

**7.08 OLAPARIB,  
Tablet 150 mg, Tablet 100 mg,  
Lynparza<sup>®</sup>,  
AstraZeneca Pty Ltd**

**1 Purpose of submission**

- 1.1 The streamlined codependent standard re-entry resubmission requested a General Schedule Authority Required Telephone/online (initial treatment) and Streamlined (continuing treatment) listing for treatment with olaparib in patients with metastatic castration resistant prostate cancer (mCRPC) where there is evidence of a BRCA1/2 pathogenic variant. The first integrated codependent submission was considered by PBAC and MSAC in March 2021.
- 1.2 A minor resubmission was also submitted to MSAC requesting a Medicare Benefits Schedule (MBS) listing of next generation sequencing (NGS) for the evaluation of BRCA1/2 pathogenic or likely pathogenic gene variants (abbreviated to pathogenic variants from herein) to determine eligibility for treatment with olaparib in patients with metastatic castration resistant prostate cancer (mCRPC). The MSAC previously deferred its decision regarding testing for BRCA1/2 pathogenic gene variants in tumour tissue from men with metastatic castration-resistant prostate cancer. MSAC foreshadowed that it would rapidly reconsider this testing if the Pharmaceutical Benefits Advisory Committee (PBAC) recommends olaparib for those patients in this population in whom a BRCA1/2 pathogenic gene variant is detected (Public Summary Document (PSD) Application 1618, March 2021).
- 1.3 Compared to the March 2021 submission, the key change in this resubmission was the nomination of standard of care (SOC) comprised of best supportive care (BSC) and cabazitaxel (75:25 split) as comparators instead of the physician's choice of a novel hormonal agent (NHA) nominated in the March 2021 submission.
- 1.4 Listing was requested on the basis of a cost-utility analysis versus the comparators. The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	<u>Test:</u> Patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC). <u>Treatment:</u> Patients with mCRPC who have failed first- or second-line physician choice of NHA treatment and have pathogenic or likely pathogenic BRCA1/2 gene variants in tumour tissue.
Prior tests	Tests to diagnose prostate cancer (initial examination can include physical examination and medical history, digital rectal examination, blood test to check for prostate-specific antigen, a transrectal ultrasound, magnetic resonance imaging). Tests to diagnose mCRPC could include prostate-specific antigen (PSA), bone and CT scans, PSMA PET scan (privately funded). Biopsy of tumour tissue.
Intervention	<u>Test:</u> Testing of tumour tissue to detect pathogenic BRCA1/2 (breast cancer gene) gene variants to determine eligibility for OLA; germline BRCA1/2 testing will be offered to patients depending on tumour tissue test outcome. <u>Treatment:</u> Olaparib 300mg (2×150mg) twice daily (total dose 600mg/day) for patients found to be positive for a selected BRCA1/2 gene variant after failed treatment with physician's choice of NHA.
Comparator	<u>Test:</u> No genetic testing. <u>Treatment:</u> mixed comparator comprised of BSC (primary) and cabazitaxel (secondary).
Outcomes	OS, PFS, health-related QoL, AEs (drug and test), analytical and clinical validity of test.
Clinical claim	For patients diagnosed with mCRPC who have failed first- or second-line NHA treatment and have a pathogenic or likely pathogenic BRCA1/2 gene variant in tumour tissue or the germline, OLA is superior in efficacy to BSC, but inferior in safety. OLA is superior in efficacy to cabazitaxel and non-inferior in safety.

Source: Table 1-1, pp39-40 of the resubmission.

AEs=adverse events; BRCA1/2=breast cancer genes 1 and 2; BSC=best supportive care, CT=computed tomography, mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent; OS=overall survival; PFS=progression-free survival; PSMA PET=prostate specific membrane antigen positron emission tomography; QoL=quality of life, Blue shading represents information previously considered by the PBAC.

- 1.5 The resubmission proposed that NGS tumour testing to identify BRCA1/2 pathogenic gene variants would occur at diagnosis of mCRPC, with olaparib used as treatment option for patients who have failed NHA treatment. If listed, olaparib will be the only non-chemotherapy PBS subsidised treatment available after failing NHA for patients with BRCA1/2 pathogenic variants.

## 2 Background

### Registration status

- 2.1 On 19th March 2021, the TGA approved olaparib for the following indication: "Treatment of adult patients with BRCA-mutated (germline and/or somatic) mCRPC who have progressed following prior therapy that included an NHA. BRCA mutation status should be determined by an experienced laboratory using a validated test method."
- 2.2 Olaparib received approval from the FDA on 19<sup>th</sup> May 2020 for treatment of adult patients with germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. Olaparib was also approved by the EMA on 3<sup>rd</sup> November 2020 for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a novel hormonal agent.

**Previous PBAC consideration**

2.3 Olaparib was previously considered by the PBAC for treatment of mCRPC in March 2021.

**Table 2: Summary of outstanding matters of concern**

Key matters of concern raised at the March 2021 meeting	How the resubmission addressed it
<p>Sequential NHA was not considered an appropriate comparator. BSC and cabazitaxel (and docetaxel where patients had not previously received docetaxel) should be considered as comparators (paragraph 7.4, olaparib PSD, March 2021)</p> <p>Due to expected transitivity issues of indirect treatment comparisons from the BRCA+ subgroup of olaparib arm of PROfound to all comers trials with BSC or cabazitaxel, the comparative results of PROfound may represent reasonable estimates over a mixed comparator (paragraphs 5.3,5.4, olaparib PSD, Mar 2021)</p>	<p>BSC and cabazitaxel nominated as comparators (75:25 split). Data for NHA from the BRCA1/2 subgroup of PROfound was used as proxy for BSC.</p> <p>A supplementary indirect comparison (including a MAIC) of olaparib versus cabazitaxel was also conducted using data from the CARD trial. Despite matching PROfound patients to CARD, given BRCA status was unknown in CARD, matching is unlikely to adjust for unmeasured confounding.</p> <p>The ESC noted that docetaxel is a relevant comparator in an increasing proportion of patients.</p>
<p>Changing clinical algorithm, removal of prior docetaxel requirement for treatment with NHA. Also, the clinical algorithm did not include the flow on to germline and cascade testing (paragraph 4.3, olaparib PSD, March 2021)</p>	<p>Updated the proposed clinical treatment algorithm (which the ESC noted supported docetaxel as a comparator). Presented subgroup analyses based on prior taxane use in the BRCA1/2 subgroup of PROfound, showing consistent benefit for olaparib.</p>
<p>The PBAC requested that MSAC advise on the likely prevalence in the Australian population with mCRPC and BRCA1/2 (paragraph 7.12, olaparib PSD, March 2021)</p>	<p>Source of BRCA1/2 prevalence of 9.7% is provided in Section 1A.1.2 of the resubmission.</p> <p>MSAC advised the range of prevalence estimates should be 7%–10% (p4, MSAC 1618, PSD, March 2021). The PBAC considered that the lower end of this range (7%) should be applied in the economic model and financial estimates as rates of BRCA1/2 prevalence appear lower in practice than reported in the literature,</p>
<p>In PROfound Cohort A, 67.5% of patients switched from NHA to olaparib following BIRC-assessed rPFS. The PBAC noted that the change in the point estimate was considerable between RPSFTM with recensoring (HR=0.28) compared to the unadjusted value (HR=0.63) and the adjusted value from the RPSFTM without recensoring (HR=0.37) (paragraph 7.11, olaparib PSD, March 2021). The PBAC considered there was insufficient justification of the methodology for treatment switching and consideration of other methods for adjustment for treatment switching for OS were not provided. (paragraph 7.11, olaparib PSD, March 2021)</p>	<p>Updated OS analysis in including justifications of the adjustment method used and the results from other adjustment methods are also presented. However, issues with adjustment for treatment remained.</p>
<p>Uncertainty in the cost-utility analysis (paragraphs 7.11, 7.14, olaparib PSD, March 2021). In particular:</p> <ul style="list-style-type: none"> <li>• The model did not reflect the codependent nature of the submission by providing a test and drug model to assess the consequences of less than perfect test performance.</li> <li>• Inappropriate application of NHA as comparator.</li> </ul>	<p>Updated economic evaluation including:</p> <ul style="list-style-type: none"> <li>• Incorporation of test/treat model structure comparing the proposed scenario (testing for BRCA1/2 pathogenic variants with eligible patients receive olaparib, other patients receive SOC) and current scenario (no testing, all patients receive SOC)</li> </ul>

*Public Summary Document – November 2021 PBAC Meeting*

Key matters of concern raised at the March 2021 meeting	How the resubmission addressed it
<ul style="list-style-type: none"> <li>The application of a 10 year time horizon. The PBAC considered a 5 year time horizon would be more appropriate.</li> <li>The model applied an OS HR adjusted for treatment switching using RPSFTM with recensoring (HR=0.28, 95%CI: 0.10, 0.79) without sufficient justification of method used.</li> <li>Time on treatment extrapolations were based on combined Cohort A and Cohort B populations (that included patients with HRR genes other than BRCA1/2) so was not representative of the model population and resulted in patients being available for treatment for longer than they were predicted to be alive.</li> <li>Utility values, though trial based were high compared to other estimates in the literature.</li> </ul> <p>The PBAC requested the resubmission to address the above issues and present an ICER of less than ██████<sup>1</sup> per QALY.</p>	<ul style="list-style-type: none"> <li>SOC comprised of 75% BSC and 25% cabazitaxel</li> <li>Reduction of time horizon to 7.5 years</li> <li>Justification for use of treatment switching</li> <li>Removal of testing costs in comparator arm</li> <li>Use of BRCA1/2 cohort to predict time on treatment</li> <li>Utility values again derived from PROfound trial</li> </ul> <p>New base case ICER was ██████<sup>1</sup>/QALY. Effective DPMQ for olaparib reduced to \$█████ (previously \$█████). This was further reduced to \$█████ in the pre-PBAC response.</p>
<p>Number of patients highly uncertain, based on prevalence of hormone sensitive prostate cancer (HSPC) (para 6.44 olaparib PSD, March 2021)</p> <p>Consideration of cascade germline testing (p4, MSAC 1618, PSD, March 2021)</p> <p>Treatment duration uncertain (para 6.44 olaparib PSD, March 2021)</p>	<p>A new financial analysis was presented that included:</p> <ul style="list-style-type: none"> <li>A new incident approach based on NHA use</li> <li>Inclusion of cascade testing to 3 relatives</li> <li>Increased time on olaparib to match economic evaluation for 2L mCRPC patients (plus an additional 100 days for 1L patients)</li> <li>Cost for germline testing due to somatic test failure was removed, resulting in overall reduction in MBS costs.</li> </ul>

Source: Table 1, p27 and Table 35, p130 of the resubmission

BIRC= blinded independent central review, BRCA=breast cancer gene, BRCAwt=BRCA-negative, BSC=best supportive care, HR=hazard ratio, MAIC=matching adjusted indirect comparison, NHA= novel hormonal agent, OS=overall survival, PMCC=Peter MacCallum Cancer Centre, rPFS=radiographic progression-free survival, RPSFTM=rank preserving structure failure time model

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

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

### **3 Requested listing**

3.1 The requested listing is shown below. The restriction requested was unchanged from the previous submission without applying the Secretariat’s previously suggested amendments (apart from addition of a grandfather listing).

Public Summary Document – November 2021 PBAC Meeting

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
OLAPARIB, tablet, 150mg, 100mg, 56 Initial treatment	2	112	2	\$ [REDACTED] (published April 2022 <sup>^</sup> ) \$ [REDACTED] (effective April 2022)	LYNPARZA® AstraZeneca Pty Ltd
OLAPARIB, tablet, 150mg, 100mg, 56 Continuing treatment	2	112	5	\$ [REDACTED] (published April 2022 <sup>^</sup> ) \$ [REDACTED] (effective April 2022)	LYNPARZA® AstraZeneca Pty Ltd
<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)				
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners				
<b>Severity:</b>	Metastatic				
<b>Condition:</b>	Carcinoma of the prostate				
<b>PBS Indication:</b>	Castration resistant metastatic carcinoma of the prostate				
<b>Treatment phase:</b>	Initial				
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency				
<b>Clinical criteria:</b>	Patient must have homologous recombination repair gene variants (germline and/or somatic) <i>BRCA1</i> or <i>BRCA2</i> AND The treatment must not be used in combination with chemotherapy or novel hormonal agents AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug AND Patient must have progressed or failed treatment following a prior novel hormonal agent treatment OR Patient must be unsuitable for novel hormonal agent treatment on the basis of predicted intolerance AND Patient must have a WHO performance status of 2 or less AND Patient must not have received prior treatment with olaparib				
<b>Treatment phase:</b>	Continuing				
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Streamlined				
<b>Clinical criteria:</b>	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug				
<b>Administrative Advice:</b>	Special Pricing Arrangements apply				

Source: Table 9-10, p54-55, Table 1-11, pp74-75 of the resubmission.

<sup>^</sup> pricing as of April 2022 after the 5-year 5% statutory anniversary price reduction, current published DPMQ is \$6,971.22.

Blue shading represents information previously considered by the PBAC

- 3.2 The resubmission proposed an effective DPMQ of \$ [REDACTED] for olaparib. This was [REDACTED] % lower than the requested effective AEMP in March 2021 (which was set at the effective price for olaparib in ovarian cancer) plus the 5% anniversary statutory price reduction expected for olaparib in April 2022 (given olaparib will not be listed until after April 2022 if the PBAC recommend listing at the November 2021 meeting). The pre-PBAC response included a further reduction in the price to \$ [REDACTED] AEMP (\$ [REDACTED] DPMQ), including the 5% statutory price reduction.

- 3.3 The recommended dose is 300mg (2×150 mg tablets) twice daily, for a total of 600 mg/day, until progression. The proposed number of repeats would allow for 3 months of treatment under the initial listing and 6 months under the continuing listing.
- 3.4 Olaparib is proposed to be used as monotherapy following progression with NHA treatment. It may be used as either first line, second line or third line therapy in mCRPC. This is broadly consistent with the TGA indication (“treatment of adult patients with BRCA-mutated (germline and/or somatic) mCRPC who have progressed following prior therapy that included an NHA). The proposed restriction also included a criterion to allow use in patients considered unsuitable for NHA treatment on the basis of predicted intolerance. The PBAC considered this criterion was not necessary and should not be included in the listing.
- 3.5 The Secretariat proposed clarifying the term ‘novel hormonal agents’ by providing a list of the specific drugs included in this category. In November 2021, darolutamide was PBS listed for non-metastatic CRPC (mOCRPC). The PBAC also considered apalutamide for both mOCRPC and metastatic hormone sensitive prostate cancer (mHSPC) at the November 2021 meeting. The list of novel hormonal drugs may require updating, should additional relevant agents be listed on the PBS for mCRPC or mOCRPC.
- 3.6 The submission proposed an Authority Required (telephone/online) restriction for initial treatment and an Authority Required (STREAMLINED) restriction level for continuing treatment (although telephone/online was also checked in the submission’s proposed continuing listing). The PBAC considered that an Authority Required (telephone/online) restriction level should apply for the both the initial and continuing listings consistent with the 1L listings for olaparib in ovarian cancer.
- 3.7 The resubmission requested transitioning arrangements (i.e. ‘grandfather’ arrangements) for an early access, non-PBS subsidised program. The resubmission stated an early access program was initiated in May 2021 and it is estimated that < 500 patients will be initiated (< 500 patients will initiate treatment in 2021 and the remainder in 2022). The submission noted eligibility criteria for the access program is aligned with the eligibility criteria for PROfound. A grandfather listing was proposed because following initiation of treatment these patients may not meet the WHO performance status criterion in the initial treatment listing and therefore would not qualify for treatment under the proposed restrictions.

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

## **4 Population and disease**

- 4.1 The March 2021 submission described the testing population (as patients with mCRPC) and the drug population (as patients with mCRPC and a BRCA1/2 gene variant). This was unchanged in the resubmission.

- 4.2 The resubmission provided an amended current clinical management algorithm, which depicted three lines of treatment in mCRPC; with NHA (either enzalutamide or abiraterone) or docetaxel as first-line; BSC, NHA, cabazitaxel or docetaxel in second-line; followed by BSC or cabazitaxel in third line. In the proposed algorithm, in addition to current options, olaparib can be used as an alternative first, second or third line treatment.
- 4.3 Olaparib is a poly(adenosine diphosphate)-ribose polymerase (PARP) inhibitor. PARP enzymes are involved in DNA transcription, cell cycle regulation and DNA repair, and the anti-tumour effect of PARP inhibitors is dependent on an underlying defect in a cancer cell's DNA damage response mechanisms. Patients with homologous recombination repair (HRR) gene pathogenic variants, such as BRCA1/2, cannot accurately repair the DNA damage and may experience more aggressive disease than those without these pathogenic variants.
- 4.4 In the submission the proportion of mCRPC patients who are expected to have a BRCA1/2 gene variant and hence likely to be treated with olaparib was based on the PROfound trial (9.7%). MSAC previously advised that between 7%–10% of the mCRPC population would be BRCA1/2 positive (p4, MSAC 1618, PSD, March 2021). The PBAC considered that clinical experience suggested that the prevalence of BRCA1/2 pathogenic variants in Australia may be lower than reported in the literature and noted this was also supported by the views presented in the sponsor hearing. The PBAC noted that of the 4,425 patients screened for inclusion in the PROfound trial, 2,792 had tissue successfully sequenced. Of those successfully tested, 269 had a BRCA1/2 gene variant only and 38 had BRCA1/2 gene variant together with another HRR gene alteration. Therefore in total, 11% (307/2792) of those successfully tested were confirmed BRCA1/2 positive, however only 6.9% (307/4425) of those screened were BRCA1/2 positive (160 of the 307 BRCA1/2 positive patients were enrolled in the PROfound trial). The PBAC considered that to some extent, the lower prevalence seen in clinical practice may reflect test failure associated with prostate cancer tumour testing. The PBAC considered that the lower end of the range suggested as reasonable by MSAC (7%) should be applied in the economic evaluation and financial estimates.

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

## **5 Comparator**

- 5.1 The resubmission nominated a mixed comparator to represent SOC, comprised of BSC and cabazitaxel assuming a 75:25 split in the modelled economic evaluation. The comparator was changed from the physician's choice of alternate NHA in the March 2021 submission following the PBAC's advice, which considered the nominated comparator did not reflect current Australian clinical practice (paragraph 7.1, olaparib PSD, March 2021).
- 5.2 In March 2021 the PBAC considered an alternate NHA was not an appropriate comparator given that the PBS listing criteria explicitly prevent sequential use of NHAs

due to the development of cross-resistance. Rather the PBAC considered that cabazitaxel, which is currently PBS listed for use following docetaxel, and BSC would be the appropriate comparators (paragraph 7.4, olaparib PSD, March 2021).

- 5.3 In March 2021 the PBAC considered that the comparator in the PROfound trial (i.e. an NHA) was a reasonable proxy for BSC, given that the majority of patients in Cohort A of the PROfound trial had progressed following a previous NHA and the lack of evidence supporting the efficacy of sequential NHA use (paragraph 7.9, olaparib PSD, March 2021).
- 5.4 The PBAC also previously considered that docetaxel would be an appropriate comparator where patients had not previously received docetaxel (paragraph 7.4, olaparib PSD, March 2021). DUSC data indicated that following a NHA, patients received either no further treatment (70.8%), docetaxel (13.6%) or cabazitaxel (9.8%). In the DUSC data, 53.8% of patients had not been treated with docetaxel prior to initiating NHA (Table 2, olaparib PSD, March 2021). The Pre-Sub-Committee Response (PSCR) argued that there is unlikely to be a significant change to treatment patterns as a result of restriction changes for NHAs as the changes reflected current practice and clinician preferences. The ESC agreed with the commentary that given recent PBAC recommendations and emerging patterns of use, the proportion of NHA-experienced but docetaxel-naïve patients is likely to be higher in the future. The ESC also noted that the amended clinical management algorithm supported inclusion of docetaxel as a comparator for olaparib.
- 5.5 The resubmission stated that no evidence was identified that directly or indirectly compared the efficacy and safety of olaparib with docetaxel given the considerable changes to the treatment paradigm since the pivotal trial data and, as such, docetaxel was not considered a comparator in the resubmission. The resubmission added that by comparing to BSC and cabazitaxel, the sponsor aimed to provide a balanced overall comparator that served as a proxy for all treatment options. The ESC also noted that outcomes for patients treated with docetaxel would be expected to differ somewhat from cabazitaxel as patients treated with docetaxel would not have received a prior taxane. However, the ESC acknowledged that inclusion of docetaxel as the comparator in 15% of patients appeared to have minimal impact on the ICER.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician commented that there are currently no other biomarker directed therapies in prostate cancer and noted the clinical need for treatments for BRCA1/2 patients. The clinician noted that the BRCA positive population is small (<10% of the CRPC population) and noted that experience with screening for clinical trials suggested that the presence of BRCA1/2 pathogenic

variants may be 5% or less of patients in the mCRPC population. The clinician stated that some patients on PARP inhibitors experience a clear, long lasting response to treatment that is clinically meaningful. The clinician also noted that toxicity is manageable with dose modifications. With regard to the PROfound study the clinician stated that use of subsequent NHAs in the control arm was a likely to represent placebo as many patients would not be suitable for treatment with chemotherapy. The clinician also noted equity issues for self-funding of BRCA testing which is not currently included in the MBS for patients with prostate cancer.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (21), and organisations (6) via the Consumer Comments facility on the PBS website in support of listing olaparib on the PBS for patients with prostate cancer. The comments from individuals described the impact of prostate cancer on patients and noted that treatment may benefit some patients with prostate cancer. Individuals also highlighted the high cost of funding the treatment outside of the PBS.
- 6.3 The PBAC noted the advice received from a number of patient support groups (Ocean Reef (WA) Prostate cancer Support Group, South Eastern Prostate Cancer Support Group, Prostate Heidelberg Cancer Support Group, Nepean/Blue Mountains Prostate Cancer Support Group) and the Prostate Cancer Foundation of Australia in support of the olaparib listing. These patient groups noted that olaparib may benefit patients with BRCA positive prostate cancer in terms of delayed disease progression, increased survival time and improved outlook, experience and quality of life.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the olaparib submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for olaparib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>1</sup>, noting also that the clinical value may be overestimated due to the questionable control arm in the PROfound trial.

### **Clinical trials**

- 6.5 The resubmission was based on:
- a single head-to-head randomised trial (PROfound), comparing olaparib to abiraterone or enzalutamide (i.e. NHA) in patients with mCRPC and BRCA1/2 gene variants who have already failed prior NHA (unchanged from the March 2021 submission) Given the lack of direct or indirect evidence for olaparib against BSC, the data from the NHA arm of PROfound was used as proxy for BSC.

---

<sup>1</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

- an indirect treatment comparison (ITC) , comparing olaparib and cabazitaxel via NHA as common reference using data from PROfound and CARD. CARD was an open label randomised trial comparing cabazitaxel and NHAs in patients with mCRPC who had received prior treatment with docetaxel and an NHA. Given that CARD did not select patients according to BRCA1/2 status, there were important transitivity issues with this comparison.
- 6.6 The PBAC and MSAC ESCs had previously considered that due to expected transitivity issues of ITCs of the BRCA1/2 subgroup in the olaparib arm of PROfound to all comers' trials of BSC or cabazitaxel, the comparative results of PROfound may represent reasonable estimates over a mixed comparator (paragraphs 5.3, 5.4, olaparib PSD, March 2021). Therefore, it might have been more appropriate for the resubmission to use results from the olaparib vs. NHA comparison in PROfound as a proxy to the effectiveness of olaparib over the nominated mixed comparator (75% BSC and 25% cabazitaxel) as per PBAC's advice. The ESC noted the results of a sensitivity analysis using this approach in the economic model were presented in the PSCR and the change had minimal impact on the ICER.
- 6.7 The resubmission also provided updated information on the proposed BRCA testing, including new systematic reviews of prognostic and accuracy studies. Results from four additional prognostic studies, including a subgroup analysis from PROfound, were presented, as well as a new concordance study comparing the proposed NGS BRCA1/2 test (QIAseq targeted DNA panel) with the NGS test used in the PROfound trial (F1CDx). The ESC noted that this data was of relevance for MSAC.
- 6.8 While MSAC had previously accepted the clinical utility of BRCA1/2 testing, uncertainties were raised with respect to prognostic effect and diagnostic performance (partially addressed in this resubmission). MSAC also requested that the modelled economic evaluation and financial estimates fully consider the cost consequences of testing, including cascade testing in patients and their relatives (not fully addressed in this resubmission). MSAC stated that it would quickly reconsider this application if the PBAC recommends funding olaparib on the PBS for this patient population (p2, MSAC 1618, March 2021).
- 6.9 The resubmission also provided additional analyses to adjust for the significant treatment switching in PROfound.
- 6.10 Details of the trials presented in the submission are provided in the tables below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
PROfound	A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations (PROfound). de Bono J, Mateo J, Fizazi K et al. Olaparib for metastatic castration-resistant prostate cancer.	October 2019  NEJM 2020; 382(22): 2091-2102
PROfound final analysis	A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations (PROfound) Final Analysis of Overall Survival and Safety Update Hussain M, Mateo J, Fizazi K et al. Survival with olaparib in metastatic castration-resistant prostate cancer.	July 2020  NEJM 2020; 383(24):2345-57.
<b>Supplementary randomised trial</b>		
TOPARP-B	Mateo J, Porta N, Bianchini D et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Mateo J, Porta N, MeGovern UB et al. TOPARP-B: A phase II randomized trial of the poly(ADP)-ribose polymerase (PARP) inhibitor olaparib for metastatic castration resistant prostate cancers (mCRPC) with DNA damage repair (DDR) alterations.	Lancet Oncol 2020; 21(1): 162-174.  J Clin Oncol 2019; 37: 5005-5005.
<b>Cabazitaxel trial informing the ITC</b>		
CARD (NCT02485691)	de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer Fizazi K, Kramer G, Eymard JC, Sternberg CN, de Bono J, Castellano D, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. Suzuki H, Castellano D, de Bono J, Sternberg CN, Fizazi K, Tombal B, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic castration-resistant prostate cancer: post-hoc analysis of the CARD study excluding chemohormonal therapy for castration-naïve disease.	N Engl J Med. 2019;381(26):2506-18.  Lancet Oncol. 2020;21(11):1513-25.  Japanese journal of Clinical Oncology. 2021;19.

Source: Table 39, pp140-141 of the resubmission.

Blue shading represents information previously considered by the PBAC

Table 4: Key features of the included evidence

Trial	N	Design	Patient population	Key outcomes	Use in modelled evaluation
<b>Olaparib vs. NHA</b>					
PROfound Cohort A+B	386	R, OL, MC	BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L pathogenic gene variants	Safety	Selected safety outcomes
PROfound Cohort A	245	R, OL, MC	BRCA1/2, ATM pathogenic gene variants	rPFS, OS, safety	EQ-5D-5L outcomes
PROfound BRCA1/2	160	R, OL, MC	BRCA1/2 pathogenic gene variants	rPFS, OS	rPFS, OS (extrapolated)
<b>Olaparib vs cabazitaxel (indirect using data from CARD for cabazitaxel)</b>					
CARD	255	R, OL, MC.	mCRPC, failed prior docetaxel and NHAs	rPFS, OS, safety	rPRS, OS (extrapolated)

Source: Table 2.4, p66 of the submission

MC=multicentre; OL=open label; OS=overall survival; R=randomised; rPFS=radiological progression-free survival.

Blue shading represents information previously considered by the PBAC

- 6.11 The PROfound trial was split into two cohorts, Cohort A, including patients with BRCA1/2 or ATM gene variants, and Cohort B, including patients with one or more of the 12 other gene variants (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L). The effectiveness results presented in the resubmission were based largely on Cohort A, with radiological progression-free survival (rPFS) and overall survival (OS) results also provided for a subgroup of patients with BRCA1/2 pathogenic variants. Safety outcomes were based on the combined Cohort A and Cohort B.
- 6.12 The resubmission provided additional baseline characteristics and efficacy data on the BRCA1/2 and BRCAwt subgroups. The resubmission used two separate datasets for the BRCAwt subgroup: all patients in Cohort B (including two patients with BRCA2) and BRCA-negative patients in Cohort A+B.
- 6.13 As BRCA1/2 status was not a stratification factor in PROfound, differences in baseline patient characteristics in the BRCA1/2 subgroup were evident across the NHA and olaparib treatment arms. Compared to the olaparib arm, NHA treated patients had poorer ECOG status (ECOG=0, 37% v 50%), higher median PSA (104.0 v 57.5) and a higher proportion had failed both docetaxel and cabazitaxel in the mCRPC setting (50.0% v 17.6%), all indicating that on average patients in the NHA arm of the BRCA1/2 subgroup may have more treatment resistant/advanced disease. Many of these factors were considered to be effect modifiers in the resubmission's indirect treatment comparison versus cabazitaxel. The PSCR argued that baseline characteristics were well balanced and the subgroup has been used as the basis for regulatory approvals across many jurisdictions. The ESC noted that baseline characteristics were well balanced across treatment arms for the Cohort A population,

suggesting that randomisation was adequate, but that some differences were evident in the BRCA1/2 subgroup.

- 6.14 NHAs will be used even earlier in the disease pathway given the PBAC recently recommended darolutamide for non-metastatic CRPC (mOCRPC). The PBAC also considered apalutamide for both mOCRPC and metastatic hormone sensitive prostate cancer (mHSPC) at the November 2021 PBAC meeting. Since NHA use on the PBS for prostate cancer is limited to one NHA once in a lifetime, patients will likely be treated with olaparib earlier than in PROfound (i.e., at diagnosis of metastatic disease rather than after failing one line of therapy in mCRPC).

### ***Comparative effectiveness***

- 6.15 A summary of key time-to-event outcomes is provided in the table below. The resubmission maintained its preferred method to adjust for treatment switching from NHA to olaparib in PROfound; i.e., rank preserving structural failure time model (RPSFTM) using Cox proportional hazards with recensoring. Further discussion on methodology and results using other approaches to adjust for treatment switching are presented below.

Table 5: Summary of rPFS and OS reported in PROfound

	Number of events/total number of patients (%)		HR (95% CI) <sup>a</sup>	Median duration (95% CI), months	
	Olaparib	NHA	HR	Olaparib	NHA
<b>Radiological progression-free survival (rPFS) – BICR assessed (data cut off: 4 June 2019)</b>					
Cohort A (ITT) <sup>b</sup> (BRCA1/2, ATM)	106/162 (65.4)	68/83 (81.9)	<b>0.34 (0.25, 0.47)</b>	7.39 (6.24, 9.33)	3.55 (1.91, 3.71)
Prior taxane (Cohort A)	72/106 (67.9)	47/52 (90.4)	<b>0.28 (0.19, 0.41)</b>	7.39 (5.82, 9.43)	1.94 (1.71, 3.52)
No Prior taxane (Cohort A)	34/56 (60.7)	21/31 (67.7)	<b>0.55 (0.32, 0.97)</b>	7.39 (5.52, 11.07)	4.07 (3.61, 6.57)
Cohort A+B	180/256 (70.3)	99/131 (75.6)	<b>0.49 (0.38, 0.63)</b>	5.82 (5.52, 7.36)	3.52 (2.20, 3.65)
BRCA1/2 (Cohort A + B)	62/102 (60.8)	51/58 (87.9)	<b>0.22 (0.15, 0.32)</b>	9.79 (7.62, 11.30 <sup>e</sup> )	2.96 (1.81, 3.55)
Prior taxane	48/72 (66.7)	34/35 (97.1)	<b>0.19 (0.12, 0.32)</b>	8.97 (7.36, 10.84)	1.91 (1.71, 3.52)
No prior taxane	14/30 (46.7)	17/23 (73.9)	<b>0.17 (0.08, 0.36)</b>	13.6 (7.39, NC)	3.71 (1.84, 6.57)
BRCAw <sup>t</sup> (Cohort B) <sup>c</sup>	74/94 (78.7)	31/48 (64.6)	0.88 (0.58, 1.36)	4.83 (3.68, 5.52)	3.32 (1.87, 5.39)
BRCAw <sup>t</sup> (Cohort A+B) <sup>c</sup>	NR	NR	NR	NR	NR
<b>Overall survival (OS) (final analysis, data cut off 20 March 2020)</b>					
Cohort A (ITT) (BRCA1/2, ATM)	91/162 (56.2)	57/83 (68.7)	<b>0.69 (0.50, 0.97)</b>	19.09 (17.35, 23.43)	14.69 (11.93, 18.79)
-Adjusted <sup>f</sup> for 67% switching	-	-	<b>0.42 (0.19, 0.91)</b>	-	11.73 (NR, NR)
Prior taxane (Cohort A)	60/106 (56.6)	41/52 (78.8)	<b>0.56 (0.38, 0.84)</b>	17.61 (15.47, 20.70)	12.12 (9.79, 14.75)
No Prior taxane (Cohort A)	31/56 (55.4)	16/31 (51.6)	1.03 (0.57, 1.92)	22.64 (17.58, 25.56)	19.88 (15.57, NE)
Cohort A+B	160/256 (62.5)	88/131 (67.2)	0.79 (0.61, 1.03)	17.31 (15.47, 18.63)	14.00 (11.47, 17.08)
BRCA1/2 (Cohort A+B)	53/102 (52.0) <sup>e</sup>	41/58 (70.7) <sup>e</sup>	<b>0.63 (0.42, 0.95)</b>	20.11 (17.35, 26.81)	14.44 (10.71, 18.89)
-Adjusted <sup>f</sup> for 69% switching	-	-	<b>0.28 (0.10, 0.79)</b>	-	-
Prior taxane	41/72 (56.9)	27/35 (77.1)	0.63 (0.39, 1.04)	17.45 (13.01, 25.30)	11.93 (8.21, 15.15)
-Adjusted <sup>f</sup> for switching	-	-	0.30 (0.08, 1.08) <sup>e</sup>	-	8-9
No prior taxane	12/30 (40.0)	14/23 (60.9)	0.51 (0.23, NR <sup>d</sup> )	NE (NE, NE)	18.79 (11.33, NE)
-Adjusted <sup>f</sup> for switching	-	-	0.13 (0.01, 1.18) <sup>e</sup>	-	8-9
BRCAw <sup>t</sup> (Cohort A+B) <sup>c</sup>	107/154 (69.5)	47/73 (64.4)	0.95 (0.68, 1.34)	15.80 (13.86, 17.31)	13.34 (11.17, 17.74)
BRCAw <sup>t</sup> (Cohort B) <sup>c</sup>	69/94 (73.4)	31/48 (64.6)	0.96 (0.63, 1.49)	14.06 (11.14, 15.87)	11.47 (8.11, 17.02)
-Adjusted <sup>c</sup> for 63% switching	-	-	0.83 (0.11, 5.98)	-	-

**Blue**=statistically significant, **Blue shading**=data previously seen by the PBAC

Source: compiled during the evaluation using data from Table 7, olaparib PBAC PSD, March 2021. Table 66, p208 of the resubmission Table 14.2.4.5, p59 and Table 14.2.5, p61 of PROfound CSR DCO2 Tables&Figures; Table 14.2.1.2.1, p761 and Table 14.2.1.4.1, p793 of PROfound CSR DCO1 Tables&Figures, Table 87, 262 of the resubmission, pp59 and 62 Attachment 2.5 of the resubmission, Table 49, p89 of Attachment 2.25 of the resubmission.

BICR=blinded independent central review; BRCA=breast cancer gene; CI=confidence interval; HR=hazard ratio; HRR=homologous recombination repair; ITT=intention to treat; NE=not estimable; NHA = novel hormonal agent (abiraterone, enzalutamide); NR = not reported; OS = overall survival; rPFS = radiological progression-free survival.

<sup>a</sup> PROfound was not alpha corrected to assess efficacy within individual subgroups these results should be interpreted with caution.

<sup>b</sup> primary end point

<sup>c</sup> two separate datasets were used for the BRCAw<sup>t</sup> subgroup: all patients in Cohort B (including two patients with BRCA2) and BRCA-negative patients in Cohort A+B.

<sup>d</sup> patients with single and co-mutations

<sup>e</sup> the number and proportion of deaths in the BRCA1/2 subgroup was not provided by the submission, but was available in Table 14.2.4.5 of the CSR addendum supplementary tables provided with the submission

<sup>f</sup> rank preserving structural failure time model (RPSFTM) cox proportional hazards model, with recensoring used to adjust for patients who crossed over from NHA to olaparib treatment.

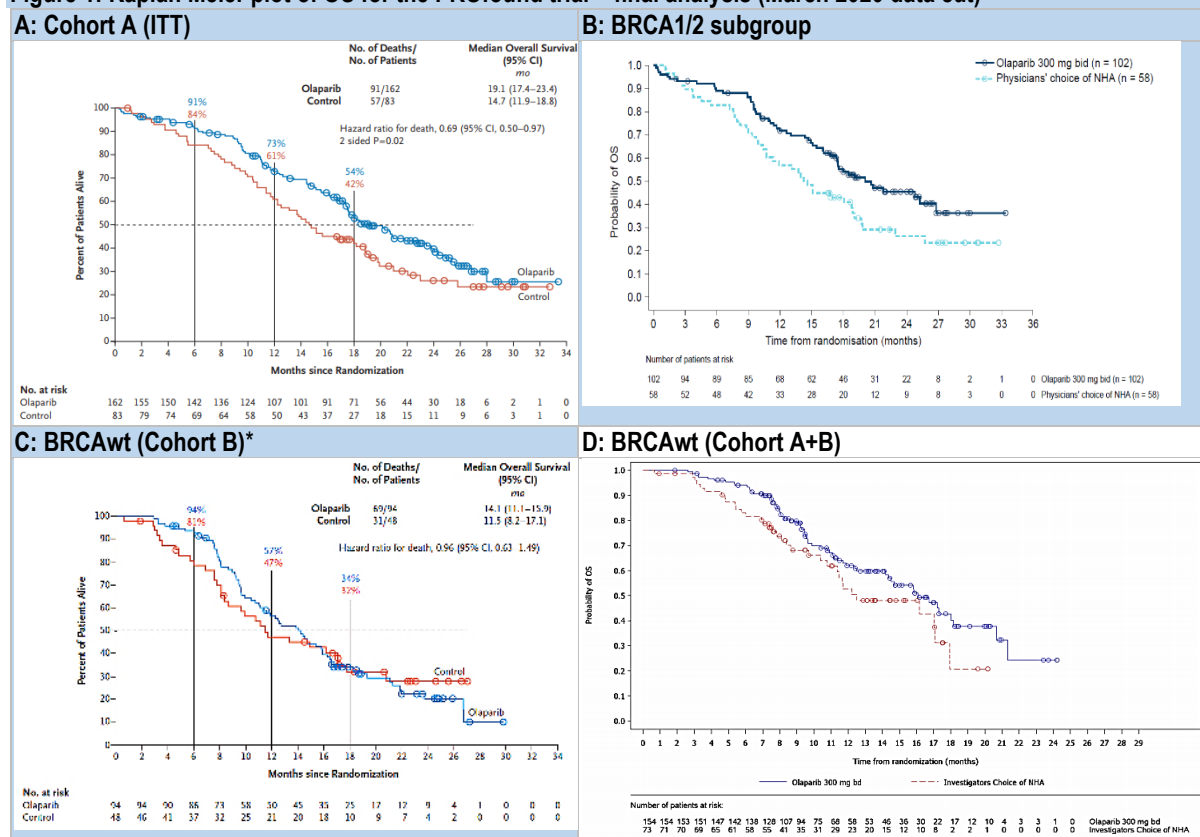
<sup>d</sup> the resubmission reported the upper CI of 0.11 which appeared to be a transcription error, no alternate source for this value was provided.

6.16 For the primary outcome of rPFS assessed by blinded independent central review (BICR) in Cohort A, there was a statistically significant advantage for olaparib compared to NHA (HR=0.34; 95% CI: 0.25, 0.47). The advantage observed for the BRCA1/2 subgroup was greater (HR=0.22; 95% CI: 0.15, 0.32), indicating a 78% reduction in the risk of radiological disease progression or death in those patients. This

survival benefit was not statistically significant in the BRCAwt subgroup (HR=0.88; 95% CI: 0.58, 1.36).

- 6.17 Subgroup analyses according to prior taxane treatment in Cohort A also indicated a benefit for olaparib versus NHA irrespective of prior taxane treatment, but the magnitude was greater in patients who had prior taxane (HR=0.28; 95%CI: 0.19, 0.41) compared to those without prior taxane treatment (HR=0.55, 95%CI: 0.32, 0.97). This potential difference in benefit for olaparib versus NHA by prior taxane use however was not observed in the BRCA1/2 subgroup, where similar HRs were observed (HR=0.19, 95%CI: 0.12, 0.32 and HR=0.17, 95%CI: 0.08, 0.36) in patients with and without prior taxane treatment, respectively.
- 6.18 The final analysis of OS showed a statistically significant advantage for olaparib, with the analysis at the March 2020 data cut indicating a 4.4 month gain in survival for olaparib-treated patients (HR=0.69; 95% CI: 0.50, 0.97) in cohort A. The analysis in the BRCA1/2 subgroup showed an incremental gain in survival of 5.7 months (HR=0.63; 95% CI: 0.42, 0.95). Similar to the rPFS results, OS in the BRCAwt subgroup was not significantly different between olaparib and NHA patients (HR=0.96, 95% CI: 0.63, 1.49).
- 6.19 The Kaplan Meier plots for OS for Cohort A and for the subgroups according to BRCA1/2 status are provided below.

Figure 1: Kaplan Meier plot of OS for the PROfound trial – final analysis (March 2020 data cut)



Blue shading = data previously seen by the PBAC

Source: Figure 1, olaparib PSD, March 2021, Figures 22, 23 and 24, pp209-210 of the resubmission. Figure 1A of Hussain et al 2020\* (used instead of Figure 20 in the resubmission due to better image clarity).

BRCAwt=BRCA1/2-negative, BIRC= blinded independent central review, rPFS=radiographic progression-free survival

\* The resubmission inconsistently used data from two different populations for the BRCAwt subgroup; rPFS results were from Cohort B and OS results were from BRCA-negative patients in both Cohort A and B. OS results for Cohort B were sourced during the evaluation.

6.20 The HRs for rPFS and OS comparing olaparib vs. NHA in the BRCAwt population were not statistically significant. The resubmission inconsistently used data from two different populations for the BRCAwt subgroup; rPFS results were from Cohort B and OS results were from BRCA-negative patients in both Cohort A and B. However, OS results for Cohort B added during the evaluation were similar to those from the BRCA-negative subgroup in Cohort A+B (HR=0.96 and 0.95, respectively).

6.21 Overall, the resubmission claimed the unadjusted results demonstrate that BRCA1/2 status is predictive of olaparib response in mCRPC. The resubmission noted the PBAC previously considered that olaparib demonstrated clinical efficacy in the BRCA1/2 subgroup and a claim of superior comparative effectiveness over BSC was reasonable (paragraph 6.32, olaparib PSD, March 2021).

### Adjustment for treatment switching

6.22 The March 2021 submission adjusted OS data for treatment switching using RPSFTM with recensoring, and the adjusted HR in the BRCA1/2 subgroup (HR=0.28) was applied to the economic model. The PBAC noted there was insufficient justification of the

method selected. The PBAC also noted that the change in the point estimate was considerable when compared to the unadjusted value (HR=0.63) and the adjusted value from the RPSFTM without recensoring (HR=0.37); the model was highly sensitive to this adjustment (paragraph 7.11, olaparib PSD, March 2021). While the results for Cohort A also varied depending on the adjustment method used, there were smaller differences among the various HRs than in the BRCA1/2 population.

- 6.23 The resubmission provided a technical report that compared methods for adjustment, particularly RPSFTM, Inverse Probability of Censoring Weighting (IPCW), and the Two-Stage Estimation (TSE). Results for Cohort A (including a third of patients with the ATM gene) are also illustrated given all validation studies presented in the resubmission and its technical report on treatment switching focused only on Cohort A.

**Table 6: Median OS and HR adjusted for switching using various methods in the resubmission**

Adjustment method	Median OS (months), NHA	HR (95% CI) Olaparib vs NHA
<b>Cohort A</b>		
ITT (Cohort A)	14.70	0.69 (0.50, 0.96)
Excluding NHA patients who switched <sup>^</sup>	10.88	0.39 (0.24, 0.65)
RPSFTM (cox proportional hazards, no recensoring)	11.99	0.50 (0.27, 0.93)
RPSFTM (cox proportional hazards, with recensoring)	11.73	0.42 (0.19, 0.91)
IPCW	14.01	0.57 (0.33, 0.97)
TSE (without recensoring)	14.33	0.66 (0.47, 0.92)
TSE (with recensoring)	15.00	0.72 (0.52, 1.01)
<b>BRCA1/2 subgroup</b>		
ITT (BRCA1/2)	14.44	0.63 (0.42, 0.95)
Excluding NHA patients who switched <sup>^</sup>	6.35	0.22 (0.11, 0.41)
RPSFTM (Cox proportional hazards, no recensoring)	9.57	0.37 (0.16, 0.83)
RPSFTM (Cox proportional hazards, with recensoring)*	9.15	0.28 (0.10, 0.79)
IPCW	13.18	0.40 (0.21, 0.77)
TSE (without recensoring)	12.43	0.47 (0.26, 0.98)
TSE (with recensoring)	12.27	0.57 (0.21, 1.05)

Source: Table 70, p215 of the resubmission; Attachment 2.25 of the resubmission and Table 14.2.4.5, CSR DCO2 Tables and Figures. IPCW=Inverse Probability of Censoring Weighting, HR=hazard ratio, ITT=intention to treat, NHA=novel hormonal agent, OS=overall survival, RPSFTM=Rank Preserving Structural Failure Time Model, TSE=Two-Stage Estimation.

\* Used in the base case economic model

<sup>^</sup> naïve method for adjustment which is likely to be biased as it removes individuals who have switched from the analysis.

- 6.24 The variability in HRs for the different methods of adjustment is likely due to the considerably smaller sample size of the BRCA1/2 subgroup (n=58 in the NHA arm), including 40/58 (69%) who switched and leaving only 18 patients (31%) who did not switch. There is a high risk of bias associated with all adjustment methods when the sample size is small. If the majority of patients switch and the sample size is very small, such methods are unlikely to produce reliable results.

- 6.25 The small sample size is particularly challenging for methods such as IPCW, which bases its adjustments on the survival experience of control patients who do not switch treatments. The resubmission also explained that the TSE may not be appropriate due

to time varying treatment, given some patients had a considerable lag between BICR-confirmed progression and switch day.

- 6.26 Overall the ESC considered that RPSFTM appeared to be the most appropriate method, given these issues for IPCW and TSE methods. However, there were concerns regarding whether the underlying assumptions for RPSFTM were met: i) randomisation and ii) common treatment effect. The resubmission presented analyses to demonstrate the plausibility of these assumptions for Cohort A, but none were conducted for the BRCA1/2 subgroup. Differences in baseline patient characteristics were noted across the treatment arms for the BRCA1/2 subgroup, suggesting the randomisation assumption was not met (see paragraph 6.13). Furthermore, given the short time period before switching and the fact that patients switched after disease progression, the commentary considered it is not possible to confirm the plausibility of the common treatment effect assumption.
- 6.27 The commentary stated that further assessment of the plausibility of the common treatment effect assumption in the BRCA1/2 subgroup is needed, including: i) sensitivity analysis varying the assumed treatment effect in switchers (as was conducted for Cohort A), ii) a comparison of PFS for patients randomised to olaparib versus the secondary PFS for patients who had switched to olaparib, and iii) a regression analysis on the survival times after disease progression, comparing NHA patients who switched to olaparib with the NHA patients who did not switch, to obtain an estimate of the effect of olaparib treatment specific to switching patients. The ESC noted that this was not provided with the PSCR but the PSCR argued that the common treatment effect was demonstrated for the Cohort A population and judged likely to hold for the BRCA population (64% of cohort A). The ESC considered that the statistical analysis report provided with the resubmission was comprehensive and transparent in its investigation of the common treatment effect, but was limited in that it did not directly address the BRCA1/2 subgroup.
- 6.28 In considering the RPSFTM method, in particular, recensoring is associated with a negative bias (i.e., underestimating the control group restricted mean survival and therefore over-estimating olaparib's treatment effect) and may not be appropriate for the BRCA1/2 data in PROfound. The technical report accompanying the resubmission also acknowledged this (p42) and recommended that results without recensoring should be used to inform the model base case as recensoring disregards important information about the treatment effect in the long term. The adjusted HR using RPSFTM with recensoring (HR=0.28) was similar to the naïve analysis excluding treatment switchers (HR=0.22). In the latter, OS in the NHA arm was based solely on the 18/58 patients who did not switch. Given the similarity in the results, it is likely the analysis using RPSFTM with recensoring also relied on the same 18 patients. The OS HR for olaparib vs. NHA using RPSFTM without recensoring was considerably higher (HR=0.37, 0.16, 0.83). The PSCR argued RPSFTM with recensoring has been accepted by NICE in their ongoing assessments of olaparib in mCRPC. The ESC noted that the NICE Committee papers on the olaparib assessment (March 2021) included both

RPSFTM analyses with and without recensoring and noted that the sponsor’s own technical report recommended that results without recensoring should be used to inform the model base case.

- 6.29 Overall, the ESC considered that the selection of RPSFTM was appropriate and was adequately justified in the resubmission. The ESC noted that the confidence intervals were wide for the unadjusted HR estimates and for HR estimates adjusted for switching with or without recensoring, with a considerable overlap in the confidence intervals. The ESC also noted that the most favourable adjusted OS HR (with recensoring, HR=0.28) was only slightly higher than the PFS HR (0.22, 95%CI 0.15, 0.32), which would appear optimistic.

### Indirect treatment comparison: olaparib vs. cabazitaxel

- 6.30 Given the absence of head-to-head trials comparing olaparib to cabazitaxel, the resubmission conducted anchored and unanchored ITCs comparing olaparib (data from PROfound) with cabazitaxel (data from CARD) through the common treatment arm of NHA.

- 6.31 The resubmission compared the subgroup of patients with BRCA1/2 and prior taxane in PROfound to the ITT population in CARD, who were required to have received prior treatment with taxanes.

**Table 7: ITC anchored analysis - adjusted and unadjusted HRs for olaparib vs. cabazitaxel**

Analysis	Olaparib vs. NHA HR (95% CI) - PROfound	Cabazitaxel vs. NHA HR (95% CI) - CARD	Olaparib vs. cabazitaxel HR (95% CI)
<b>rPFS</b>			
MAIC (n*=56)	0.18 (0.04, 0.75)	0.54 (0.40 to 0.73)	0.33 (0.07, 1.43) <sup>^</sup>
Unadjusted Bucher ITC (n=107)	0.19 (0.12, 0.32)		0.36 (0.20, 0.64)
<b>OS unadjusted for treatment switching</b>			
MAIC (n*=56)	0.49 (0.27, 0.89)	0.64 (0.46 to 0.89)	0.77 (0.39, 1.51)
Unadjusted Bucher ITC (n=107)	0.63 (0.39, 1.04)		0.99 (0.55, 1.78)
<b>RPSFTM OS with re-censoring</b>			
MAIC (n*=56)	0.216 (0.108, 0.433)	0.64 (0.46 to 0.89)	0.338 (0.156, 0.729) <sup>^</sup>
Unadjusted Bucher ITC (n=107)	0.301 (0.168, 0.539)		0.470 (0.241, 0.919)
<b>RPSFTM OS without re-censoring</b>			
MAIC (n*=56)	0.281 (0.146, 0.542)	0.64 (0.46 to 0.89)	0.439 (0.210, 0.916)
Unadjusted Bucher ITC (n=107)	0.381 (0.229, 0.634)		0.596 (0.325, 1.092)

Source: Tables 18-21, Attachment 2.24 of the resubmission.

\* Effective sample size

<sup>^</sup> used in the economic model

CI=confidence interval, HR=hazard ratio, ITC=indirect treatment comparison, MAIC=matching-adjusted indirect comparison, NHA=novel hormonal agent, OS=overall survival, rPFS= radiographic progression-free survival, RPSFTM=rank preserving structural failure time model

- 6.32 Based on the ITCs comparing olaparib (data from PROfound) with cabazitaxel (data from CARD) through the common treatment arm of NHA, the HRs are likely to be unreliable because:

- There were a number of important differences in baseline disease characteristics between patients in CARD and PROfound that were not adjusted for in the MAIC,

in particular the BRCA1/2 status in CARD was unknown. This is likely to be a key unmeasured confounder. The ESC noted that taxane benefit is likely to be lower in the BRCA1/2 subgroup and this difference may bias against olaparib.

- The MAIC was based on the BRCA1/2 subgroup with prior taxane treatment in PROfound, given all patients in CARD were required to have failed prior docetaxel. Due to this approach, the effective sample size for the BRCA1/2 with prior taxane subgroup of PROfound was reduced to N=56 for the anchored analysis and N=35 for the unanchored analysis. As previously mentioned, survival results in the post-hoc subgroup analysis of BRCA1/2 according to prior taxane treatment in PROfound were unreliable due to small patient population and lack of adjustment for baseline characteristics, which were unbalanced across treatment groups.
- Furthermore, none of the analyses to select matching variables in the MAIC were based on data from the BRCA1/2 subpopulation, and were instead based on Cohort A of PROfound. As a result, some prognostic factors (e.g. LDH) highlighted by the resubmission were not included. No reasons for these omissions were provided in the resubmission.

### Comparative harms

6.33 The safety data presented from the PROfound trial was based on both Cohort A and Cohort B. Thus, along with the 245 patients in Cohort A, an additional 141 patients in Cohort B (those with 12 other gene variants) were included. Safety results for the proposed PBS population, patients with BRCA1/2 pathogenic gene variants, were not available. However the ESC considered that BRCA1/2 status would not be expected to impact on safety outcomes.

6.34 The following table provides a summary of treatment-related AEs in the combined Cohorts A and B of PROfound. The resubmission did not provide any statistical comparisons of the occurrence of AEs in the olaparib and NHA groups. These results were unchanged from the previous submission.

**Table 8: Summary of key adverse events Cohort A and Cohort B of PROfound**

<b>AEs causally related to trial treatment</b>	<b>Olaparib (N=256) n (%)</b>	<b>NHA (N=130) n (%)</b>
Any AE	210 (82.0%)	63 (48.5%)
AE ≥ Grade 3	83 (32.4%)	12 (9.2%)
AE with outcome=death	1 (0.4%)	1 (0.8%)
SAE (including events with outcome=death)	36 (14.1%)	6 (4.6%)
AE leading to discontinuation	35 (13.7%)	6 (4.6%)
AE leading to dose reduction	52 (20.3%)	6 (4.6%)
AE leading to dose interruption	90 (35.2%)	11 (8.5%)

Source: Table 2-32, p100 of the March 2021 submission. Blue shading=data previously seen by the PBAC  
AE=adverse event; NHA=novel hormonal agent; SAE=serious adverse event

6.35 Significantly greater proportions of patients treated with olaparib experienced any AE, AE ≥ Grade 3, serious AE, AE leading to discontinuation, AE leading to dose reduction

and AE leading to dose interruption in Cohort A + B. However, there was no difference in AEs that resulted in death between the two treatment arms.

- 6.36 The resubmission maintained that the safety and tolerability profile of olaparib in PROfound was consistent with the known safety and tolerability profile of olaparib and considered to be mostly manageable and acceptable in this population. The PBAC (paragraph 6.25, olaparib PSD, March 2021) previously considered this to be reasonable for some AEs, such as the occurrence of anaemia associated with olaparib, which had been cited as a relevant AE in the November 2019 consideration of olaparib for ovarian cancer (paragraph 7.15, November 2019 PSD).
- 6.37 The PBAC previously noted (paragraph 6.26, olaparib PSD, March 2021) that the EMA had considered there were uncertainties associated with the potential risks of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), new primary malignancies and pneumonitis for olaparib, which require monitoring in the post-marketing setting.
- 6.38 The PSCR to the March 2021 submission stated that while the events of MDS/AML and pneumonitis are being monitored, no MDS/AML cases were noted in the PROfound trial and that a low occurrence of pneumonitis was observed in both the olaparib (2.0%) and NHA (1.5%) arms of the trial. The resubmission also added (p202) that AML and MDS are known serious but rare side effects of treatment with PARP inhibitors (reported in <1.5% of patients), these AEs were of special interest in the PROfound trial, but no cases were reported in either treatment arm during the trial or the 30-day safety follow-up period (PROfound CSR, page 26).
- 6.39 The resubmission stated that in Cohort A, skeletal related events (SREs) occurred in 15.4% of patients in the olaparib arm and 22.9% of patients in the NHA arm. A stratified log-rank test of time to first symptomatic SRE for olaparib vs NHA showed olaparib significantly delayed the time to first SRE (HR=0.37; 95% CI 0.20 to 0.70). As the frequency of SREs in the BRCA1/2 population of PROfound was not available, data for Cohort A was used as a proxy for the economic evaluation.
- 6.40 The resubmission's economic model included AEs such as anaemia, neutropenia, pulmonary embolism and vomiting, along with SREs. Overall, the identified risks for olaparib were consistent with its safety profile in ovarian cancer.
- 6.41 The resubmission also presented a comparison of safety outcomes for 'any grade' and 'grade 3-4' AEs comparing olaparib (data from PROfound) with cabazitaxel (data from CARD) through the common treatment arm of NHA, using the Bucher method. The HRs are likely to be unreliable for the same reasons as identified for the OS and PFS HRs (paragraph 6.33). The conclusion of superior safety versus cabazitaxel was based on an unadjusted ITC using the ITT populations of the two trials, and as such may not be reliable. The PBAC considered the conclusion of non-inferior safety was more appropriate, noting that the safety profiles of olaparib and cabazitaxel are different.

## Benefits and harms

6.42 A summary of the comparative benefits and harms for olaparib versus NHA (proxy for BSC) is presented in the table below. Due to the uncertain results and conclusion for the ITC of olaparib versus cabazitaxel, a benefits and harms summary was not constructed versus cabazitaxel.

Table 9: Summary of comparative benefits and harms for olaparib and NHA

<b>Benefits - PROfound</b>						
<b>rPFS – BRCA1/2 subgroup</b>		<b>Olaparib N=102</b>	<b>NHA (proxy BSC) N=58</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>	
Event n/N (%)		62/102 (60.8)	51/58 (87.9)	-	<b>0.22 (0.15, 0.32)</b>	
% progression-free (95% CI)		NR	NR	-		
Median months to rPFS (95% CI)		9.79 (7.62, 11.20)	2.96 (1.81, 3.55)	6.83		
% progression-free at 6 mths (95% CI)		NR	NR	-		
% progression-free at 12 mths (95%CI)		NR	NR	-		
<b>Overall survival – BRCA1/2 subgroup</b>						
Died n (%)		53 (52.0%)	41 (70.7%)	-	<b>0.63 (0.42, 0.95)</b>	
% alive (95% CI)		48.0% (NR)	29.3% (NR)	-		
Median months to death (95% CI)		20.11 (17.35, 26.81)	14.44 (10.71, 18.89)	5.7		
% alive at 6 months (95% CI)		NR	NR	-		
% alive at 12 months (95% CI)		NR	NR	-		
<b>Harms – PROfound</b>						
<b>Cohort A + B of PROfound</b>	<b>Olaparib N=256</b>	<b>NHA N=130</b>	<b>RR (95% CI)</b>	<b>Events/100 patients</b>		<b>RD (95% CI)</b>
				<b>Olaparib</b>	<b>NHA</b>	
Anaemia	52 (22.7%)	7 (5.4%)	3.77 (1.76, 8.07)	23	5	0.15 (0.09, 0.21)
Neutropenia	10 (3.9%)	0 (0.0%)	10.70 (0.63, 181.25)	4	0	0.04 (0.01, 0.07)
Pneumonia	8 (3.1%)	3 (2.3%)	1.35 (0.37, 5.02)	3	2	0.01 (-0.03, 0.04)

Source: Compiled during the evaluation

BRCA=breast cancer gene; CI=confidence interval; HR=hazard ratio; NHA=novel hormonal agent; NR=not reported; RD=risk difference; rPFS=radiological progression-free survival; RR=relative risk

6.43 On the basis of the evidence presented by the submission for the BRCA1/2 subgroup, no statements regarding the number of patients progression-free or number of patients alive when treated with olaparib compared to NHA can be made, given the required data was not provided by the submission. In regard to harms, for every 100 patients treated with olaparib, approximately 18 additional patients would experience anaemia, 4 additional patients would experience neutropenia and 1 additional patient would experience pneumonia.

## Clinical claim

6.44 The resubmission claimed olaparib was superior in efficacy and inferior in safety to BSC, although it was added the toxicity burden was manageable in mCRPC patients with BRCA1/2 pathogenic variants who had previously progressed on NHAs.

6.45 Based on the PROfound trial, and assuming that data from the NHA arm of the trial reasonably represent BSC, the claim of superior effectiveness and inferior safety against BSC was reasonable. However, the magnitude of the estimated survival benefit

is uncertain because the trial was not powered to assess efficacy within individual subgroups. Furthermore, BRCA1/2 status was not a stratification factor in PROfound and baseline imbalances between the two treatment arms (e.g., on ECOG status, PSA levels and prior taxane use) were detected, which may bias results.

- 6.46 In the BRCA1/2 subgroup, 69% of patients in the NHA arm switched to subsequent olaparib treatment post disease progression. This means the unadjusted OS result (HR =0.63, 95%CI: 0.42, 0.95) would bias against olaparib, and analyses to adjust treatment switching were used to correct for this bias. The resubmission's preferred method, RPSFTM with recensoring, estimated a significantly lower HR of 0.28 (95%CI: 0.10, 0.79).
- 6.47 The resubmission claimed that olaparib was superior to cabazitaxel with respect to both effectiveness and safety.
- 6.48 Based on the ITCs comparing olaparib (data from PROfound) with cabazitaxel (data from CARD) through the common treatment arm of NHA, the resubmission's claim of superior efficacy and safety against cabazitaxel may not be reasonable, mainly due to important differences in baseline characteristics between the two trial populations which could not be adjusted for and the unreliable survival results in the small post-hoc subgroup of BRCA1/2 patients with prior taxane treatment in PROfound. Therefore, it may be more appropriate to use the comparative results of olaparib vs. NHAs in PROfound to represent estimates of effectiveness of olaparib over a mixed comparator, as per the PBAC's prior advice (paragraphs 5.3,5.4, olaparib PSD, Mar 2021). The PSCR accepted the claim of non-inferior safety may be more appropriate given the safety ITC was unadjusted and based on the ITT populations in the two trials.
- 6.49 The PBAC considered that the claim of superior comparative effectiveness versus the mixed comparator (75% BSC and 25% cabazitaxel) was reasonable.
- 6.50 The PBAC considered that the claim of inferior comparative safety compared with BSC was reasonable. The PBAC considered that the claim of non-inferior safety compared with taxane chemotherapy was reasonable, noting that their safety profiles are different.

### ***Economic analysis***

- 6.51 In March 2021, the PBAC advised (paragraphs 7.11 and 7.14, olaparib PSD, March 2021) that a revised model was required, considering:
- A test-treat structure to assess the consequences of less than perfect test performance;
  - BSC, cabazitaxel as comparators. If NHA use was to be considered a proxy for BSC, the costs associated with NHA use should be removed;
  - 5 year time horizon;
  - The material uncertainty about the treatment effect for OS used in the model. The model had applied OS HR adjusted for treatment switching (RPSFTM with

recensoring, HR=0.28) which was considerably lower than the unadjusted OS (HR=0.63) and the adjusted value from the RPSFTM model without recensoring (HR=0.37);

- Use time on treatment extrapolation more representative of the model population;
  - Alternate utility values, utility values in the model although trial based were high compared to other estimates in the literature; and
  - Present an ICER of less than \$55,000 to < \$75,000 per QALY.
- 6.52 The MSAC also requested that cost of additional germline and cascade testing should be included in the economic evaluation (P4, MSAC 1618 PSD, March 2021).
- 6.53 The resubmission presented a new stepped economic evaluation including the requested changes, except for: i) a more reliable treatment effect for OS, ii) a 5 year time horizon, iii) alternate utility values and iv) cost of cascade testing.
- 6.54 The new model was based on the PROfound trial, comparing two test-treat scenarios for mCRPC patients who have failed previous treatment with NHA:
- Proposed scenario: patients are tested for BRCA1/2 pathogenic variants and those with BRCA1/2 pathogenic gene variants receive olaparib, those without receive standard of care (SOC), vs
  - Current scenario: where all patients receive SOC (75% BSC, 25% cabazitaxel)
- 6.55 Key components of the new model and differences from the March 2021 model are summarised in the following table.

Public Summary Document – November 2021 PBAC Meeting

Table 10: Summary of model structure and rationale

Component	March 2021	Current model	Justification/comments
Comparator	Subsequent alternate NHA	SOC (BSC 75%, cabazitaxel 25%)	This was reasonable, although docetaxel may also be a relevant comparator given a likely high proportion of patients without prior docetaxel treatment.
Time horizon	10 years in the base case	7.5 years in the model base case versus 3 years in trial	The PBAC previously considered a 5-year time horizon would be more appropriate (para 7.11, olaparib PSD, March 2021). Sponsor stated 5-years would not capture OLA survival benefit based on the Weibull extrapolation accepted by NICE.
Outcomes	Progression-free years gained, life-years gained, quality-adjusted life years gained, AEs	No change	This was appropriate.
Methods used to generate results	Partitioned survival model.	Decision tree Partitioned survival model.	This approach was reasonable, but did not include the implications of cascade testing nor time to receive test result.
Health states	Progression free (PF) Progressed disease (PD) Death	No change	This was appropriate.
Utilities	Health state utilities based on Cohort A PROfound data. Time to death disutilities estimated from PROfound data modelled separately AE and SRE disutilities based on literature	No change	The PBAC had previously raised concern about utilities values from PROfound given they were much higher than those reported in the literature.
Cycle length	1 month, half cycle correction applied	No change	This was appropriate
Transition probabilities	No specific transition probabilities were modelled; health state allocation was determined by PFS and OS curves, which were based on PROfound data with extrapolation (NHA as proxy for BSC).	As for the March 2021 submission, however NHA from PROfound was used as proxy for BSC) For cabazitaxel, efficacy estimates were from MAIC with CARD trial using NHA as common comparator.	Partition survival modelling approach was appropriate, but PBAC recommended the use of the NHA arm in PROfound as a proxy for standard care arm to avoid additional uncertainty from indirect treatment comparisons (para 5.4, olaparib PSD, March 2021).
Test parameters	The model did not have a test - treat structure so had assumed perfect test performance.	Test accuracy: PROfound concordance study where sensitivity and specificity were both 100%	Concordance study does not account for failed biopsies and missed somatic pathogenic variants. Sensitivity expected to be below 100%.
False positives/negatives	Assumed no false positive/negatives in base case.	Test assumed to have no false positives/negatives in	Failed biopsies and missed somatic pathogenic variants likely to result in

*Public Summary Document – November 2021 PBAC Meeting*

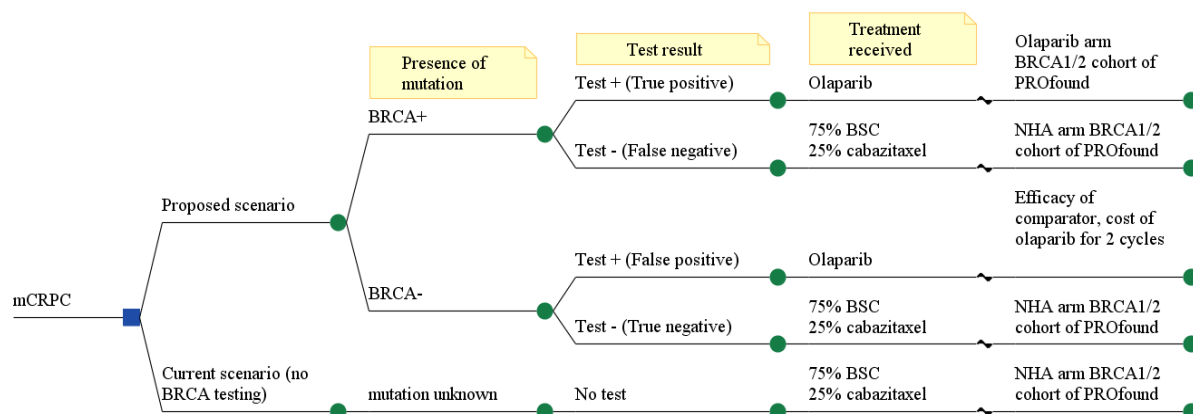
<b>Component</b>	<b>March 2021</b>	<b>Current model</b>	<b>Justification/comments</b>
		base case. In sensitivity analyses, false negatives modelled as SOC, false positives same efficacy as SOC with 2 cycles of olaparib	false negatives. BRCA1/2 subgroup of PROfound were used to model patients with and without BRCA1/2 pathogenic variants. No justification was given for the limit of olaparib to 2 cycles for false positives.

Source: compiled during the evaluation, Table 90, p283 of the resubmission

AE=adverse events, NA=not applicable; OS=overall survival; PFS=progression-free survival, rPFS=radiographic progression free survival.

- 6.56 The modelled economic evaluation was a cost-utility analysis using a decision tree (for the testing component) followed by a partitioned survival model with three health states: progression free survival (PFS), progressed disease (PD), and death. While the model had adopted a test-treat structure, in the base case, both sensitivity and specificity of the BRCA1/2 test were set to 100%, thus the model base case assumed perfect test performance, which may not be appropriate (see also paragraph 6.87).
- 6.57 No utility decrements were associated with testing in the model. Patients in the proposed scenario were assumed to receive one test for BRCA1/2 pathogenic variants with no time delay. This may not be realistic since somatic testing alone could take 4-6 weeks. In PROfound, somatic testing also failed in 31.0% of cases using archival tissue, and therefore patients may require a new biopsy followed by somatic testing or a germline test preceded by genetic counselling, all of which will result in delays to treatment. The PBAC considered that the submission’s estimate of the proportion of patients who are BRCA1/2 positive was high and that the lower end of the range considered reasonable by MSAC (7%) should be applied in the economic evaluation and financial estimates (see also paragraph 4.4). This change increased the ICER to \$55,000 to < \$75,000/QALY).
- 6.58 Cascade testing to identify family members of BRCA1/2 pathogenic variant positive patients was also not included in the model, which was not appropriate given MSAC had requested such costs be considered in the modelled economic evaluation (p4, 1618 PSD, March 2021). The evaluation estimated the ICER would increase to \$55,000 to < \$75,000/QALY where cascade testing of 3 relatives was included.

Figure 2: Structure of the decision tree model



- 6.59 The treatment component model structure was similar to the original submission. For both treatment arms (olaparib arm for patients with BRCA1/2 pathogenic variant in the proposed scenario; SOC arm for patients without BRCA1/2 pathogenic variants in the proposed scenario and all patients in current scenario), patients enter the model in the PF state, at the end of each cycle they either remain in the PF state, progress to PD or die. Patients in the PD health state either remain in that health state or die.
- 6.60 The resubmission used a time horizon of 7.5 years, which the resubmission considered a compromise between the PBAC request of 5 years (para 7.11, olaparib PSD, March 2021) and the treatment effects of olaparib. Reducing the time horizon to the requested 5 years resulted in a small increase in the ICER, as only 0.73% of patients in the proposed scenario and 0.0% of patients in the current scenario are alive at 5 years.
- 6.61 The population included in the modelled economic evaluation was updated from the March 2021 submission and consisted of patients with mCRPC who had previously failed NHA, the test and treat structure meant the model should include results for both BRCA1/2 positive and negative patients. Only data from the subgroup of patients with BRCA1/2 pathogenic variants in PROfound were used to inform the model. This underestimated survival estimates for patients without BRCA1/2 pathogenic variants, but is unlikely to affect the incremental results. This population were also at least second line mCRPC, whereas in practice with NHA use occurring earlier in the treatment pathway, patients may become eligible for olaparib as first line treatment in mCRPC.
- 6.62 The resubmission relied on the same data and approach to extrapolating PFS and OS as the March 2021 submission. Only KM data from olaparib treated BRCA1/2 subgroup of PROfound were used. Data from the NHA arm of PROfound were not used and the PFS and OS curves for SOC were instead estimated by applying HRs to olaparib data.
- 6.63 Data for the BRCA1/2 subgroup of the NHA arm of PROfound was used as a proxy for BSC whereas efficacy of olaparib versus cabazitaxel was based on an MAIC using data from the CARD trial. The results of the MAIC are highly uncertain due to significant

transitivity issues between PROfound (conducted in patients with HRR genes) and CARD (which was an all comers trial).

- 6.64 Graphs depicting extrapolated and observed data were presented in the resubmission, however they were not exhaustive, nor in a format that permitted easy assessment of the goodness of fit of the extrapolated functions versus observed. For this reason, numeric KM data were sought from the sponsor during the evaluation and the data provided were used to compare extrapolations and validate the model. Significant reprogramming of the model was also undertaken to generate the goodness of fit graphs since the model's original structure only permitted one selected function to be displayed at any one time. Lastly, as some requested KM data were unable to be provided by the sponsor (e.g., PFS, OS from the CARD trial and PFS for BRCA1/2wt patients from PROfound), aspects of the modelled extrapolation were unable to be independently validated.
- 6.65 It may have been more appropriate to consider the NHA arm of PROfound as proxy for a mixed comparator (BSC, cabazitaxel and docetaxel where patients had not previously received docetaxel). The PBAC had considered this a pragmatic option given transitivity issues with comparing data from the BRCA1/2 subgroup of PROfound and that derived with an all comers trial, where the BRCA status of participants are unknown (para 5.4, olaparib PSD, March 2021).
- 6.66 The model used fitted data from cycle 1, which is a deviation from the preferred approach of applying KM data until it becomes unreliable due to small numbers of patients remaining events free. The resubmission argued its approach was appropriate given the maturity of the data (i.e., 60.4% maturity with 148 events out of 245 patients for OS). Sensitivity analysis conducted during the evaluation using KM followed by extrapolated data showed while the ICER did not significantly increase, it did increase above \$55,000 to < \$75,000 per QALY gained.
- 6.67 The SOC arm assumed a mix of 75% BSC and 25% cabazitaxel, and its PFS and OS were estimated with weighted average HRs of olaparib versus NHA from PROfound (as proxy for BSC) and olaparib versus cabazitaxel from the MAIC. A summary of the included hazard ratios and methodology is given in the table below. To calculate the SOC extrapolations the inverse hazard ratios (1/HR) were applied to the olaparib extrapolations for PFS and OS.

**Table 11: Summary of hazard ratios used in the economic analysis**

	OLA vs BSC	OLA vs cabazitaxel	OLA vs SOC	SOC vs OLA (used in model)
Data source	PROfound BRCA1/2 subgroup NHA arm proxy for BSC	PROfound BRCA1/2 subgroup and CARD (BRCA1/2 status unknown)	PROfound BRCA1/2 subgroup and CARD (BRCA1/2 status unknown)	PROfound BRCA1/2 subgroup and CARD (BRCA1/2 status unknown)
Method	PFS: no adjustment to NHA arm OS: Adjust for treatment switching RPSFTM, cox proportional hazards with recensoring	PFS: MAIC with unadjusted NHA as common comparator OS: MAIC, NHA adjusted for treatment switching with recensoring as common comparator	PFS & OS: Weighted average 75% OLA vs BSC HR 25% OLA vs cabazitaxel HR	$\frac{1}{\text{OLA vs SOC HR}}$
PFS HR	0.22	0.33	0.24	4.17
OS HR	0.28	0.34	0.29	3.42

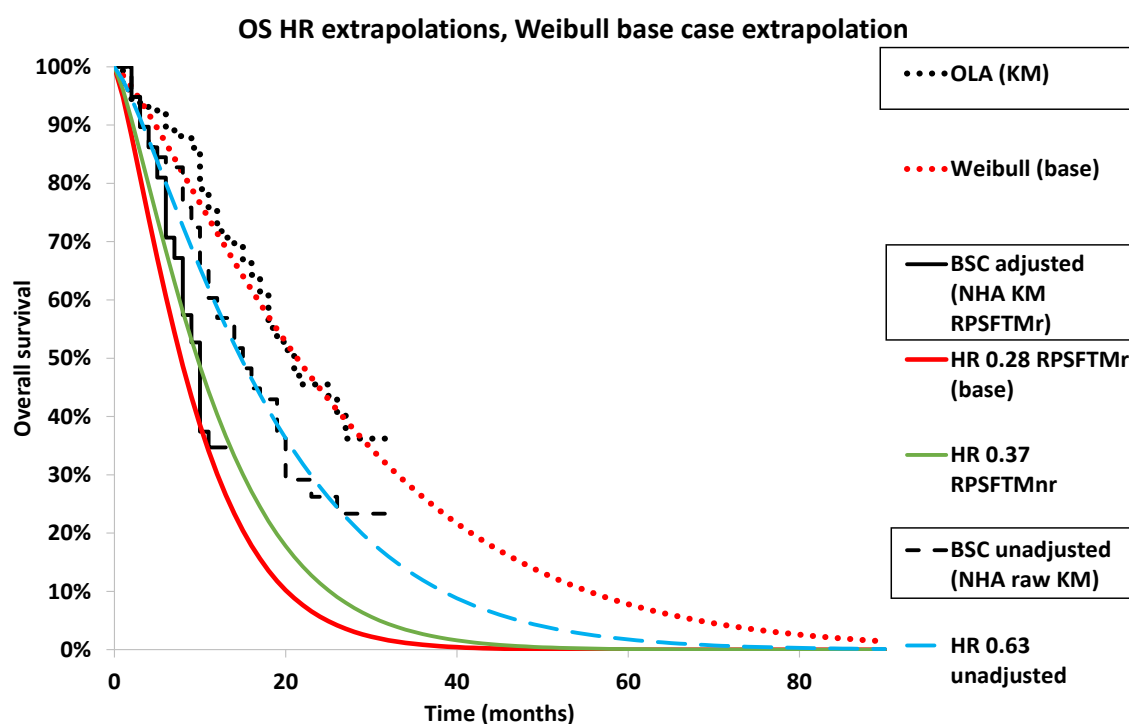
Source: Table 99-101, p321-322, Table 105-108, p328-330

BRCA1/2= BRCA1/2 pathogenic variant, BSC=best supportive care, HR=hazard ratio, NHA=novel hormonal agent, OLA=olaparib, OS=overall survival, PFS=progression free survival, RPSFTM= rank preserving structural failure time model, SOC=standard of care

- 6.68 Treatment duration for olaparib was based on KM data from the BRCA1/2 subgroup of PROfound, extrapolated from cycle 1. This resulted in an average treatment duration of 332 days (10.9 months) for patients treated with olaparib. Time on treatment for cabazitaxel was estimated using time in PFS for olaparib and applying the inverted MAIC HR for PFS for olaparib versus cabazitaxel based on the CARD trial (i.e.,  $1/0.33= 3.03$ ).
- 6.69 A Gompertz function was chosen for PFS extrapolation, based on lowest AIC/BIC and visual fit for olaparib. The model was insensitive to change in PFS extrapolations.
- 6.70 A Weibull function was chosen for OS extrapolation, based on clinical plausibility, visual fit of the olaparib KM data and recommendation from a previous NICE STA for olaparib. This differed from the previous submission where Gompertz was the chosen extrapolation (lowest AIC/BIC values), but appeared reasonable.
- 6.71 All OS extrapolations consistently underestimated the treatment switching adjusted KM OS data for NHA, which was used to proxy BSC. If NHA data is only used to proxy BSC, slight underestimation versus KM data may be reasonable, given NHA may be more efficacious than BSC. However, if NHA data is to represent survival of patients receiving SOC (i.e., both BSC and cabazitaxel/docetaxel) as was recommended by the PBAC for the previous submission (para 5.4, olaparib PSD March 2021), then a consistent underestimation of observed survival in the comparator arm would not be reasonable and favoured olaparib.
- 6.72 There was considerable uncertainty around adjustment for treatment switching, in particular, recensoring. As illustrated in the figure below, OS for BSC treated patients increased if the adjustment did not include recensoring (results for RPSFTM method shown). Treatment switching adjustment without recensoring also appeared to

visually fit the NHA KM data better than the base case. The model was very sensitive to the assumed OS HRs for olaparib versus SOC. The ESC noted that any small change in the HR has a large impact on the modelled cost effectiveness of olaparib and as such, considered it would be appropriate to take a conservative approach to the choice of HRs applied in the economic evaluation. Recognising the uncertainty in the comparison of olaparib and cabazitaxel, the pre-PBAC response proposed that a weighted HR of 0.30 be applied to the total SoC arm, calculated using the RPSFTM with recensoring (HR=0.28) applied to the 75% of patients receiving BSC and RPSFTM without recensoring (HR=0.37) applied to the 25% of patients receiving cabazitaxel. This change increased the ICER slightly to \$55,000 to < \$75,000/QALY (or \$45,000 to < \$55,000/QALY applying the reduced price in the pre-PBAC response). The PBAC noted that applying a HR of 0.37 for the total SoC arm resulted in an ICER of \$55,000 to < \$75,000/QALY. This was reduced to \$55,000 to < \$75,000/QALY when the revised price in the pre-PBAC response was applied.

Figure 3: Impact of treatment switching on overall survival extrapolations



Source: compiled during the evaluation

BSC=best supportive care, CI=confidence interval, Gen.=general, HR=hazard ratio, KM=Kaplan-Meier, NHA=novel hormonal agent, OS=overall survival, RPSFTMr=rank preserving structural failure time model with recensoring, RPSFTMnr=rank preserving structural failure time model without recensoring

6.73 A Gompertz function was chosen for time to treatment discontinuation (TTD) on olaparib extrapolation. No AIC/BIC values were presented but the Gompertz function visually fitted the olaparib KM data well. The model was moderately sensitive to change in TTD extrapolation for olaparib.

- 6.74 Visual assessment of cabazitaxel KM data and extrapolations was not possible for PFS, OS or TTD because no data was provided.
- 6.75 Utility values were modelled similarly to the March 2021 submission, where EQ-5D-5L data from Cohort A of PROfound were converted to utility values using Australian weights. The resubmission argued that a time to death disutility approach was appropriate based on previous PBAC submissions in small cell carcinoma and non-small cell lung cancer, and “multiple metastatic cancer HTA submissions to NICE” (p338 of the resubmission). However, no mCRPC specific evidence relating to this approach was presented. The resubmission did not address any of the concerns raised by the PBAC in March 2021 on utility values. The ESC noted that the utility values appeared to be high for all health states, particularly for post-progression, and that alternative values had not been explored. QoL data were sourced from Cohort A, which may not be representative of the BRCA1/2 population. Further, no information was provided on when QoL was assessed in PROfound nor how many patients had provided data, and the ESC noted that there was therefore potential for attrition bias in the QoL data. The PBAC noted that removal of the time to death utility adjustments increased the ICER by 4.5% to \$55,000 to < \$75,000/QALY (\$55,000 to < \$75,000 based on the revised price in the pre-PBAC response).
- 6.76 Incidence of adverse events and skeletal-related events were sourced from PROfound for both olaparib and SOC (with NHA as proxy for SOC). Disutilities were sourced from published literature and NICE technology appraisals, as with the March 2021 submission.
- 6.77 All patients in the proposed scenario were assumed to receive one BRCA1/2 test at a cost of \$1,200 each. This could be either a tumour tissue test, or a germline test if somatic testing was not feasible. This likely underestimated the true cost of testing as it did not account for re-biopsying that may occur in practice, cost of archival tissue retrieval and review, or further germline testing followed by cascade testing in patients with BRCA1/2 pathogenic variants. Cost of genetic counselling was also not discussed.
- 6.78 Costs for olaparib, cabazitaxel and concomitant therapies all appeared to be reasonably estimated. The cost of chemo-administration was based on hospital cost for administration of chemotherapy and was higher than the MBS item 13950 (\$112.40) for chemo administration, however the overall impact of this difference to the modelled ICER was small. Adverse event, skeletal related event and disease management costs also had very little impact on the incremental costs as they were either small or applied similarly in both the proposed and current scenarios. The ESC noted that the cost of the “current scenario” appeared high (\$██████ undiscounted at 7.5 years, see Table 13). The PBAC noted that this appeared to be driven by terminal care costs, where a one-off cost of \$██████ was applied to the proportion of patients who die in each cycle. This was higher than the value assumed in the March

2021 submission of \$ [REDACTED] per event, however, these costs were similar across the proposed and current scenarios and thus did not significantly alter the ICER.

6.79 Key drivers of the model are described in the table below.

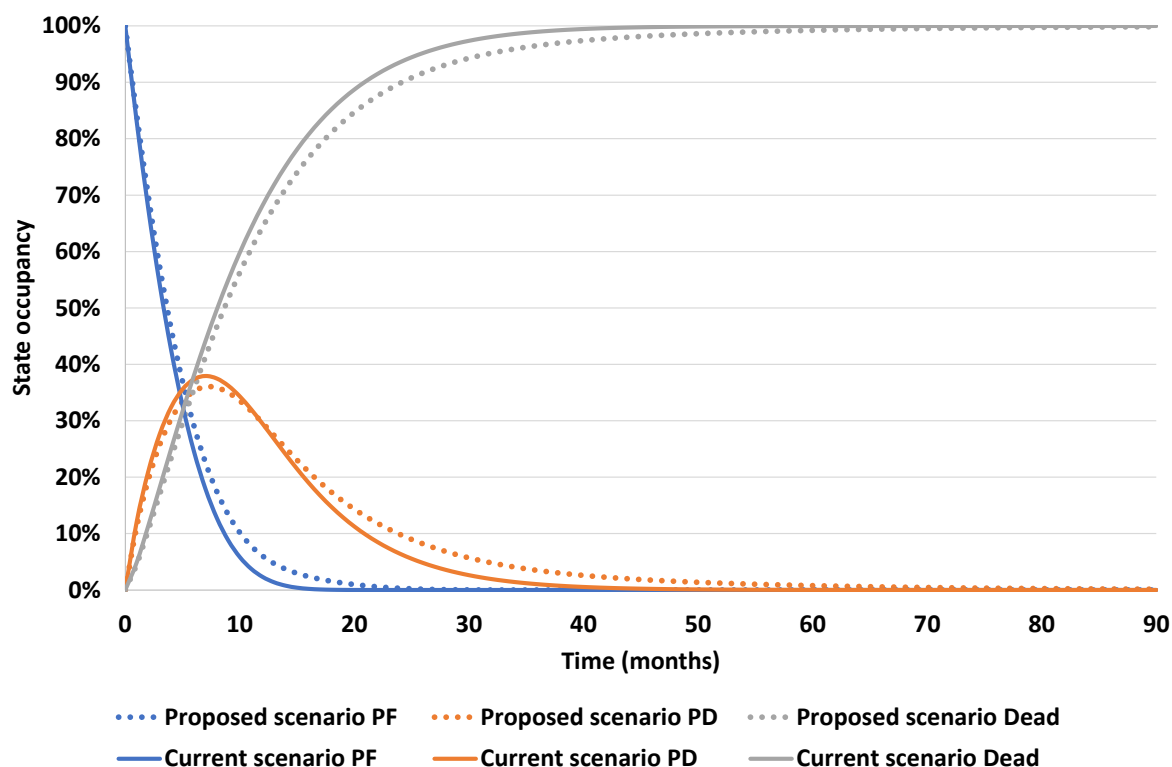
**Table 12: Key drivers of the model**

Description	Method/Value	Impact
Treatment switching adjustment	Methods to adjust for treatment switching were highly uncertain. The criteria for meeting RPSFTM were not completely justified and recensoring was likely to result in bias towards olaparib	High favours proposed scenario
OS extrapolation choice	Extrapolation choice drove the additional LYG for olaparib over SOC	High, favours proposed scenario
Cost of BRCA1/2 testing	Given that 90.3% patients in the proposed scenario and 100% of patients in the current scenario accrue the same treatment costs and benefits per patient, the cost of testing is a large contributor to the incremental costs	High, favours current scenario
Cost of olaparib	Given that 90.3% patients in the proposed scenario and 100% of patients in the current scenario accrue same treatment costs and benefits per patient, cost of olaparib is a large driver of the incremental costs	High, favours current scenario
Prevalence of BRCA1/2	Prevalence drives the proportion of patients in proposed scenario who receive olaparib. In the base case this is 9.7% from PROfound, which is near the upper end of the expected range 7-10%.	Moderate, favours proposed scenario
Utilities	Values for model health states taken from PROfound, with time to death disutility modelled separately.	Moderate, favours proposed scenario

Source: compiled during the evaluation

6.80 The following cohort trace of the model demonstrates the small incremental gains expected with the availability of olaparib at the mCRPC population level given only 9.7% of patients were estimated to have BRCA1/2 genetic variants.

Figure 4: Cohort trace for base case economic model



Source: compiled during the evaluation

PD=progressive disease, PF=progression free

Note this includes both treated (9.7%) and untreated (90.3%) patients in the proposed scenario arm.

6.81 The results of the stepped analysis are presented in the table below.

Table 13: Results of the stepped economic evaluation

Step and component	Proposed scenario	Current scenario	Increment
<b>Step 1: trial-based - 36 month time horizon with costs of AEs and SRE management included</b>			
Costs <sup>a</sup> (\$)	[redacted]	[redacted]	[redacted]
LY	0.92	0.83	0.10
Incremental cost/extra LY gained			[redacted] <sup>1</sup>
<b>Step 2: 7.5 year time horizon</b>			
Costs (\$)	[redacted]	[redacted]	[redacted]
LY	0.97	0.83	0.13
Incremental cost/extra LY gained			[redacted] <sup>2</sup>
<b>Step 3: 7.5 year time horizon with discounted utilities and costs</b>			
Costs (\$)	[redacted]	[redacted]	[redacted]
LY	0.93	0.81	0.12
Incremental discounted cost/extra LY gained			[redacted] <sup>2</sup>
QALY	0.55	0.47	0.09
Incremental discounted cost/extra QALY gained (base case)			[redacted] <sup>3</sup>

<sup>a</sup> undiscounted results generated during the evaluation

Source: Table 145, p372 of the resubmission and compiled during the evaluation

Note: Table 145 of the resubmission does not present undiscounted results.

AE=adverse event; LY=life year; QALY=quality adjusted life year; SRE=skeletal-related event

The redacted values correspond to the following ranges:

<sup>1</sup> \$45,000 to < \$55,000

<sup>2</sup> \$35,000 to < \$45,000

<sup>3</sup> \$55,000 to < \$75,000

- 6.82 The estimated base case ICER for the proposed scenario (testing and treat with olaparib for those with BRCA1/2 pathogenic variant) versus current scenario (no testing and all patients receive SOC) was \$55,000 to < \$75,000 per QALY gained. The ESC noted that the incremental costs and QALYs as shown in Table 13 appeared small because only 9.7% of patients are assumed to be BRCA1/2 positive. For BRCA1/2 patients the average cost was \$ [REDACTED] and patients accumulated an average of 2.02 life years and 1.35 QALYs (discounted, over the 7.5 year time horizon).
- 6.83 The stepped analysis demonstrated that the majority of the survival benefit and costs were accrued in the first 3 years of the model, suggesting changes in the ICER across the 7.5 year time horizon were the result of a small proportion of patients with longer survival. At year 3 ~3.4% of patients in the proposed scenario were expected to be alive (25.6% of patients with BRCA1/2 pathogenic variants receiving olaparib, 1.0% of patients without BRCA1/2 pathogenic variants receiving standard care) versus 1% patients in the current scenario (i.e. 1% patients receiving standard care). At 7.5 years, ~0.1% of proposed scenario arm (1.4% patients with BRCA1/2 pathogenic variants receiving olaparib, 0.0% of patients without BRCA1/2 pathogenic variants receiving standard care) are estimated to still be alive and 0.0% of patients in the current scenario. The ESC considered that a time horizon of 5 years remained appropriate but noted that this had a small impact on the ICER. The PBAC agreed with the ESC and maintained that a time horizon of 5 years was appropriate, particularly in the context of uncertainty regarding OS benefit due to adjustment for treatment switching and the choice of OS extrapolation functions.
- 6.84 Results of key sensitivity analyses demonstrated the model was robust to changes that affected patients who receive SOC (as they accounted for 90.3% of patients in the proposed scenario and 100% patients in the current scenario). Therefore, the model was most sensitive to model inputs which affected the patients receiving olaparib, such as:
- Treatment switching adjustment: without recensoring ICER increased to \$55,000 to < \$75,000 per QALY gained, with no adjustment for treatment switching ICER increased to \$115,000 to < \$135,000 per QALY gained.
  - Choice of OS extrapolation: with different choice of function the ICER ranged from \$35,000 to < \$45,000 (loglogistic) to \$75,000 to < \$95,000 (Gompertz) per QALY gained.
  - Cost of BRCA1/2 pathogenic variant test: This cost drove a large proportion of the incremental costs between the proposed and current scenarios and without it the ICER reduced to \$45,000 to < \$55,000 per QALY gained.
- 6.85 The commentary noted concerns with the assumed testing strategy. Where germline testing follows failed somatic testing sensitivity would be reduced to below 76%, since

tumour test failure was 31% in PROfound and approximately 50% of patients with BRCA1/2 pathogenic variants will have somatic only pathogenic variants. Reducing sensitivity to 76% increased the ICER to \$55,000 to < \$75,000/QALY (\$55,000 to < \$75,000/QALY using the revised price in the pre-PBAC response). The PBAC considered that there may be a substantial proportion of patients for whom the tissue sample is not adequate for BRCA testing. The pre-PBAC response argued the test sensitivity should be calculated based on successful samples. The pre-PBAC response stated that a test failure rate of 10% would be expected in clinical practice and with 50% of patients having germline BRCA mutations, the sensitivity of BRCA testing would be approximately 95%. Reducing sensitivity to 95% resulted in an ICER of \$55,000 to < \$75,000/QALY (\$55,000 to < \$75,000/QALY using the price proposed in the pre-PBAC response).

Table 14: Results of sensitivity analyses

Sensitivity analyses	Incremental cost (\$)	Incremental QALY	ICER	% Δ ICER
<b>Base case</b>		0.09		-
<b>Time horizon (base 7.5 years)</b>				
Time horizon 5 years		0.08		+1.5%
<b>BRCA1/2 prevalence</b>				
7% prevalence (base case 9.7%)		0.06		+9.0%
<b>Test accuracy (base sens 100%, spec 100%)</b>				
Sens 76% spec 100% (31.0% failed somatic test, 59.4% somatic BRCA1/2 and 8.1% germline only, Somatic test sens 100%)		0.06		+7.4%
Sens 95%, spec 100%		0.08		+1.2%
<b>Comparator (25% cabazitaxel, 75% BSC)</b>				
25% docetaxel (efficacy=cabazitaxel) 75% BSC		0.09		+5.0%
25% docetaxel (efficacy=BSC) 75% BSC		0.09		+2.9%
Assume 100% BSC		0.09		+4.5%
Assume 100% cabazitaxel		0.08		-13.4%
53.8% docetaxel, 10% cabazitaxel, 36.2% BSC^		0.08		+4.2%
<b>Choice of HR (base weighted 75% BSC, 25% cabazitaxel, PFS 0.24, OS 0.29)</b>				
Assume BSC and cabazitaxel equal to NHA arm PFS 0.22, OS 0.28)		0.09		-0.8%
Without recensoring (base with recensoring)		0.07		+16.9%
No treatment switching adjustment		0.04		+116.1%
<b>Utilities</b>				
Health state only (no time to death disutilities applied)		0.08		+4.5%
<b>Multivariate analysis (MA)</b>				
MA1: Cabazitaxel=BSC=NHA efficacy, treatment switching adjustment without recensoring		0.08		+15.2%
MA2: Sensitivity 76% (incl. test failure), cascade testing		0.06		+11.3%
MA3: MA1&MA2		0.06		+28.0%
MA4: MA3& chemo admin corrected		0.06		+28.2%
MA5: MA4 & docetaxel replace cabazitaxel		0.06		+32.6%
MA6: MA4 & utilities health state only		0.05		+34.0%

Source: Table 155, p380-381 and compiled during the submission

Δ=change, BRCA1/2=BRCA1/2 pathogenic variant, BSC=best supportive care, FP=false positive for BRCA1/2 pathogenic variant, ICER=incremental cost-effectiveness ratio, MA=multivariate analysis, NHA= novel hormonal agent, OLA=olaparib OS=overall survival,

## Public Summary Document – November 2021 PBAC Meeting

PFS=progression free survival, pt=patient, QALY=quality adjusted life year, rels=relatives, sens=sensitivity, spec=specificity, SRE=skeletal related events, TTD=time to treatment discontinuation

^This analysis is presented as an upper bound of docetaxel use. In Table 2 olaparib PSD, March 2021, 46.2% of patients were expected to have had prior docetaxel use, suggesting up to 53.8% could receive it in second line mCRPC. 10% cabazitaxel is presented as paragraph 5.3, olaparib PDS, March 2021 and BSC % is estimated as 100%-53.8%-10%.

\*resubmission presented KM until cycles 15-18 with ICERs ranging from [REDACTED] to [REDACTED] per QALY gained.

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$45,000 to < \$55,000

<sup>3</sup> \$115,000 to < \$135,000

<sup>4</sup> \$75,000 to < \$95,000

6.86 While the ICER was not sensitive to some parameter and structural inputs individually, some had a larger impact in combination and may represent a more accurate estimation of the ICER. Several plausible multivariate scenarios suggest the base case ICER of the proposed scenario versus the current scenario was probably underestimated. For example, when the model included somatic test failures, cost of cascade testing, and cost of archival tumour tissue retrieval, the ICER increased to \$55,000 to < \$75,000 per QALY gained.

6.87 In addition, when chemotherapy administration cost was corrected; and the NHA arm of PROfound was assumed to represent SOC (25% cabazitaxel, 75% BSC); and there was treatment switching without recensoring, the ICER increased to \$75,000 to < \$95,000 per QALY gained. Additional changes, such as use of utilities unadjusted for separate time to death disutilities, resulted in increasing ICERs up to \$75,000 to < \$95,000 per QALY gained. With uncertainty around the treatment switching adjustment not captured here, there is potential for the true ICER to be higher than these figures.

6.88 The PBAC considered that the prevalence of BRCA1/2 pathogenic variants should be revised to from 9.7% to 7% in the economic model (paragraph 4.4). Reducing the proportion of patients who test positive for BRCA from 9.7% to 7% increased the ICER (based on HR=0.37) from \$55,000 to < \$75,000 to \$55,000 to < \$75,000.

### **Drug cost/patient/course**

6.89 The drug cost/patient/course was reduced from \$ [REDACTED] to \$ [REDACTED] at the price proposed in the pre-PBAC response. The following table outlines the drug cost per patient for both olaparib and cabazitaxel across the model and the financial estimates. Total cost per patient per course were similar between the model and the financials, and differed mainly due to a slightly different calculation for the average time on treatment. The financials also presented an estimated cost for patients receiving olaparib first line, though the longer treatment duration could not be validated. The ESC noted that the model applied a lower mean dose of olaparib per day than the previous submission (549 mg/day and 600 mg/day, respectively). The resubmission model and financial estimates also applied a longer median treatment duration for olaparib than the previous submission (332 days and 243 days, respectively).

Table 15: Drug cost per patient

	Olaparib			Cabazitaxel		
	PROfound	Model	Financials	CARD	Model	Financials
Mean dose	600 mg/day	549 mg/day	600 mg/day	NR <sup>a</sup>	38.20mg/3 weeks <sup>b</sup>	55mg/3 weeks
Mean [median] duration	277.4 days <sup>c</sup>	332 days	332 days (2L) 435 days (1L)	[154 days <sup>d</sup> ]	158 days <sup>e</sup>	160 days
Total mg administered	NR	182,124mg	182,427mg (2L) 238,962mg (1L) (includes 92% dose intensity)	NC	287mg <sup>b</sup>	418mg
Cost/patient/month	-	\$ [REDACTED]	NR	-	\$1,549.19	NR
With admin/cc therapies		\$ [REDACTED]	NR	-	\$2,385.04	NR
Cost/patient/course	-	\$ [REDACTED] <sup>f</sup>	\$ [REDACTED] (2L) \$ [REDACTED] (1L)	-	\$8,033.95	\$8,129.74
With admin/cc therapies		\$ [REDACTED]	NR	-	\$12,368.54	NR

Source: compiled during the evaluation

cc=concomitant therapies, NC= not calculable, NR=not reported

<sup>a</sup> 25mg/m<sup>2</sup> intended dose

<sup>b</sup> based on 20mg/m<sup>2</sup> dose. Model assumes no vial sharing, so actual allocated dose was 55mg every 3 weeks for a total of 413mg, costs based on no vial sharing.

<sup>c</sup> Only available for Cohort A+B (not BRCA1/2 subgroup). Actual treatment duration excluding dose interruptions was 263.3 days. Model used BRCA1/2 subgroup but mean was not reported.

<sup>d</sup> median reported 7.0 actual treatment days

<sup>e</sup> equal to 7.5 actual treatment days

<sup>f</sup> \$ [REDACTED] with the revised price in the pre-PBAC response (\$ [REDACTED] AEMP)

### Estimated PBS usage & financial implications

6.90 The resubmission provided new predicted use and financial implications associated with testing and treating for olaparib. The main changes were:

- Incident rather than prevalent approach to project annual patient numbers;
- Inclusion of cascade testing costs to 3 relatives;
- Reduction of cost of olaparib;
- Increased time on treatment to match the economic analysis;
- Removal of subsequent germline testing for patients in whom tumour testing was not feasible or not successful as MSAC recommended that laboratories should not be able to claim twice for somatic and germline testing for the same patient; and
- Changes in use and financial impact of other medicines due to change in comparator.

6.91 The following table summarises the parameters and data sources applied in the financial analysis. Comparable values from the March 2021 financial model are also presented for reference.

Public Summary Document – November 2021 PBAC Meeting

Table 16: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
<b>Eligible population</b>			
Incident patients (2L: prev NHA use in mCRPC)	Yr 1: █ <sup>1</sup> Yr 2: █ <sup>1</sup> Yr 3: █ <sup>1</sup> Yr 4: █ <sup>1</sup> Yr 5: █ <sup>1</sup> Yr 6: █ <sup>1</sup>	Estimated using NHA initiations 2016-2020 from 10% PBS sample with average annual growth rate (6.86%) applied based on 2016-2019 figures: - % receive BRCA1/2 test (█-█%) - Sponsor's assumption (increased over time) - % BRCA1/2 prevalence (9.7%) - i.e. eligible for olaparib-PROfound data - % patients progress from NHA to further treatment (█%) - Sponsor assumption	Data sources were reasonable, though the progression from NHA was not justified. The average growth rate excluded 2020 from the calculations as COVID-19 was assumed to have impacted initiations, but used the 2020 value to predict future years. It might be more appropriate to estimate what 2020 numbers should have been and carry those through (as numbers are likely to rise above predicted growth rate following pandemic). It was noted that in the economic analysis, uptake of BRCA1/2 testing was assumed to be 100%.
Incident patients (1L: prev NHA use in mCRPC)	Yr 1: █ <sup>1</sup> Yr 2: █ <sup>1</sup> Yr 3: █ <sup>1</sup> Yr 4: █ <sup>1</sup> Yr 5: █ <sup>1</sup> Yr 6: █ <sup>1</sup>	Estimated using the NHA initiating patients (n), treatment algorithm and probability of metastatic CRPC to calculate total number of CRPC patients receiving NHA (n/(82%*84%)) multiplied proportion of patients who are non-metastatic (16%) : - %high-risk of distant mets (35%) - DARO PSD July 2020 - % uptake NHA (50%) - APA PSD Nov 2020 - %progress on NHA (█%) Sponsor assumption - %receive BRCA1/2 test (█-█%) - Sponsor's assumption (increased over time) - %BRCA1/2 prevalence (9.7%) - PROfound data	The two incident populations were calculated independently so there may be some small potential for double counting. The PBAC also noted that the BRCA1/2 prevalence applied should be based on the lower end of the estimates considered reasonable by MSAC (7%, see also paragraph 4.4)
Total patients eligible to initiate treatment	Current Yr 1: █ <sup>1</sup> Yr 2: █ <sup>1</sup> Yr 3: █ <sup>1</sup> Yr 4: █ <sup>1</sup> Yr 5: █ <sup>1</sup> Yr 6: █ <sup>1</sup> Mar21 █ <sup>1</sup> █ <sup>2</sup> █ <sup>2</sup>	Incident patients 1L and 2L combined	Potential underestimate due to omission of prevalent patients who would also be treated and also likely underestimate of NHA initiation estimations (rows above)
Grandfathered	Yr 1: █ <sup>1</sup>	Estimated by sponsor	Unchanged from the March 2021 submission.
<b>Treatment utilisation</b>			
Uptake rate	Yr 1-6: █% Mar21 Yr 1-6: 95%	Uptake (█%) - Sponsor assumption that █% of patients agreeing to test would receive treatment	The PBAC considered that the uptake rate is likely to be less than 100% in clinical practice and should be reduced to 95%.

Public Summary Document – November 2021 PBAC Meeting

Data	Value	Source	Comment														
Number initiating treatment	<table border="1"> <tr> <td>Current</td> <td>Mar21</td> </tr> <tr> <td>Yr 1: █*,1</td> <td>█*,1</td> </tr> <tr> <td>Yr 2: █1</td> <td>█1</td> </tr> <tr> <td>Yr 3: █1</td> <td>█1</td> </tr> <tr> <td>Yr 4: █1</td> <td>█1</td> </tr> <tr> <td>Yr 5: █1</td> <td>█1</td> </tr> <tr> <td>Yr 6: █1</td> <td>█2</td> </tr> </table>	Current	Mar21	Yr 1: █*,1	█*,1	Yr 2: █1	█1	Yr 3: █1	█1	Yr 4: █1	█1	Yr 5: █1	█1	Yr 6: █1	█2	<p>Total eligible multiplied by uptake rate plus 100% of grandfathered patients</p> <p>*Year 1 includes █1 grandfathered patients</p>	
Current	Mar21																
Yr 1: █*,1	█*,1																
Yr 2: █1	█1																
Yr 3: █1	█1																
Yr 4: █1	█1																
Yr 5: █1	█1																
Yr 6: █1	█2																
Scripts dispensed	<table border="1"> <tr> <td>Current</td> <td>Mar21</td> </tr> <tr> <td>Yr 1: █2</td> <td>█2</td> </tr> <tr> <td>Yr 2: █2</td> <td>█2</td> </tr> <tr> <td>Yr 3: █2</td> <td>█2</td> </tr> <tr> <td>Yr 4: █2</td> <td>█2</td> </tr> <tr> <td>Yr 5: █2</td> <td>█2</td> </tr> <tr> <td>Yr 6: █2</td> <td>█2</td> </tr> </table>	Current	Mar21	Yr 1: █2	█2	Yr 2: █2	█2	Yr 3: █2	█2	Yr 4: █2	█2	Yr 5: █2	█2	Yr 6: █2	█2	<p>Incident patient months based on an assumed average time on treatment of 10.9months 2L (model), █ months 1L (AZ data on file), multiplied by 11.94 scripts per year (1 script=1 pack of 112 tablets, 4 tablets per day, dosing at █% compliance)</p> <p>Grandfathered patients expected to have received █ months of treatment prior to PBS listing (i.e. █ of 2L treatment duration)</p>	<p>The 2L time on treatment was based on the average time on treatment when the model. The time on treatment for the 1L mCRPC patients could not be verified. The PBAC considered that the time on treatment for all patients (both 1L and 2L) should be based on the average time on treatment applied in the model (10.9 months).</p>
Current	Mar21																
Yr 1: █2	█2																
Yr 2: █2	█2																
Yr 3: █2	█2																
Yr 4: █2	█2																
Yr 5: █2	█2																
Yr 6: █2	█2																
Concomitant treatments	Not costed	Concomitant treatments were not discussed	This was inconsistent with the economic analysis, where olaparib was associated with a different mix of concomitant therapies than cabazitaxel.														
AE/SRE therapies	Not costed	AE/SRE therapies were not discussed	This was inconsistent with the economic analysis, where olaparib was associated with a different probability and variety of AEs and SREs.														
Subsequent treatments	Not costed	Subsequent treatment was not discussed	This was consistent with the economic analysis. With earlier treatment commencement of NHAs patients may opt for olaparib earlier in their treatment pathway than in PROfound and therefore there may be opportunities for later lines of treatment.														
<b>PBS/RPBS Costs</b>																	
Olaparib	\$█ per 28 day supply	DPMQ (effective)	Costs were consistent with the economic analysis.														
Cabazitaxel	\$1,068.61	PBS codes 4376H, 7236W 60mg/1.5ml injection once every 21 days for 5.2months (dose 38.2mg per administration as per economic model, no vial sharing assumed)	Drug compliance was assumed to be 100%, with 91.9% dosage for olaparib, consistent with the economic analysis. Weighted cost of cabazitaxel differed slightly from economic analysis (\$1,068.85) because of a different public/private split No vial sharing was assumed for cabazitaxel, consistent with the economic analysis.														
PBS/RPBS split	Olaparib: 95.11%: 4.89% Cabazitaxel: 96.62%:3.38%	Olaparib based on existing PBS Item statistics for abiraterone acetate and enzalutamide Cabazitaxel based on existing PBS Item statistics for cabazitaxel	The public private split used in the economic analysis was 31.5%:68.5% resulting in slightly different weighted cost of cabazitaxel.														
Public/ private split	Cabazitaxel: 31.94%: 68.06%																

Public Summary Document – November 2021 PBAC Meeting

Data	Value	Source	Comment
Patient co-payment	Olaparib - \$11.85 PBS - \$5.27 RPBS Cabazitaxel - \$16.12 PBS - \$5.69 RPBS	Olaparib average co-payment was based on the current weighted mean co-payment of abiraterone and enzalutamide Cabazitaxel average co-payment based on weighted mean co-payment of cabazitaxel	
<b>MBS costs</b>			
Somatic BRCA1/2 test	\$960	Item similar to 73301, \$1,200 at 80% fee	All patients assumed to start with somatic testing. MSAC advised that where a somatic test was inconclusive, a germline test can be used, but providers can only charge for the one fee (p3, MSAC1618 PSD, March2021).
Archival tissue review	\$68	Item 72860 \$85 at 80% fee	This cost was not included in the economic model.
Germline BRCA1/2 (after positive somatic test)	\$320 per test	Item 73302 \$400 at 80% fee	This cost was not included in the economic analysis. Note this is different to the March 2021 submission where 37% of patients were assumed to require a germline test because the somatic test was not feasible or not successful. In this resubmission, a further germline test was only able to be billed on MBS for patients who have a positive somatic test.
Germline BRCA1/2 testing for relatives	\$320 per test	Item 73297 \$400 at 80% fee. Total cost \$480 per patient eligible for olaparib, i.e. 50% somatic BRCA1/2 patients will be germline BRCA1/2, each with 3 relatives tested though cascade testing	This cost was not included in the economic analysis. Rate of somatic only BRCA1/2 was higher in PROfound (59.4%).
Chemo administration	\$89.12 per admin	Item 13950 \$111.40* at 80% fee	The economic analysis used a higher weighted average cost based on this item and the NEP.

Source: Table 159, p 388, Table 163, p392, Table 164, p393, Table 169 p 396, 'Grandfathered patients' p400, Tables 175,-177 p402, Table 178 p403, Section 4.2.3 p403, Table 182, p405, Table 185 p 407, Table 191, p410 and compiled during the evaluation

1L=first line, 2L=second line, AE=adverse event, BRCA1/2=BRCA1/2 pathogenic variant, GF=grandfathering, m0CRPC=non-metastatic castrate resistant prostate cancer, MBS=Medicare Benefits Schedule, mCRPC=metastatic castrate resistant prostate cancer, NHA= novel hormonal agent, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Schedule of Pharmaceutical Benefits, SRE=skeletal related event

Some PBS and MBS costs have changed since the resubmission was compiled. The cost differences are small and therefore have not been updated during the evaluation.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

6.92 The following table presents the estimated use and financial impact of olaparib.

Public Summary Document – November 2021 PBAC Meeting

Table 17: Estimation of use and financial impact of the proposed medicine

	2022	2023	2024	2025	2026	2027
<b>Estimation of number of treated patients</b>						
<b>2L: previous NHA use in mCRPC</b>						
Incident NHA use	2	2	2	2	2	2
mCRPC patients tested for BRCA1/2	2	2	2	2	2	2
Patients who progress to 2L treatment	2	2	2	2	2	2
2L patients who initiate olaparib	1	1	1	1	1	1
<b>1L: prev NHA use in m0CRPC</b>						
Incident NHA use in m0CRPC	2	2	2	2	2	2
Total progress to mCRPC	1	1	1	1	1	1
Total 1L patients tested for BRCA1/2	1	1	1	1	1	1
Total 1L patients initiate olaparib	1	1	1	1	1	1
Total 1L patients treated with olaparib	1	1	1	1	1	1
Grandfathered	1					
Total initial patients for olaparib	1	1	1	1	1	1
Total initial patients olaparib (Mar21)	1	1	1	1	1	2
Total continuing patient olaparib	1	1	1	1	1	1
Total continuing patients olaparib (Mar21)	1	1	1	1	1	1
<b>Estimated number of olaparib scripts (PBS/RPBS) and cost (effective) to PBS/RPBS</b>						
2L mCRPC	2	2	2	2	2	2
1L mCRPC	1	1	1	1	1	1
Grandfathered	1	1	1	1	1	1
Total olaparib scripts	2	2	2	2	2	2
Total olaparib scripts (Mar21)	2	2	2	2	2	2
Net cost of olaparib to PBS/RPBS	3	3	3	3	3	3
Net cost olaparib to PBS/RPBS (Mar21)	4	4	4	4	4	4
<b>Estimation changes in use and financial impact of currently listed treatments</b>						
Patients on comparators TMs displaced by PBS listing of olaparib (2L +1L)	1	1	1	1	1	1
Reduction in cabazitaxel scripts	1	1	2	2	2	2
Total cost offset to PBS/RPBS	4	4	4	4	4	4
Total cost offsets to PBS/RPBS (Mar21)	4	4	4	4	4	4
<b>Estimated financial implications for the PBS/RPBS and the health budget</b>						
Net cost PBS/RPBS (net cost offsets)	3	3	3	3	3	3
Net cost PBS/RPBS (net cost offsets) (Mar21)	4	4	4	4	4	4
Net cost to MBS	4	4	4	4	4	4
Net cost to MBS (Mar21)	4	4	4	4	4	4
Net change to government budget	3	3	3	3	3	5
Net change to government budget (Mar21)	3	3	3	3	3	3

Blue highlight represent estimates from the March 2021 submission, these were extracted from the last commentary during the evaluation. Source: Table 162, p391, Table 164, p393, Table 166, p395, Table 169 p 396, 'Grandfathered patients' p400, , Tables 175,-178 p402-403, Tables 183-186 p405-407, Table 188-190 p408-409, Tables 192-196 p412-413, Table 198 p414 and compiled during the evaluation 1L=first line, 2L=second line, BRCA1/2=BRCA1/2 pathogenic variant, GF=grandfathering, m0CRPC=non-metastatic castrate resistant prostate cancer, MBS=Medicare Benefits Schedule, mCRPC=metastatic castrate resistant prostate cancer, NHA=novel hormonal agent, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Schedule of Pharmaceutical Benefits

<sup>a</sup> estimated by assuming 37% of patients for whom tumour testing was not feasible or not successful, based on PROfound data.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$10 million to < \$20 million

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$20 million to < \$30 million

6.93 At year 6, the estimated number of patients was < 500 and the net cost to the PBS/RPBS would be \$10 million to < \$20 million. The net cost to the PBS/RPBS was estimated to be approximately \$70 million to < \$80 million, net cost to the MBS \$20 million to < \$30 million, and total net cost to the government of approximately \$100 million to < \$200 million over the first six years of listing. The financial estimates may be underestimated due to:

- An underestimate of NHA use based on 2020 data which is likely lower due to the COVID-19 pandemic. The PBAC considered the impact of this may have been at least partly offset by use of a growth rate of 6.86% which was higher than that applied in the March 21 submission (5%, although applied to prevalent patients);
- An underestimate of patients eligible to access olaparib as the prevalent population was not included. The PBAC expected the prevalent population to be relatively small given the poor prognosis for the proposed patient population (the median survival in the comparator arm of PROfound was less than 12 months after adjustment for cross-over);
- An underestimate of the proportion of patients progressing from NHA. In current practice there are limited treatment options for mCRPC patients, as such NHA use may be more protracted than if other treatment options were available. The PBAC acknowledged the potential for earlier treatment with olaparib but considered this risk could be managed with the RSA;
- A proportion of patients may receive docetaxel in practice, rather than cabazitaxel, which would reduce offset costs;
- Adverse event costs were not included and are likely to be higher for patients receiving olaparib based on the economic analysis; and
- No cost for potential re-biopsying was included. While this is in line with the economic analysis and the resubmission's suggestion that patients who fail somatic testing go on to germline testing, this is a scenario that could require >30% of patients to receive genetic counselling (not currently available on MBS) in order to acquire a germline BRCA1/2 test. Furthermore, >50% of BRCA1/2 pathogenic variants are somatic only (i.e., they will be missed by a germline test alone). Therefore, re-biopsy may be preferable in practice.

6.94 The financial estimates may be overestimated as:

- Comparator costs may be underestimated. As NHAs are adopted earlier in practice, docetaxel use in mCRPC may increase which could also result in sequential docetaxel to cabazitaxel treatment as an option for a proportion of patients;
- The financial estimates did not include concomitant treatment costs, which may be higher for patients receiving cabazitaxel than olaparib, based on the economic analysis; and

- In practice some patients may know their germline status prior to mCRPC (e.g., previously identified through cascade testing of a relative with a BRCA1/2 pathogenic variant) and therefore will not need to undergo somatic testing. However, this is unlikely to significantly reduce overall testing costs as even when germline status has been identified in all patients prior to mCRPC, approximately 95% of mCRPC patients will still need to undergo somatic testing. This is because <5% of mCRPC patients are expected to have germline BRCA1/2 pathogenic variants (less than half of the 9.7% of patients with any BRCA1/2 pathogenic variant), and the remaining >95% will be tested for somatic BRCA1/2 pathogenic variants.
- 6.95 The financial estimates were sensitive to changes to the numbers of patients eligible for olaparib: annual growth rate for NHA initiation, BRCA1/2 prevalence, progression from NHA, and NHA initiation incidence.
- 6.96 Overall the ESC considered the net costs of olaparib are likely to be underestimated. The PBAC acknowledged both the cost of olaparib and the overall net cost to the PBS/RPBS may be underestimated for the reasons outlined above. However, in terms of the cost of olaparib the PBAC considered that the following inputs would have a relatively large impact and hence the costs in the submission were likely to be overestimated:
- The BRCA1/2 prevalence which the PBAC considered should be reduced from 9.7% to 7%. In addition, the PBAC considered that test failure due to inadequate tumour tissue for BRCA testing may further reduce the number of patients treated in practice.
  - The uptake rate which the PBAC considered is likely to be less than 100% in clinical practice and should be reduced to 95%.
- 6.97 In addition, the PBAC noted a longer treatment duration was applied for 1L patients. Noting that the cost-effectiveness of a longer treatment duration had not been assessed, the PBAC considered the treatment duration for the 1L patients should be revised to 10.9 months as per 2L patients. The PBAC noted the risk of a longer treatment duration could be managed with the RSA.

### ***Quality use of medicines***

- 6.98 This section was unchanged from the March 2021 submission. Quality of use medicine activities focused on education and training of health professionals and establishment of BRCA1/2 tumour and germline testing capacity for mCRPC to tackle an identified risk of delays in patients getting their test results for BRCA1/2.

### ***Financial management – risk sharing arrangements***

- 6.99 The resubmission did not propose a risk-sharing agreement, but the Sponsor indicated it was willing to work with PBAC and Department of Health to determine a risk sharing agreement. The PBAC considered that an RSA with ■% rebate on expenditure above

the caps would be required to address uncertainty in the treated patient population, especially given ongoing changes in the clinical algorithm for prostate cancer. The PBAC noted that the caps would need to reflect revised financial estimates as outlined in paragraphs 6.96 and 6.97.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended olaparib for the treatment of metastatic castration resistant prostate cancer in patients with BRCA1 and BRCA2 pathogenic gene variants. The PBAC is satisfied that olaparib provides, for some patients, a significant improvement in efficacy over standard care (SoC), based on the results of the PROfound study. The PBAC considered that the mixed comparator of best supportive care (BSC) and cabazitaxel sufficiently reflected SoC in current Australian clinical practice, and the comparator arm from the PROfound study could reasonably be used as a proxy for BSC. The PBAC noted that the resubmission had addressed a number of its previous concerns with the economic model and considered that with the revised price proposed in the pre-PBAC response the ICER was within a cost-effective range despite some remaining uncertainty regarding the extent of the overall survival gain and the BRCA testing component.
- 7.2 The resubmission provided an amended current clinical management algorithm, which depicted three lines of treatment in mCRPC; with NHA (either enzalutamide or abiraterone) or docetaxel as first-line; BSC, NHA, cabazitaxel or docetaxel in second-line; followed by BSC or cabazitaxel in third line. In the proposed algorithm, olaparib could be used as an alternative first, second, or third line treatment. The PBAC considered that this place in therapy for olaparib is appropriate.
- 7.3 The PBAC considered the requested restriction reflected the proposed place in therapy and was consistent with the TGA indication (“treatment of adult patients with BRCA-mutated (germline and/or somatic) mCRPC who have progressed following prior therapy that included an NHA”). The proposed restriction also included a criterion to allow use in patients considered unsuitable for NHA treatment on the basis of predicted intolerance. The PBAC considered this criterion was not required and should not be included in the listing. The PBAC considered it would be appropriate to clarify the term ‘novel hormonal agents’ in the restriction by providing a list of the specific drugs included in this category. The PBAC considered that an Authority Required (Telephone/online) restriction level would be appropriate for both initial and continuing listings.
- 7.4 The resubmission nominated a mixed comparator to represent SoC, comprised of BSC and cabazitaxel assuming a 75:25 split in the modelled economic evaluation. The PBAC previously considered that docetaxel would also be an appropriate comparator where patients had not previously received docetaxel (paragraph 7.4, olaparib PSD, March 2021), and outcomes for patients treated with docetaxel would be expected to differ

somewhat from cabazitaxel as patients treated with docetaxel would not have received a prior taxane. However, the PBAC noted that inclusion of docetaxel as the comparator in 15% of patients appeared to have minimal impact on the ICER. The PBAC considered that the mixed comparator of BSC and cabazitaxel sufficiently reflected SoC in current Australian clinical practice.

- 7.5 The PBAC noted that as in the previous submission the comparison with BSC was based on the BRCA1/2 subgroup of the PROfound trial. The PBAC recalled that it had previously advised that the comparator arm from the PROfound study could reasonably be used as a proxy for SoC and concluded that olaparib was superior in terms of efficacy and inferior in terms of safety compared to BSC (paragraph 7.9 and 7.10, olaparib PSD, March 2021 PBAC meeting).
- 7.6 The PBAC noted that 67.5% of patients in the NHA arm of Cohort A of PROfound received subsequent treatment with olaparib. The PBAC noted that the resubmission presented additional justification for the RPSFTM method of adjustment for this treatment switching and that this method resulted in an overall survival hazard ratio (HR) of 0.28 (95% CI: 0.10, 0.79) with recensoring and 0.37 (95% CI: 0.16, 0.83) without recensoring. The PBAC considered that the selection of RPSFTM was adequately justified in the resubmission. The PBAC noted that the two statistical approaches used to adjust for switching (with and without recensoring) produced materially different point estimates for the HR. The PBAC noted the ESC's advice that the confidence intervals were wide for the estimated unadjusted and adjusted HRs with considerable overlap in the 95% confidence intervals. The PBAC considered that there was remaining uncertainty about the treatment effect for OS and agreed with the ESC that, given the available clinical data, it would be appropriate to take a conservative approach to the choice of HRs applied in the economic evaluation (see also paragraph 7.9).
- 7.7 For the comparison with cabazitaxel the resubmission presented an anchored matching-adjusted indirect comparison (MAIC) using NHA as the common treatment arm. The MAIC matched the subgroup of patients with BRCA1/2 and prior taxane in PROfound to the ITT population in CARD, who were required to have received prior treatment with taxanes. The PBAC considered that the results of this comparison were highly uncertain due to important differences in baseline characteristics between the two trial populations which could not be adjusted for (such as BRCA status) and the unreliable survival results in the small post-hoc subgroup of BRCA1/2 patients with prior taxane treatment in PROfound. Therefore, the PBAC again considered it would be more appropriate to use the comparative results of olaparib vs. NHAs in PROfound to represent estimates of effectiveness of olaparib over a mixed comparator (paragraphs 5.3,5.4, olaparib PSD, March 2021 PBAC meeting). The PBAC considered that the claim of non-inferior safety compared with taxane chemotherapy was reasonable, noting that their safety profiles are different.

- 7.8 The PBAC noted that the resubmission had addressed a number of its previous concerns with the economic model, including: a test-treat structure to assess the consequences of less than perfect test performance; BSC and cabazitaxel as comparators and revised time on treatment extrapolation.
- 7.9 The PBAC previously advised that the resubmission should address the material uncertainty about the treatment effect for OS used in the model. The model in the previous submission applied the OS HR adjusted for treatment switching using RPSFTM with recensoring (HR=0.28) which was considerably lower than the adjusted value from the RPSFTM model without recensoring (HR=0.37). This was unchanged in the resubmission for the comparison with BSC (75% of patients) and a HR of 0.34 was applied in the comparison with cabazitaxel (25% of patients). Recognising the uncertainty in the comparison of olaparib and cabazitaxel, the pre-PBAC response proposed that a weighted HR of 0.30 be applied to the total SoC arm, calculated using the RPSFTM HR with recensoring (0.28) applied to the 75% of patients receiving BSC and the RPSFTM HR without recensoring (0.37) applied to the 25% of patients receiving cabazitaxel. The ICER for this scenario using the reduced price in the pre-PBAC response was \$45,000 to < \$55,000/QALY. The PBAC noted that using a HR of 0.37 for the total SoC arm increased the ICER to of \$55,000 to < \$75,000/QALY.
- 7.10 The PBAC noted that the resubmission reduced the time horizon from 10 years to 7.5 years, however again considered the appropriate time horizon to be 5 years. Although, it was further noted that the ICER based on a 5 year horizon was similar to that for a 7.5 year horizon (paragraph 6.85).
- 7.11 The PBAC noted concerns previously raised regarding the utility values applied in the model were not addressed, however further noted that the values used were sourced from the PROfound trial and that removal of the time to death utility adjustments had a relatively small impact on the ICER (paragraph 6.77).
- 7.12 The PBAC noted that there were a number of areas of uncertainty in the economic model associated with BRCA testing, including cascade testing, test failure rate and test sensitivity. The PBAC considered that there may be a substantial proportion of patients for whom the tissue sample is not adequate for BRCA testing. The pre-PBAC response argued the test sensitivity should be calculated based on successful samples and stated that a test failure rate of 10% would be expected in clinical practice and with 50% of patients having germline BRCA mutations, the sensitivity of BRCA testing would be approximately 95%. The PBAC noted that decreasing the sensitivity to 95% had a small impact on the ICER (paragraph 6.87) and when this was reduced to 76% based on the test failure rate for PROfound, the ICER remained below \$55,000 to < \$75,000/QALY using the revised price in the pre-PBAC response. Reducing the proportion of patients who test positive for BRCA from 9.7% to 7% increased the ICER (based on HR=0.37) from \$55,000 to < \$75,000 to \$55,000 to < \$75,000/QALY.
- 7.13 Overall, the PBAC considered that the resubmission's economic evaluation had addressed a number of the areas of uncertainty previously identified and that with the

reduced price presented in the pre-PBAC response the ICER was within an acceptably cost-effective range. There remained some uncertainty regarding the extent of the overall survival gain and assumptions regarding BRCA testing, however the ICER remained within an acceptable range for all reasonable sensitivity analyses for these inputs.

- 7.14 The PBAC considered that the net financial costs remained uncertain and that overall the cost of olaparib was likely to be overestimated. The PBAC considered that the financial estimates should be revised such that:
- The BRCA1/2 prevalence is reduced to 7%. In addition, the PBAC considered that test failure due to inadequate tumour tissue for BRCA testing may further reduce the number of patients treated in practice.
  - The uptake rate is reduced to 95%.
  - The treatment duration for 1L patients is reduced to 10.9 months (as per 2L patients) in line with the economic model.
- 7.15 The PBAC considered that an RSA with 100% rebate on expenditure above the caps would be required to address the uncertainty in the treated patient population, noting that the caps would need to reflect revised financial estimates as outlined in paragraph 7.14.
- 7.16 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for olaparib:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies, on the basis of improved overall survival;
  - b) The treatment is not expected to address a high and urgent unmet clinical need because there are other treatments available for mCRPC;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

Add indication (8022 – Castration resistant metastatic carcinoma of the prostate) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OLAPARIB					
olaparib 150 mg tablet, 56	New	2	112	2	Lynparza
olaparib 100 mg tablet, 56	New	2	112	2	Lynparza
<b>Restriction Summary [New 1]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					
<b>Administrative advice:</b> Where the term 'novel hormonal drug' appears in this restriction, it refers to: (i) abiraterone, (ii) apalutamide [pending Nov 21 PBAC meeting outcome], (iii) darolutamide, (iv) enzalutamide					
<b>Administrative Advice:</b> Special Pricing Arrangements Apply					
<b>Indication:</b> Castration resistant metastatic carcinoma of the prostate					
<b>Treatment Phase:</b> Initial treatment					
<b>Clinical criteria:</b> The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene mutation.					
<b>AND</b>					
<b>Clinical criteria:</b> The treatment must not be subsidised in combination with chemotherapy					
<b>AND</b>					
<b>Clinical criteria:</b> The condition must have progressed following prior treatment that included a novel hormonal drug for this condition (metastatic/non-metastatic disease)					
<b>AND</b>					
<b>Clinical criteria</b> Patient must have a WHO performance status of 2 or less					
<b>Treatment criteria:</b> Patient must be undergoing treatment with this drug for the first time					
<b>Restriction Summary [New 2]</b>					
<b>Indication:</b> Castration resistant metastatic carcinoma of the prostate					
<b>Treatment Phase:</b> Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' arrangements					
<b>Clinical Criteria</b> Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [insert listing date]					
<b>AND</b>					
<b>Clinical criteria:</b>					

Public Summary Document – November 2021 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
	The condition must be associated with a class 4 or 5 BRCA1 or BRCA2 gene mutation.				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	The treatment must not be subsidised in combination with chemotherapy				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	The condition must have progressed following prior treatment that included a novel hormonal drug for this condition (metastatic/non-metastatic disease), prior to initiating non-PBS subsidised treatment with this drug				
	<b>AND</b>				
	<b>Clinical criteria</b>				
	Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment				
	<b>Treatment criteria:</b>				
	Patient must be undergoing continuing treatment with this drug where non-PBS-subsidised treatment was for untreated (with this drug) disease which also has not progressed on non-PBS subsidised treatment				
	<b>Administrative advice:</b> Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.				
	<b>Administrative advice:</b> This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.				

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
OLAPARIB					
olaparib 150 mg tablet, 56	New	2	112	5	Lynparza
olaparib 100 mg tablet, 56	New	2	112	5	Lynparza
<b>Restriction Summary [New 3]</b>					
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)				
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.				
	<b>Indication:</b> Castration resistant metastatic carcinoma of the prostate				
	<b>Treatment Phase:</b> Continuing treatment				
	<b>Clinical criteria:</b>				
	Patient must have previously received PBS-subsidised treatment with this drug for this condition				
	<b>AND</b>				
	<b>Clinical criteria:</b>				
	Patient must not have developed disease progression while receiving treatment with this drug for this condition.				
	<b>AND</b>				

	<b>Clinical criteria:</b>
	The treatment must not be subsidised in combination with chemotherapy

## 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

In discussion with the Department during the listing process, a minor amendment to the clinical criterion was agreed to as follows: "the treatment must not be subsidised in combination with chemotherapy or a novel hormonal drug."