d
Drug costs based on the revised CMA						
Cost/patient/month ^a	\$3,648.16 ^b	\$ ^c	\$ ^b	-	-	-
Cost/patient/year	\$44,416	\$	\$	-	-	-

Source: compiled during the evaluation.

AEMP = approved ex-manufacturer price; APA = apalutamide; CMA = cost-minimisation approach; DPMQ = dispensed price for maximum quantity; MBS = Medical Benefits Schedule; MPRED = methylprednisolone; OAA = originator brand of abiraterone acetate; P = prednisone/prednisolone; SAA = SoluMatrix™ abiraterone acetate

[^] Mean dose was not reported, this is the dosage specified to be used in the trial protocols.

* Mean durations were not reported in the trial reports, therefore median durations are stated here instead.

^a Per pack for 30 days of treatment.

^b DPMQ

^c AEMP

Estimated PBS usage & financial implications

6.36 This submission was not considered by DUSC. The submission applied an epidemiological approach to the financial estimates, with assumptions and parameters and based on the July 2022 apalutamide resubmission for mHSPC.

6.37 Table 10 summarises the key inputs in the financial estimates. The financial model estimated costs by low volume and high volume disease populations.

Table 10: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
Incident mHSPC patients	$Y_i = (68.95 \times Y_i) + 2420.4$	Table 15, apalutamide PSD July 2022	Previously accepted by PBAC.
Adjustment to incident mHSPC patient numbers	-8%	DUSC data and paragraph 7.13, apalutamide PSD July 2022	Previously accepted by PBAC.
% incident patients with LV and HV disease	LV: 47.7% HV: 52.3%	Table 15, apalutamide PSD July 2022	Previously accepted by PBAC.

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Data	Value	Source	Comment																																																																
% untreated patients in Yi remaining eligible in Yi+1. Used to derive prevalent population	<table border="1"> <thead> <tr> <th>Year</th> <th>LV</th> <th>HV</th> <th>Total</th> </tr> </thead> <tbody> <tr><td>1</td><td>1,187</td><td>1,302</td><td>2,489</td></tr> <tr><td>2</td><td>903</td><td>920</td><td>1,823</td></tr> <tr><td>3</td><td>706</td><td>632</td><td>1,338</td></tr> <tr><td>4</td><td>581</td><td>443</td><td>1,024</td></tr> <tr><td>5</td><td>491</td><td>293</td><td>784</td></tr> <tr><td>6</td><td>434</td><td>220</td><td>654</td></tr> </tbody> </table>	Year	LV	HV	Total	1	1,187	1,302	2,489	2	903	920	1,823	3	706	632	1,338	4	581	443	1,024	5	491	293	784	6	434	220	654	Prevalent patients in Year 2 onwards were estimated as a proportion of untreated patients from the previous year who remain with mHSPC.	The same methodology was used to estimate prevalent patients in the apalutamide July 2022 resubmission. However, the apalutamide resubmission included prevalent patients in Year 1 only. The inclusion of prevalent patients in Years 2-6 was not reasonable and had a considerable impact on patient numbers, and resultant cost. The submission provided no justification for this. Of note, the requested listing excludes patients who remain on ADT after 6 months without starting an NHA.																																				
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1	1,187	1,302	2,489																																																																
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Treatment utilisation																																																																			
Uptake apalutamide rate (patients eligible for substitution)	<table border="1"> <thead> <tr> <th colspan="4">LV</th> </tr> <tr> <th>Year</th> <th>Incidence</th> <th colspan="2">Prevalence</th> </tr> </thead> <tbody> <tr><td>1</td><td>50%</td><td colspan="2">40%</td></tr> <tr><td>2</td><td>60%</td><td colspan="2">50%</td></tr> <tr><td>3</td><td>65%</td><td colspan="2">55%</td></tr> <tr><td>4</td><td>70%</td><td colspan="2">57%</td></tr> <tr><td>5</td><td>72.5%</td><td colspan="2">59%</td></tr> <tr><td>6</td><td>75%</td><td colspan="2">60%</td></tr> <tr> <th colspan="4">HV</th> </tr> <tr> <th>Year</th> <th>Incidence</th> <th colspan="2">Prevalence</th> </tr> <tr><td>1</td><td>60%</td><td colspan="2">50%</td></tr> <tr><td>2</td><td>75%</td><td colspan="2">65%</td></tr> <tr><td>3</td><td>82%</td><td colspan="2">72%</td></tr> <tr><td>4</td><td>90%</td><td colspan="2">80%</td></tr> <tr><td>5</td><td>90%</td><td colspan="2">80%</td></tr> <tr><td>6</td><td>90%</td><td colspan="2">80%</td></tr> </tbody> </table>	LV				Year	Incidence	Prevalence		1	50%	40%		2	60%	50%		3	65%	55%		4	70%	57%		5	72.5%	59%		6	75%	60%		HV				Year	Incidence	Prevalence		1	60%	50%		2	75%	65%		3	82%	72%		4	90%	80%		5	90%	80%		6	90%	80%		Assumption (Table 15, apalutamide PSD July 2022)	Previously accepted by PBAC.
LV																																																																			
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Uptake of SAA+MPRED	Year 1: 10% Year 2: 20% Year 3: 30% Year 4: 40% Year 5: 45% Year 6: 50%	Assumption	Uncertain. The ESC considered that the uptake rates of SAA+MPRED would be lower, given that SAA+MPRED has an inferior safety profile to apalutamide and considering the likely listing of enzalutamide and darolutamide.																																																																
Persistence (treatment duration – proportion on treatment each year)	<table border="1"> <thead> <tr> <th>Year</th> <th>LV</th> <th>HV</th> </tr> </thead> <tbody> <tr><td>1</td><td>92.4%</td><td>88.1%</td></tr> <tr><td>2</td><td>82.3%</td><td>65.4%</td></tr> <tr><td>3</td><td>69.1%</td><td>44.8%</td></tr> <tr><td>4</td><td>53.8%</td><td>31.3%</td></tr> <tr><td>5</td><td>27.1%</td><td>19.6%</td></tr> <tr><td>6</td><td>6.3%</td><td>12.0%</td></tr> </tbody> </table>	Year	LV	HV	1	92.4%	88.1%	2	82.3%	65.4%	3	69.1%	44.8%	4	53.8%	31.3%	5	27.1%	19.6%	6	6.3%	12.0%	Table 15, apalutamide PSD July 2022	Previously accepted by PBAC.																																											
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6	6.3%	12.0%																																																																	
Total number treated each year	Year 1: 264 Year 2: 827 Year 3: 1,590 Year 4: 2,498 Year 5: 3,272 Year 6: 3,920	Number of patients initiating treatment × % on treatment each year.	Accuracy may be limited by the accuracy of the % on treatment each year.																																																																
Scripts dispensed	11.7 scripts/year	12.18 SAA+MPRED scripts per a year x compliance of 95.88% from TITAN.	Assuming SAA+MPRED would have the same compliance as apalutamide from TITAN did not appear to be reasonable as SAA+MPRED has an inferior safety profile and patients are likely to interrupt or discontinue treatment.																																																																

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Data	Value	Source	Comment
		Table 15, apalutamide PSD July 2022	
Costs			
SAA+MPRED	Public DPMQ = \$█	Requested DPMQ	Based on the cost-minimisation compared to apalutamide. This was reduced to \$█ in the pre-PBAC response.
Apalutamide	Public DPMQ = \$3,714.58	PBS	-
Patient co-payment	Average: \$9.68 PBS: \$9.91 RPBS: \$4.92	Based on Services Australia data for abiraterone acetate (2698B, 11206T) and enzalutamide (10174L) in mCRPC over the period January 2022 to December 2022.	Reasonable (general co-payment was \$30)
MBS costs	First year of treatment (new patients): \$15.65 (12 x 66509) \$13.65 (3 x 66506) Subsequent years (persistence patients): \$15.65 (12 x 66509)	66506, 66509 for ALT, AST, bilirubin and serum potassium	The health care cost associated with SAA+MPRED may be underestimated.
MBS rebate	80%	-	-

Source: Table 4.1.1, p159-160 of the submission

AEMP = approved ex-manufacturer price; ADT = androgen deprivation treatment; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub-Committee; HV = high volume; LV = low volume; MBS = Medical Benefits Schedule; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; MPRED = methylprednisolone; NHA = novel hormonal agent; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; PSD = public summary document; SAA = SoluMatrix™ abiraterone acetate; Yr = year.

6.38 Table 11 summarises the estimated net financial implications to the PBS/RPBS for the proposed listing of SAA+MPRED over the first six years (assumed as 2023 to 2028). Although the submission estimated the incident and prevalent patient population by LV and HV disease, the estimated costs were based on the two population groups combined.

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Table 11: Estimated use and financial implications to the PBS/RPBS and MBS for the proposed listing of SAA+MPRED

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients with mHSPC						
Incident patients	1	1	1	1	1	1
Prevalent patients	1	1	1	1	1	1
Total patients	2	1	1	1	1	1
Estimated number of patients eligible for the requested restriction (willing to commence treatment with apalutamide)						
Incident patients	1	1	1	1	1	1
Prevalent patients	1	1	1	1	1	3
Total eligible	1	1	1	1	1	1
Estimated number of patients treated with SAA+MPRED (10-50%)						
Total patients on treatment	3	1	1	1	1	1
Total patients newly initiating treatment	3	1	1	1	1	1
Estimated use and net cost of SAA+MPRED to PBS/RPBS (DPMQ \$ [redacted])						
Number of scripts	1	2	4	5	6	7
Cost PBS/RPBS (\$)	8	9	10	11	11	11
Net cost^a PBS/RPBS (\$)	8	9	10	11	11	11
Estimated reduction in the use and net cost of apalutamide to PBS/RPBS (DPMQ \$3,714.58)						
Number of scripts	-2	-2	-4	-5	-6	-7
Cost PBS/RPBS (\$)	-12	-12	-12	-12	-12	-12
Net cost^a PBS/RPBS (\$)	-12	-12	-12	-12	-12	-12
Net financial implications to PBS/RPBS due to listing SAA+MPRED						
Net cost^a PBS/RPBS (\$)	-12	-12	-12	-12	-12	-12
Net cost to the MBS due to listing SAA+MPRED						
Number of services	1	4	5	6	7	13
Net cost to MBS (\$)	14	14	14	14	14	14
Net financial implications to the government						
Total net cost PBS/RPBS/MBS (\$)	-12	-12	-12	-12	-12	-12
Revised financial impact using the pre-PBAC DPMQ for SAA+MPRED (DPMQ = \$ [redacted])						
Net financial implications to PBS/RPBS due to listing SAA+MPRED						
Net cost^a PBS/RPBS (\$)	-12	-12	-12	-12	-12	-12
Total net cost PBS/RPBS/MBS (\$)	-12	-12	-12	-12	-12	-12

Source: Table 4.2-1 to Table 4.5-3, p164-170 of the submission

DPMQ = dispensed price for maximum quantity; mHSPC = metastatic hormone-sensitive prostate cancer; MBS = Medical Benefits Schedule; MPRED = methylprednisolone; PBS = Pharmaceutical Benefits Scheme, PSD = public summary document, RPBS = Repatriation Pharmaceutical Benefits Scheme, SAA = SoluMatrix™ abiraterone acetate

^a Net cost implies cost to the PBS/RPBS and/or MBS less patient co-payment

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ < 500

⁴ 10,000 to < 20,000

⁵ 20,000 to < 30,000

⁶ 30,000 to < 40,000

⁷ 40,000 to < 50,000

⁸ \$10 million to < \$20 million

⁹ \$30 million to < \$40 million

¹⁰ \$60 million to < \$70 million

¹¹ \$100 million to < \$200 million

¹² net cost save

¹³ 50,000 to < 60,000

¹⁴ \$0 to < \$10 million

- 6.39 The net cost to the PBS/RPBS for the proposed listing of SAA+MPRED in mHSPC was estimated to be a saving over the first six years of listing. Including the MBS monitoring costs (total of \$0 to < \$10 million over 6 years) would reduce the net cost savings to the government to \$0 to < \$10 million. The net cost savings was due to the lower proposed price of SAA+MPRED compared to apalutamide.
- 6.40 When the pre-PBAC revised DPMQ of SAA+MPRED was used in the calculations, the estimated saving to the PBS/RPBS over the first six years of listing was \$0 to < \$10 million, and the net saving to government was \$0 to < \$10 million.
- 6.41 The projected savings to government were unlikely to be realised as although the submission's estimates included MBS costs for additional laboratory tests associated with SAA+MPRED, costs associated with potential hospitalisations for additional severe AEs were not included. Other concerns with the submission's estimates included:
- Eligible and treated patient numbers: the submission included prevalent patients in each of the 6 years of listing. For apalutamide, the financial estimates included prevalent patients in Year 1 only. The PBAC had previously considered the estimation of prevalent patients was uncertain and that incident patients would be more likely to receive treatment (Table 15, apalutamide PSD July 2022 PBAC meeting). Of note, the requested listing excludes patients who remain on ADT after 6 months without starting an NHA;
 - Uptake rate: the submission assumed uptake for SAA+MPRED would increase from 10% in Year 1 to 50% in Year 6. While the clinical evidence indicates that SAA+MPRED vs apalutamide were generally comparable in terms of efficacy, the results for safety indicate SAA+MPRED had significantly higher rates of Grade 3-4 AEs;
 - Compliance rate: the submission assumed compliance to treatment would be consistent with apalutamide (95.88%). However, given SAA+MPRED inferior safety profile, more patients are likely to discontinue treatment and switch to another NHA);
 - Change in use of NHA therapy in the mCRPC setting: the submission did not remove costs of NHA for mCRPC on PBS for patients already treated with SAA+MPRED for mHSPC. Whereas in the apalutamide financial estimates a reduction in cost of subsequent NHA was applied for those treated with apalutamide.

Quality Use of Medicines

- 6.42 Consistent with the SAA+MPRED March 2022 resubmission for mCRPC, the sponsor intends to educate clinicians and pharmacists on the differences between OAA+P and SAA+MPRED to ensure appropriate use and dosing of the medication. The PBAC also noted that there was potential for the incorrect medicinal product pack to be prescribed and dispensed, as abiraterone is packaged with 30 methylprednisolone

tablets for the mHSPC indication and with 60 methylprednisolone tablets for the mCRPC indication.

Financial Management – Risk Sharing Arrangements

- 6.43 The submission stated that the Sponsor expects to join the same RSA as apalutamide for use beyond the annual subsidisation caps upon listing. For apalutamide, the PBAC considered that a RSA with a rebate for use beyond annual subsidisation caps, which were based on the estimated PBS/RPBS expenditure would be reasonable to mitigate the risk that patients would remain on apalutamide for longer than estimated from the TITAN trial and the risk that use in patients with HV disease suitable for docetaxel would not be cost-effective (paragraph 7.14, apalutamide PSD July 2022 PBAC meeting).

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of the composite pack of abiraterone acetate and methylprednisolone (SAA+MPRED) tablets for the treatment of metastatic hormone sensitive prostate cancer (mHSPC) on a CMA versus apalutamide. The PBAC considered that SAA+MPRED, in combination with androgen deprivation therapy (ADT), was non-inferior to apalutamide plus ADT in terms of efficacy and although it was inferior in terms of safety that the cost offsets applied in the CMA were reasonable. The PBAC advised that SAA+MPRED should join the existing RSA for novel hormonal agents (NHAs) in this setting.
- 7.2 The PBAC noted the input from the Medical Oncology Group of Australia (MOGA) which strongly supported the listing of SAA+MPRED on the PBS for the treatment of mHSPC.
- 7.3 The PBAC considered that the proposed restriction for SAA+MPRED that mirrored that for apalutamide was appropriate. The PBAC reiterated that treatment with a NHA should be restricted to once per lifetime and hence, patients who receive SAA+MPRED through the PBS for mHSPC should not receive subsidy for another NHA in the castrate resistant setting. The PBAC considered that although the LATITUDE trial required patients to have initiated treatment with SAA+MPRED within 3 months of commencing ADT, the restriction for SAA+MPRED should align with the apalutamide restriction in that SAA+MPRED should be initiated within 6 months of commencing ADT. The PBAC noted that this should allow patients sufficient time to access the required specialists. The PBAC also considered that the restriction should not prevent the use of SAA+MPRED as dual therapy (with ADT) or as triple therapy (with ADT and docetaxel) to increase clinical choice. The PBAC advised that a grandfather restriction was not required for the reason that the restriction does not inadvertently prevent such patients from transitioning to PBS-subsidised supply where they meet the same circumstances that the general population must meet.

- 7.4 The PBAC considered that the nominated comparator, apalutamide, was appropriate as, at the time of consideration, it was the only NHA listed on the PBS for mHSPC. The PBAC noted that enzalutamide and darolutamide had previously been recommended for listing and could be considered near market comparators.
- 7.5 The PBAC noted that there was no available evidence for SAA+MPRED + ADT in patients with mHSPC and that the clinical evidence presented was derived from two trials (LATITUDE AND STAMPEDE) comparing the originator brand of abiraterone acetate with prednisone/prednisolone (OAA+P) + ADT with ADT alone. The PBAC recalled that it had previously considered that SAA+MPRED was bioequivalent to OAA+P in the metastatic castrate resistant prostate cancer (mCRPC) setting (paragraph 7.2, SAA+MPRED PSD, November 2022) and considered that the formulations would be bioequivalent in the mHSPC setting.
- 7.6 The PBAC noted that the submission was based on indirect treatment comparisons (ITCs) between OAA+P + ADT (LATITUDE and STAMPEDE trials) and apalutamide + ADT (TITAN trial), with ADT ± placebo as the common reference. The PBAC noted that the ITCs resulted in no statistically significant differences between OAA+P + ADT and apalutamide + ADT in terms of either radiographic progression free survival (HR = 0.98; 95% CI: 0.74, 1.29) or overall survival (HR = 0.97; 95% CI: 0.77, 1.22).
- 7.7 The PBAC noted that OAA+P was associated with a number of adverse events such as osteoporosis and cataracts that were attributable to the effect of mineralocorticoid excess due to the effect of abiraterone on adrenal suppression and the required concomitant long-term oral corticosteroid administration. Compared to apalutamide, the PBAC noted that patient receiving OAA+P were significantly more likely to experience Grade 3-4 adverse events and Grade ≥ 3 hypertension and significantly less likely to experience Grade ≥ 3 rash.
- 7.8 Overall, the PBAC considered that, given bioequivalence had previously been established between SAA+MPRED and OAA+P, SAA+MPRED + ADT was non-inferior to apalutamide + ADT in terms of efficacy but inferior in terms of safety.
- 7.9 The PBAC noted that the submission presented a CMA between SAA+MPRED and apalutamide. The PBAC considered that the equi-effective doses were:
SAA 500 mg + MPRED 4 mg daily = apalutamide 240 mg daily
- 7.10 The PBAC noted that the submission included monitoring costs and costs associated with managing Grade ≥ 3 hypertension in the CMA and that additional costs associated with managing hypokalaemia, osteoporosis and cataracts were applied in the pre-PBAC response. The PBAC considered that the costs included in the CMA were appropriate.
- 7.11 The PBAC noted that the time horizon applied to the CMA was two years. Although noting that the expected duration of NHA treatment would exceed 24 months, the PBAC considered that the CMA captured the adverse event costs associated with the use of SAA+MPRED and the related mineralocorticoid excess appropriately.

- 7.12 The PBAC noted that apalutamide was the nominated main comparator; however, considered that enzalutamide and darolutamide, which have also been recommended for mHSPC, were also relevant alternative therapies. The PBAC advised that the price of SAA+MPRED should therefore be no higher than the price of apalutamide, enzalutamide or darolutamide based on the daily cost at recommended doses (SAA 500 mg + MPRED 4 mg daily is equi-effective to apalutamide 240 mg daily, enzalutamide 160 mg daily and darolutamide 1,200 mg daily), and incorporating the additional offsets included in the CMA.
- 7.13 The PBAC noted that the utilisation and financial impact estimates were based on the July 2022 submission for apalutamide. The PBAC considered that, to be consistent, the assumptions applied in the CMA should be applied to the financial estimates in terms of compliance and monitoring costs. Further, the PBAC considered that prevalent patients should only be included in Year 1 of the utilisation estimates and that the cost of NHA therapy in the mCRPC setting should be removed. Overall, the PBAC considered that the listing of SAA+MPRED would likely be cost neutral or result in a modest save to the PBS as, although the uptake was uncertain, it would only replace therapies that are either of equivalent cost or more expensive.
- 7.14 The PBAC advised that SAA+MPRED should join the existing RSA for NHAs in the mHSPC setting.
- 7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because SAA+MPRED is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over apalutamide, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add indication to new medicinal product pack (that has 30 methylprednisolone 4 mg tablets) as follows:

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Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT	PBS item code	Max. qty packs	Max. qty units	No. Of Rpts	Available brands
medicinal product pack					
ABIRATERONE (&) METHYLPREDNISOLONE					
abiraterone acetate 125 mg tablet [120] (& methylprednisolone 4 mg tablet [30], 1 pack	NEW MP	1	1	5	Yonsa MPRED
Safety Net Rule Penalty Applies?: No					
Restriction Summary / Treatment of Concept: Authority Required					
	Indication: Metastatic castration sensitive carcinoma of the prostate				
	Clinical criteria:				
	The treatment must be/have been initiated within 6 months of treatment initiation with androgen deprivation therapy				
	AND				
	Clinical criteria				
	Patient must only receive subsidy for one novel hormonal drug per lifetime for prostate cancer (regardless of whether a drug was subsidised under a metastatic/non-metastatic indication); or				
	Patient must only receive subsidy for a subsequent novel hormonal drug where there has been a severe intolerance to another novel hormonal drug leading to permanent treatment cessation				
	AND				
	Clinical criteria:				
	Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug				
	Treatment criteria:				
	Patient must be undergoing concurrent androgen deprivation therapy				
	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) abiraterone + methylprednisolone (iii) apalutamide, (iv) darolutamide, (v) enzalutamide.				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

8.2 Flow-on changes:

Where the following Administrative Advice appears in a drug listing,

	<p>Administrative Advice: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide, (iii) darolutamide, (iv) enzalutamide.</p>
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replace with new administrative advice (below) and retire the above administrative advice.

	<p>Administrative Advice: Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) abiraterone + methylprednisolone (iii) apalutamide, (iv) darolutamide, (v) enzalutamide.</p>
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	<p>2698B / abiraterone acetate 250 mg tablet, 120 1206T / abiraterone acetate 500 mg tablet, 60</p> <p>13263C / abiraterone acetate 125 mg tablet [120] (&) methylprednisolone 4 mg tablet [60], 1 pack</p> <p>12992T / apalutamide 60 mg tablet, 120 13288J / apalutamide 60 mg tablet, 120</p> <p>7236W / cabazitaxel 4376H / cabazitaxel</p> <p>12684N / darolutamide 300 mg tablet, 112 <i>Further darolutamide PBS item code pending from the May 2023 intra-cycle PBAC meeting</i></p> <p>10174L / enzalutamide 40 mg capsule, 112 13118K / enzalutamide 40 mg capsule, 112 <i>Further enzalutamide PBS item code pending from the March 2023 PBAC meeting</i></p> <p>12932P / olaparib 100 mg tablet, 56 12929L / olaparib 150 mg tablet, 56 12921C / olaparib 100 mg tablet, 56 12913P / olaparib 150 mg tablet, 56</p>
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9 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.

10 Sponsor's Comment

Sun Pharma ANZ welcomes the PBAC's decision and looks forward to having Yonsa MPRED available on the PBS as an alternative treatment option for patients with mHSPC.