Evidence summary on abiraterone acetate in combination with prednisone and enzalutamide for individuals with metastatic castration-resistant prostate cancer

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Context of the Assessment

The Health Technology Assessment Council (HTAC) reviewed the clinical and cost-effectiveness evidence and recommendations of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines considering the inclusion of abiraterone acetate in the complementary list of the WHO Essential Medicines List (EML) in 2019, and enzalutamide which was added to the complementary list in 2021. Both drugs are indicated for metastatic castration-resistant prostate cancer

In addition, the HTAC considered available local and/or international Clinical Practice Guidelines (CPGs), and conducted a costing and budget impact analysis to determine the cost to the government for financing these drugs.

As for the economic evaluation, abiraterone acetate in combination with prednisone and enzalutamide were compared directly to each other. Among the comparators in the studies included by the WHO, only bicalutamide and docetaxel are included in the Philippine National Formulary (PNF). However, these two medications are ***not specifically indicated*** for metastatic castration-resistant prostate cancer (mCRPC). In an official consultation with the Philippine Society for Medical Oncology (PSMO) and cancer experts from the HTAC, abiraterone acetate in combination with prednisone, and enzalutamide are being used for the treatment of mCRPC in the clinical setting. On the other hand, docetaxel and bicalutamide, which are drugs listed in the Philippine National Formulary for locally advanced or metastatic prostate cancer are ***not being used*** for mCRPC in the clinical setting.

On **04 October 2022**, the HTAC posted its preliminary recommendation for the government financing of abiraterone acetate and enzalutamide through its inclusion in the PNF, which was posted for appeals until **18 October 2022**. Last 10 October 2022, the HTAC received two appeals for the preliminary recommendation on **enzalutamide** - one from the proponent (*Philippine Society of Urologic Oncology [PSUO]*) appealing to consider clinical evidence (i.e., abiraterone has higher risk of hospitalization, emergency department visits, and length of hospital stay than enzalutamide, and thus will increase costs related to these outcomes for abiraterone) that have impact on the economic evaluation of both abiraterone and enzalutamide; and one from the manufacturer (*Astellas Pharma Inc.*) submitting a reduced price offer for enzalutamide. The clinical studies submitted by the first appellant were reviewed. However, these were not considered to merit changes in the assessment because none of the studies have provided supporting evidence for their appeal. As for the appeal for costing analysis using the reduced price offer, this was considered, and used for the finalization of the costing and budget impact analysis.

Policy Questions

- Should **abiraterone acetate** (250 mg per tablet), in combination with prednisone, be included in the Philippine National Formulary for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC)?
- Should **enzalutamide** (40 mg per tablet) be included in the Philippine National Formulary for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC)?

Research Questions

Clinical Assessment

- What is the efficacy/effectiveness and safety of **abiraterone acetate** in combination with prednisone compared with other treatments (*including enzalutamide*) or placebo in terms of (a) overall survival, (b) progression-free survival, (c) health-related quality of life, and (d) occurrence of all adverse events among adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on androgen deprivation therapy?
- What is the efficacy/effectiveness and safety of **enzalutamide** compared with other treatments (*including abiraterone acetate, in combination with prednisone*) or placebo in terms of (a) overall survival, (b) progression-free survival, (c) health-related quality of life, and (d) occurrence of all adverse events among adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on androgen deprivation therapy?

Economic Assessment

- What is the associated medication cost per patient of using **abiraterone acetate** in combination with prednisone compared with **enzalutamide** for individuals with mCRPC?
- What is the total medication cost for the expected number of individuals using **abiraterone acetate** in combination with prednisone compared with **enzalutamide**?

Key Findings

The HTAC concluded with the following findings based on its decision framework as stipulated in Republic Act 11223 or the *Universal Healthcare Act*:

Criteria	Drug	Malignancy-Related Bone Disease
Clinical Efficacy / Effectiveness	Abiraterone acetate in combination with Prednisone	In four studies, abiraterone acetate in combination with prednisone was shown to have ***better efficacy*** as compared with placebo, prednisolone, and bicalutamide in terms of prolonging overall survival (3.9 to 4.2 months) and PFS, and reducing PSA progression.
	Enzalutamide	In four studies, enzalutamide was shown to have ***better efficacy*** with placebo, prednisolone, and bicalutamide in terms of overall survival (2.2 to 4.8 months), PFS, and reducing time to PSA progression.
Clinical Safety	Abiraterone acetate in combination with Prednisone	Abiraterone acetate in combination with prednisone has ***a favorable safety profile*** compared to placebo, showing a lower incidence of grade ≥ 3 adverse events, but a higher incidence of cardiac disorders, increased alanine aminotransferase, and hypertension.
	Enzalutamide	Enzalutamide has ***a favorable safety profile*** compared to placebo in terms of higher risk for grade 3 or higher adverse events (e.g., abnormality in liver tests and seizures).
Affordability and Viability		Abiraterone acetate in combination with prednisone have ***much lower associated medical costs*** per individual than enzalutamide, making it a cheaper option in treating individuals with mCRPC. The estimated individual cost of treatment (i.e. cost of drug regimen and administration) for individuals with mCRPC is **₱779,447.58** for abiraterone acetate in combination with prednisone and **₱984,040.00** for enzalutamide. The estimated cost of treatment (i.e. cost of drug regimen and administration) for all potential users per year is **₱7.15 B** for abiraterone acetate in combination with prednisone and **₱9.03 B** for enzalutamide. The cost savings accrued for all potential users per year when abiraterone acetate in combination with prednisone is used over enzalutamide is **₱1.88 B**.
		The estimated budget impact (*i.e., cost of drug regimen and administration*) for all expected individuals with mCRPC from 2022 to 2024 is **₱31.88 B** for abiraterone acetate in combination with prednisone and **₱40.25 B** for enzalutamide. The cost savings accrued among all users for 3 years when abiraterone acetate in combination with prednisone is used over enzalutamide is estimated to be **₱8.37 B**. Overall, the total cost of treatment using abiraterone acetate in combination with prednisone is ***generally cheaper*** than enzalutamide.

Cost-effectiveness		The cost-effectiveness of abiraterone acetate, in combination with prednisone, or enzalutamide ***cannot be ascertained*** due to the lack of locally adaptable evidence.

I. Summary of clinical efficacy and safety evidence and recommendations of the WHO and CPGs

WHO approved indication in the EML	Clinical Evidence from WHO EML	Supporting Clinical Practice Guidelines
Treatment of metastatic castration-resistant prostate cancer (mCRPC)	**ABIRATERONE ACETATE** *Clinical research question:* *What is the effectiveness and safety of abiraterone acetate with prednisone compared with other treatments or placebo in terms of (a) overall survival, (b) progression-free survival, (c) health-related quality of life, and (d) occurrence of all adverse events among adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on androgen deprivation therapy?* The WHO added abiraterone acetate to the complementary list of EML in 2019. This drug was recommended for patients with metastatic castration-resistant prostate cancer (mCRPC). The following were the clinical evidence considered for their positive recommendation: **General Findings:** ● **Efficacy**: The Committee noted that abiraterone acetate and enzalutamide have each been shown to be effective treatments for metastatic castration-resistant prostate cancer, both in chemotherapy-naive and in pre-treated patients. The Committee noted that abiraterone acetate had not shown any relevant clinical advantage over enzalutamide in terms of efficacy outcomes. ● **Safety**: The Committee noted that abiraterone acetate had not shown any relevant clinical advantage over enzalutamide in terms of safety outcomes.	Local guidelines are the main evidence used by oncological societies. However, in the absence of local guidelines, medical oncologists in the Philippines refer to guidelines developed by NCCN, ASCO, and ESMO (Catedral et al, 2020). ASCO (2017) Guidelines for Second-Line Hormonal therapy for Chemotherapy-Naïve CRPC ***Abiraterone acetate plus prednisone*** or enzalutamide should be offered for ***second-line*** hormonal treatment after first-line hormonal treatment failure for chemotherapy-naïve men who develop CRPC and have radiographic evidence of metastases (M1a/M1s CRPC) because these agents have been shown to significantly increase radiographic progression-free survival and overall survival *(PCO type: evidence based [three randomized controlled trials]; Strength of PCO: strong)* **NCCN, 2022** *(p. MS-55, PROS-14)* NCCN recommends ***Abiraterone acetate + androgen deprivation therapy + [prednisone or methylprednisolone]*** for the treatment of patients with metastatic CRPC with adenocarcinoma but not for small cell/neuroendocrine prostate cancer . Specially, it is recommended as:

	Evidence considered by the WHO **A. Systematic Reviews** *Kang et al, 2017 [Network meta-analysis of 8 RCTs; 2 RCTs with Abiraterone acetate as treatment]* *Interventions: Androgen receptor pathway targeted agents (including 1st and 2nd line abiraterone acetate in combination with prednisone)* *Comparator: Other androgen receptor pathway agents or control arms (placebo, prednisolone, bicalutamide)* *Quality assessment: RoB assessment results not specified in the study* *Median follow-up: 20.2 to 49.2 months (no pooled follow-up period)* *Efficacy outcomes:* ● **Overall survival (OS):** The hazard of death is 22% lower in the abiraterone acetate arm (HR 0.78, 95%CI 0.61 to 0.98) compared to prednisolone, bicalutamide, or placebo. ● **Progression-free survival (PFS):** There is no significant difference in the hazard of disease progression in the abiraterone acetate arm compared with those in the prednisolone, bicalutamide, or placebo arm (HR 0.59, 95%CI 0.35 to 1.0). ● **Time to prostate-specific antigen (PSA) progression:** The hazard of progression of PSA levels is 44%lower among those who were in the abiraterone acetate group as compared with those in the prednisolone, bicalutamide, and placebo groups (HR 0.56, 95% CI 0.35 to 0.91). **B. Randomized Controlled Trials** *COU-AA-301 trial, 2011 [Phase III RCT]* *Interventions: Abiraterone acetate in combination with prednisone (2nd line)* *Comparator: Placebo* *Efficacy outcomes:* ● **Overall survival (OS):** Overall survival was significantly longer in the abiraterone acetate-prednisone arm compared to the	**> Preferred treatment** for mCRPC ***without prior novel hormone therapy*** with or without prior docetaxel (PROS-15): ● **Category I recommendation** : *Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.* ● Evidence blocks for M1 CRPC with no prior hormone therapy and **no prior docetaxel** (*PROS-15B*) ○ 4 - **Very effective:** *Cure unlikely but sometimes provides long-term survival advantage* ○ 4 - **Occasionally toxic:** *Rare significant toxicities or low-grade toxicities only; little interference with ADLs* ○ 5 - **High quality:** *Multiple well-designed randomized trials and/or meta-analyses* ○ 5 - **Highly consistent:** *Multiple trials with similar outcomes* ○ 2 - **Expensive** ● Evidence blocks for M1 CRPC with no prior hormone therapy but **with prior docetaxel**: (*PROS-15C*) ○ 4 - **Very effective:** *Cure unlikely but sometimes provides long-term survival advantage* ○ 4 - **Occasionally toxic:** *Rare significant toxicities or low-grade toxicities only; little interference with ADLs* ○ 5 - **High quality:** *Multiple well-designed*

	control arm (14.8 months vs 10.9 months; diff. 3.9). The hazard of death is 35% lower among those who were in the abiraterone acetate group, as compared with those in the placebo (Hazard Ratio (HR) 0.65, 95%CI 0.54 to 0.77; p<0.001). ● **Progression-free survival (PFS)**: Abiraterone acetate showed significantly favorable progression-free survival as compared to placebo (5.6 months vs 3.6 months; diff 2). The hazard of disease progression is 33% lower among those who were in the abiraterone acetate group, as compared with those in the placebo (HR 0.67, 95%CI 0.59 to 0.78; p<0.001). ● **Time to prostate-specific antigen (PSA) progression**: Abiraterone acetate was significantly associated with decreased time to PSA progression as compared to placebo (10.2 months vs 6.6 months; diff 3.6). The hazard of progression of PSA levels is 42% lower among those who were in the abiraterone acetate group as compared with those in the placebo group (HR 0.58, 95%CI 0.46 to 0.73; p<0.001). *Safety outcome:* ● **Adverse events**: There were more deaths, treatment discontinuations, and treatment discontinuations due to adverse events in the placebo arm compared to the abiraterone acetate arm. Common adverse events in the treatment group include fatigue, back pain, nausea, constipation, bone pain, and arthralgia. ○ [RR not specified in WHO and the actual study] *COU-AA-302 trial, 2015: [Phase III RCT]* *Interventions: Abiraterone Acetate in combination with prednisone (1st line)* *Comparator: Placebo* *Efficacy outcome:* ● **Overall survival (OS):** Overall survival was significantly longer in the abiraterone acetate-prednisone arm compared to the	*randomized trials and/or meta-analyses* ○ 4 - **Mainly consistent:** *Multiple trials with some variability in outcome* ○ 2 - **Expensive** **> Other recommended regimens category** for mCRPC ***with prior novel hormone therapy*** with or without prior docetaxel (PROS-15): ● **Category 2A recommendation:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. ● Evidence blocks for M1 CRPC with prior novel hormone therapy but with **no prior docetaxel**: (*PROS-15C*) ○ 3 - **Moderately effective:** *Modest impact on survival, but often provides control of disease* ○ 4 - **Occasionally toxic:** *Rare significant toxicities or low-grade toxicities only; little interference with ADLs* ○ 4 - **Good quality:** *One or more well-designed randomized trials* ○ 4 - **Mainly consistent:** *Multiple trials with some variability in outcome* ○ 2 - **Expensive** ● Evidence blocks for M1 CRPC with prior novel hormone therapy and **with prior docetaxel**: (*PROS-15D*) ○ 2 - **Minimally effective:** *No, or unknown impact on survival, but sometimes provides control of disease* ○ 4 - **Occasionally toxic:** *Rare significant*

	control arm (34.7 months vs. 30.3 months; diff: 4.4). The hazard of death is 19%times lower among those who were in the abiraterone acetate group, as compared with those in the placebo (HR 0.81, 95%CI 0.70 to 0.93; p=0.0033). *Safety outcome:* ● **Any adverse events:** Urinary tract infection (UTI) was observed more frequently in the abiraterone acetate arm compared to placebo *(no RR stated)*. ○ [RR not specified in WHO EML application and the actual study] ● **Adverse events of special interest:** The most common Grade 3 adverse events of special interest reported in the abiraterone acetate arm were cardiac disorders, increased alanine aminotransferase, and hypertension. ○ [RR not specified in WHO and the actual study] **C. Observational Studies** *Pilon et al, 2017 [Retrospective Analysis]* *Interventions: abiraterone acetate in combination with prednisone (1st and 2nd line)* *Comparator: Enzalutamide* *Safety outcomes:* ● **Discontinuation of treatment:** Compared with patients initiated on enzalutamide, patients initiated on abiraterone acetate had significantly fewer discontinuations of mCRPC treatments. The hazard of treatment discontinuation due to adverse events is 27% lower among those in the abiraterone acetate arm than enzalutamide (HR 0.73, 95%CI 0.59-0.91 p=0.004) and 39%lower than any prostate cancer treatments (HR 0.61, 95%CI 0.45-0.83, p=0.002) at three months and the result was maintained up to 24 months. ○ Median duration for abiraterone acetate: 18.3 months, p<0.001	*toxicities or low-grade toxicities only; little interference with ADLs* ○ 3 - **Average quality:** *Low quality randomized trial(s) or well-designed non-randomized trial(s)* ○ 3 - **May be consistent:** *Few trials or only trials with few patients, whether randomized or not, with some variability in outcome* ○ 2 - **Expensive** **ESMO-Magnitude of Clinical Benefit Scale V1.1 (2020)** *(pp. 1128)* ● Abiraterone acetate [ESMO-MCBS v1.1 scores: 4] is recommended for asymptomatic/ mildly symptomatic men with Chemotherapy-naive mCRPC [I, A]. ● In patients with mCRPC in the post-docetaxel setting, abiraterone acetate [ESMO-MCBS v1.1 score: 4] is recommended [I, A] ● The use of a second androgen-receptor inhibitor (abirateroneacetate after enzalutamide or vice versa) is **NOT** recommended [II, D]. *Levels of Evidence (*Supplementary Table S4*): ● *I = Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity* ● *II = Small randomized trials or large randomized*

	○ Median duration for enzalutamide: 14.2 months, p<0.001	*trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity* *Grades of Recommendation (*Supplementary Table S4*): ● *A = Strong evidence for efficacy with a substantial clinical benefit, strongly recommended* ● *B = Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended* ● *C = Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional* ● *D = Moderate evidence against efficacy or for adverse outcome, generally not recommended* National Kidney and Transplant Institute - Philippine CPG for the Diagnosis and Management of Prostate Cancer (2021) (*p. 5*) Among patients with newly- diagnosed prostate cancer and M1 metastasis, either asymptomatic with high or very high-risk features of disease, or symptomatic regardless of risk ● NKTI suggests the addition of docetaxel alone or ***abiraterone acetate*** alone to androgen deprivation therapy ● Certainty of Evidence: Very low ● Strength of Recommendation: Weak

WHO approved indication in the EML	Clinical Evidence from WHO EML	Supporting Clinical Practice Guidelines
Treatment of metastatic castration-resistant prostate cancer (mCRPC)	***ENZALUTAMIDE*** *Clinical research question:* What is the effectiveness and safety of enzalutamide compared with other treatments or placebo in terms of (a) overall survival, (b) progression-free survival, (c) health-related quality of life, and (d) occurrence of all adverse events among adult men with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on androgen deprivation therapy (ADT)? The WHO added enzalutamide to the complementary list of EML in 2021 with an individual square box listing which indicates that enzalutamide can be a therapeutic alternative to abiraterone acetate. This drug was recommended for patients with metastatic castration-resistant prostate cancer (mCRPC). While the application for enzalutamide was initially rejected in 2019, the Committee recognized the drug's potential to regulate the market price of abiraterone acetate as its direct comparator. The following were the clinical evidence considered for their positive recommendation: **General Findings** ● **Efficacy/Effectiveness:** The Committee noted that enzalutamide for metastatic, castration-resistant prostate cancer largely meets the EML criteria for survival benefit (i.e. at least 4 to 6 months survival gain) and the European Society of Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 score, and appears to demonstrate comparable efficacy to abiraterone acetate (i.e., non-inferior).	Local guidelines are the main evidence used by oncological societies. However, in the absence of local guidelines, medical oncologists in the Philippines refer to guidelines developed by NCCN, ASCO, and ESMO (Catedral et al, 2020). ASCO (2017) Guidelines for Second-Line Hormonal therapy for Chemotherapy-Naïve, Castration-Resistant Prostate Cancer Abiraterone acetate plus prednisone or ***enzalutamide*** should be offered for ***second-line*** hormonal treatment after first-line hormonal treatment failure for chemotherapy-naïve men who develop CRPC and have radiographic evidence of metastases (M1a/M1s CRPC) because these agents have been shown to significantly increase radiographic progression-free survival and overall survival *(PCO type: evidence based [three randomized controlled trials]; Strength of PCO: strong)* **NCCN, 2022** *(p. MS-57, PROS-14)* NCCN recommended enzalutamide for the treatment of patients with **metastatic CRPC** with adenocarcinoma but not for small cell/neuroendocrine prostate cancer. Specifically it is recommended as: **> Preferred treatment** for mCRPC ***without prior***

	• **Safety:** The Committee noted that enzalutamide for metastatic, castration-resistant prostate cancer demonstrates comparable safety to abiraterone acetate. Enzalutamide has a different mechanism of action and a different toxicity profile, making it a first-choice medicine in patients not eligible to be treated with or unable to tolerate abiraterone acetate. **Evidence considered by the WHO** **A. Systematic Reviews** Kang et al, 2017 *[Network meta-analysis of 8 RCTs; 4 RCTs with enzalutamide as treatment]* *Interventions: Androgen receptor pathway targeted agents (including 1st and 2nd line enzalutamide)* *Comparator: Other androgen receptor pathway agents or control arms (placebo, prednisolone, bicalutamide)* *Quality assessment: RoB assessment results not specified in the study* *Median follow-up: 14.4 to 31 months (no pooled follow-up period)* *Efficacy outcomes:* • **Overall survival (OS):** The hazard of death is 22% lower in the enzalutamide arm (HR 0.78, 95%CI 0.61 to 0.98) compared to prednisolone, bicalutamide, or placebo. • **Progression-free survival (PFS)**: The hazard of disease progression is 64% lower in the enzalutamide arm compared with those in the prednisolone, bicalutamide, or placebo arm (HR 0.36, 95%CI 0.21 to 0.59) • **Time to prostate-specific antigen (PSA) progression**: The hazard of progression of PSA levels decreased by 56%among those who were in the enzalutamide group as compared with those in the prednisolone, bicalutamide, and placebo groups (HR 0.56, 95%CI 0.35 to 0.91) Roviello et al, 2016 *[Network meta-analysis of 8 RCTs, 4 RCTs with*	***novel hormone therapy*** with or without prior docetaxel (PROS-15): • **Category I recommendation** : *Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.* • Evidence blocks for M1 CRPC with no prior hormone therapy and **no prior docetaxel** (*PROS-15B*) ○ 4 - **Very effective:** *Cure unlikely but sometimes provides long-term survival advantage* ○ 4 - **Occasionally toxic:** *Rare significant toxicities or low-grade toxicities only; little interference with ADLs* ○ 5 - **High quality:** *Multiple well-designed randomized trials and/or meta-analyses* ○ 5 - **Highly consistent:** *Multiple trials with similar outcomes* ○ 2 - **Expensive** • Evidence blocks for M1 CRPC with no prior hormone therapy but **with prior docetaxel**: (*PROS-15C*) ○ 4 - **Very effective:** *Cure unlikely but sometimes provides long-term survival advantage* ○ 4 - **Occasionally toxic:** *Rare significant toxicities or low-grade toxicities only; little interference with ADLs* ○ 4 - **Good quality:** *One or more well-designed randomized trials* ○ 4 - **Mainly consistent:** *Multiple trials with some variability in outcome*

	enzalutamide as treatment] *Interventions: Androgen receptor pathway targeted agents (including 1st and 2nd line enzalutamide)* *Comparator: Other androgen receptor pathway targeted agents, bicalutamide, or placebo* *Quality assessment: Median Jadad score: 5 (high level of quality)* *Median follow-up: 14.4 to 31 months (no pooled follow-up period)* *Efficacy outcomes:* ● **Overall survival (OS):** Pooled analysis of androgen receptor pathway targeted agents (enzalutamide, abiraterone acetate, orteronel) revealed significantly increased overall survival compared with placebo or prednisone. The hazard of death is 21% lower among those who were in the treatment arm compared with those in the comparator arm (HR 0.79, 95%CI 0.71 to 0.87, p<0.00001). ● **Progression-free survival (PFS)**: Pooled analysis of androgen receptor pathway targeted agents revealed significantly improved progression-free survival. The hazard of disease progression is 52% lower among those who were in the treatment arm compared with those in the comparator arm (HR 0.48, 95%Ci 0.37 to 0.62, p<0.00001). ● **Time to prostate-specific antigen (PSA) progression:** Pooled analysis of androgen receptor pathway targeted agents revealed significantly improved prostate-specific antigen (PSA) progression. The hazard of PSA progression is 63% lower among those who were in the treatment arm compared with those in the comparator arm (HR 0.37, 95%Ci 0.24 to 0.59, p<0.00001). *Safety outcome:* ● **Adverse events:** The incidence of grade 3 or higher adverse events was moderately higher with androgen receptor pathway targeted agents compared to control arms but not statistically significant (RR=1.11, 95%CI, 0.98 to 1.25, p=0.09).	○ 2 - **Expensive** **> Other recommended regimens category** for mCRPC ***with prior novel hormone therapy*** with or without prior docetaxel (PROS-15): ● **Category 2A recommendation:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. ● Evidence blocks for M1 CRPC with prior novel hormone therapy but **no prior docetaxel**: (*PROS-15C*) ○ 3 - **Moderately effective:** *Modest impact on survival, but often provides control of disease* ○ 4 - **Occasionally toxic:** *Rare significant toxicities or low-grade toxicities only; little interference with ADLs* ○ 4 - **Good quality:** *One or more well-designed randomized trials* ○ 4 - **Mainly consistent:** *Multiple trials with some variability in outcome* ○ 2 - **Expensive** ● Evidence blocks for M1 CRPC with prior novel hormone therapy and **with prior docetaxel**: (*PROS-15D*) ○ 2 - **Minimally effective:** *No, or unknown impact on survival, but sometimes provides control of disease* ○ 4 - **Occasionally toxic:** *Rare significant toxicities or low-grade toxicities only; little interference with ADLs* ○ 3 - **Average quality:** *Low quality*

B. Randomized Control Trials

AFFIRM trial, 2012 [Phase III RCT]

Interventions: Enzalutamide (2nd line)
Comparator: Placebo

Efficacy outcomes:

- **Overall survival (OS):** Overall survival was longer in the enzalutamide arm compared to the placebo arm [18.4 months vs. 13.6 months; diff. 4.8]. The hazard of death is 37% lower among those who were in the enzalutamide group, as compared with those in the placebo group (HR 0.63, 95%CI 0.53 to 0.75, p<0.001).
- **Progression-free survival (PFS)**: Progression-free survival is observed to be longer in the enzalutamide arm than the placebo arm [8.3 months vs. 2.9 months; diff 5.4]. The hazard of disease progression is 60% lower among those who were in the enzalutamide group, as compared with those in the placebo group (HR 0.40, 95%CI 0.35 to 0.47, p<0.001).

Safety outcome:

- **Adverse events**: In general, the incidence of grade 3 or higher adverse events was lower in the enzalutamide arm compared to the placebo arm. However, grade 3 or higher fatigue, diarrhea, musculoskeletal pain, headache, and seizures occurred slightly more frequently in the enzalutamide arm.
  - Median time to any initial adverse event of grade 3 or higher was 8.4 months longer in the enzalutamide group than in the placebo group (12.6 vs. 4.2 months; diff 8.4).
  - [RR not specified in WHO and the actual study]

PREVAIL trial, 2014 [Phase III RCT]

Interventions: Enzalutamide (1st line)

randomized trial(s) or well-designed non-randomized trial(s)
  - 3 - **May be consistent:** *Few trials or only trials with few patients, whether randomized or not, with some variability in outcome*
  - 2 - **Expensive**

ESMO-MCBS V1.1 (2020) *(pp. 1128)*

- Enzalutamide [ESMO-MCBS v1.1 scores: 4] is recommended for asymptomatic / mildly symptomatic men with chemotherapy-naive mCRPC [I, A].
- In patients with mCRPC in the post-docetaxel setting, enzalutamide [ESMO-MCBS v1.1 score: 4] is recommended [I, A]
- The use of a second AR inhibitor (abiraterone acetate after enzalutamide or vice versa) is **NOT** recommended [II, D].
  - *Levels of Evidence (pp.20):
    - *I = Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity*
    - *II = Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity*
  - **Grades of Recommendation:*
    - *A = Strong evidence for efficacy with a substantial clinical benefit, strongly recommended*

	Comparator: Placebo *Efficacy outcomes:* ● **Overall survival (OS)**: Overall survival was longer in the enzalutamide arm compared to the placebo arm [32.4 months vs. 30.2 months; diff 2.2]. The hazard of death is 29% lower among those who were in the enzalutamide group compared with those in the placebo group. (HR 0.71, 95%CI, 0.60 to 0.84, p<0.001). *Safety outcome:* ● **Adverse events**: More grade 3 or higher adverse events were reported in the enzalutamide arm than the placebo arm. ○ [RR not specified in WHO and the actual study] **C. Observational Studies** *Pilon et al, 2017 [Retrospective study]* *Interventions: Enzalutamide (1st and 2nd line)* *Comparator: Abiraterone acetate in combination with prednisone* ● **Discontinuation of treatment**: Compared with patients initiated on enzalutamide, patients initiated on abiraterone acetate had significantly fewer discontinuations of mCRPC treatments. The hazard of disease progression or adverse events is 27% lower among those in the abiraterone acetate arm than enzalutamide (HR 0.73, 95%CI 0.59-0.91 p=0.004) and 39% lower than any prostate cancer treatments (HR 0.61, 95%CI 0.45-0.83, p=0.002) at three months and the result was maintained up to 24 months. ○ Median duration for abiraterone acetate: 18.3 months, p<0.001 ○ Median duration for enzalutamide: 14.2 months, p<0.001	○ *B = Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended* ○ *C = Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional* ○ *D = Moderate evidence against efficacy or for adverse outcome, generally not recommended* **National Kidney and Transplant Institute - Philippine CPG for the Diagnosis and Management of Prostate Cancer (2021):** *(pp. 30)* Enzalutamide was mentioned in the recommendations from other international CPGs, but no specific recommendation from NKTI on the use of enzalutamide was found.

II. Costing analysis

For the revised costing analysis, the direct medical cost items included were the: (1) reduced price offer for the cost of drug regimen (including the adjunct treatment of prednisone for abiraterone acetate); and the (2) cost of other direct medical cost items [cost of aspartate transaminase and alanine transaminase] at the third-party payer/government perspective. From these, the final costing outputs were the total cost of treatment regimen per patient and for all expected users. Regimens and resource utilization were consulted with the Philippine Society on Medical Oncology (PSMO). Costing analysis remains the same for first- or second-line treatment because the treatment regimen is the same across lines of treatment. The HTA Division assumed that treatment is given until disease progression for abiraterone acetate in combination with prednisone and enzalutamide, thus the duration of treatment used was one year for the costing analysis. For purposes of this costing analysis, we calculated the cost for one (1) year of treatment.

Abiraterone acetate in combination with prednisone and enzalutamide were compared directly to each other. Among the comparators in the studies included by the WHO, only bicalutamide and docetaxel are included in the Philippine National Formulary (PNF). However, these two medications are ***not specifically indicated*** for metastatic castration-resistant prostate cancer (mCRPC). In an official consultation with the Philippine Society for Medical Oncology (PSMO) and cancer experts from the HTAC, abiraterone acetate in combination with prednisone, and enzalutamide are being used for the treatment of mCRPC in the clinical setting. On the other hand, docetaxel and bicalutamide, which are drugs listed in the Philippine National Formulary for locally advanced or metastatic prostate cancer. are ***not being used*** for mCRPC in the clinical setting.

The unit costs of both abiraterone acetate and enzalutamide were from the price offered by local distributors (as mentioned by PSMO; Patheon Inc, Johnson & Johnson, Inc., Zuellig Pharma, Globo Asiatico Enterprises, Inc. for abiraterone acetate; Astellas Pharma Philippines, Inc. for enzalutamide) while the DPRI price was used for the adjunct treatment of prednisone specific to abiraterone acetate. The table below indicates the unit costs and assumptions used in the analysis.

The total cost of treatment which includes the drug regimen and administration per patient is **₱779,447.58** for abiraterone acetate in combination with prednisone and **₱984,040.00** for enzalutamide per year.

The total number of users were extrapolated using the estimated prevalence rate of individuals with mCRPC from PSMO and GLOBOCAN 2020 multiplied by the projected population in the Philippines for 2022 (PSA, 2021). From this, the computed total incurred costs for the government are as follows: **₱7.15B** for abiraterone acetate in combination with prednisone and **₱9.03 B** for enzalutamide. The cost savings accrued when abiraterone acetate is used over enzalutamide is estimated to be at **₱1.88 B**.

Parameter	INTERVENTION		Remarks / Assumptions	Reference
	Abiraterone acetate 250 mg	Enzalutamide 40 mg		
Part 1: Cost of drug regimen				
Unit cost of drug (A)	₱491.67	₱670.00		Reduced Price offer received from the appeals period *as of 10 October 2022*
Frequency of use per cycle (B)	4	4		PSMO Letter; MIMS (2022)
Duration of drug regimen (C)	365	365	For one year of treatment	
A*B*C=Total cost of drug regimen (D)	₱717,833.33	₱978,200.00		
Cost of Prednisone (*given concurrently with abiraterone acetate*)				
Unit cost of medicine (A)	₱2.45		Assume 1 yer of treatment	10 mg/tab DOH DPRI, 2020
Number of dosage units per unit time (B) (tabs / day)	1			PSMO, 2022, MIMS (2022)
Dosing regimen	one tab once a day			PSMO, 2022
Duration of treatment course (C) (in days)	365			
Total cost of intervention/comparator per patient per treatment course (D) =A*B*C	₱894.25			
TOTAL COSTING OF DRUG REGIMEN (E) [Intervention / Comparator (D)]	**₱718,727.58**	**₱978,200.00**		

Part 2: Other costs (e.g., cost of monitoring, cost of AE management)				
Other cost item: SGOT (AST) Test for 1 year				
Unit Cost of Item 1	₱180.00	₱180.00	Every two weeks for the first three months of treatment, and monthly thereafter: (52 weeks / 4 quarters) = 13 weeks per 3 months = 13/2 Weeks = ~7 SGOT 9 months * 1 = 9 SGOT 7 + 9 = 16	PhP 180 (SPMC rates from PSMO, 2022)
Number of tests needed per year	16	16		PSMO (2022)
Sub-Total	₱2,880.00	₱2,880.00		
Other cost item: SGPT (ALT) Test for 1 year				
Unit Cost of Item 2	₱185.00	₱185.00	Every two weeks for the first three months of treatment, and monthly thereafter: (52 weeks / 4 quarters) = 13 weeks per 3 months = 13/2 Weeks = ~7 SGPT 9 months * 1 = 9 SGPT 7 + 9 = 16	PhP 185 (SPMC rates from PSMO, 2022)
Number of tests needed per year	16	16		PSMO (2022)
Sub-Total	₱2,960.00	₱2,960.00		
Other cost item: Serum Potassium				
Unit Cost of Item 3	₱280.00		Every two weeks for the first three months of treatment, and monthly thereafter: (52 weeks / 4 quarters) = 13 weeks per 3 months = 13/2 Weeks = ~7 Serum K 9 months * 1 = 9 Serum K 7 + 9 = 16	PGH, 2020
Number of tests needed per year	16			PSMO (2022)
Sub-Total	₱4,480.00			

Other cost item: 2D Echocardiogram				
Unit Cost of Item 4	₱3,150.00		Every two weeks for the first three months of treatment, and monthly thereafter: (52 weeks / 4 quarters) = 13 weeks per 3 months = 13/2 Weeks = ~7 2D Echo 9 months * 1 = 9 2D Echo 7 + 9 = 16	PGH Schedule of Fees (2020)
Number of tests needed per year	16			PSMO (2022): Prior to treatment
Sub-Total	₱50,400			
Total Associated Costs per Individual				
TOTAL (E)	₱60,720.00	₱5,840.00	For one year of treatment	
Total Cost of Treatment Regimen for all users per year				
Total Cost of Treatment Regimen per patient (F=D+E)	**₱779,447.58**	**₱984,040.00**	For one year of treatment	
Incremental cost of treatment		-₱204,592.42		
Total Cost of Treatment Regimen for all users per year				
Expected number of patients who will use the drug (G)	9,178	9,178		
Total Cost of Treatment Regimen for all users (H=F*G)	**₱7,153,769,919.83**	**₱9,031,519,120.00**	For one year of treatment	
in billions	₱7.15	**₱9.03**		
Incremental cost of treatment (in billions)		₱-1.88		

III. Budget Impact Analysis

The budget impact analysis over a 3-year horizon for abiraterone acetate compared to enzalutamide was performed using data from sources indicated in Annex A. The prevalence and incidence of mCRPC in the Philippines for 2023 and 2024 were derived from the GLOBOCAN 2020 which was provided by the PSMO. The expected number of patients being given abiraterone acetate and enzalutamide was then estimated by multiplying the total 2022 projected population by the PSA based on the 2015 POPCEN, and the prevalence and incidence rates from the GLOBOCAN 2020. Both abiraterone acetate in combination with prednisone and enzalutamide are to be given to individuals with mCRPC until disease progression. The estimated total cost of treatment with abiraterone acetate and enzalutamide for 3 years is **₱31.88 B** and **₱40.25 B** respectively, with cost savings of **₱8.37 B** when abiraterone acetate in combination with prednisone is used over enzalutamide.

Year	Measure	Total projected population	Rate (prostate)	Rate (metastatic)	Rate (castration resistant)	New Users per year	Projected patients taking either abiraterone acetate in combination with PD or enzalutamide
2022	**Prevalence**	111,572,254	0.0004896	0.2	0.84	9178	9178
2023	**Incidence**	112,892,781	0.000234	0.2	0.84	4439	**13617**
2024	**Incidence**	114,163,719	0.000234	0.2	0.84	4489	**18106**

Parameter/Year	Projected No. of Individuals Taking Both Drugs	INTERVENTION		Remarks	References
		Abiraterone Acetate	Enzalutamide		
Cost per patient per year	[redacted]	₱779,447.58	**₱984,040.00**	Projected new cases of individuals with bone metastases based on GLOBOCAN data for the Philippines	N/A
2022	48.96/100000	₱7.15	**₱9.03**		Official PSMO Correspondence
2023	23.4/100000	₱10.61	**₱13.40**		
2024	23.4/100000	₱14.11	**₱17.82**		

TOTAL COST FOR 3 YEARS	**₱31.88**	**₱40.25**		N/A
Incremental Cost of Treatment for all users for 3 years		**₱8.37**		

IV. Summary of cost-effectiveness evidence and recommendations of the WHO

The cost-effectiveness studies were extracted from the WHO Selection and Use of Essential Medicines 2019 and 2021. However, the studies used in their review came from high-income countries (*and not locally adaptable*) and only one of these studies provided a direct comparison of the two drugs of interest.

Table 4.1. Cost-effectiveness studies from WHO

WHO approved indication in the EML	Remarks on Cost-effectiveness from WHO Review for Essential Medicines listing
First- or second-line for patients who have metastatic castration-resistant prostate cancer (mCRPC)	***Abiraterone Acetate*** Cost-effectiveness studies using prices from originator companies were reviewed by the WHO to assess the cost-effectiveness of abiraterone acetate compared to best supportive care. The application to WHO EML did not cite the data sources for the prices reported. The WHO noted that many of these studies were affiliated with pharmaceutical manufacturers at the time of publication. The cost-effectiveness of abiraterone acetate has been studied in the following: **[UK]** *UK NICE, 2016 [Technical appraisal of CEA]* *Intervention: Abiraterone acetate followed by docetaxel followed by best supportive care* *Comparator: Best supportive care followed by docetaxel followed by abiraterone acetate* *Quality assessment: N/A* An HTA review specific to the UK setting used a discrete event simulation model - a Weibull distribution for prediction equations model with an annual discount rate of 3.5%. In the cost-effectiveness analysis submitted by Janssen to UK NICE,

	the model tracked patients at an individual level through a sequence of treatments until they reached a maximum age of 100 years, to reflect a lifetime horizon. The perspective used was that of a publicly-funded health care system (i.e., UK NHS). The cost-effectiveness threshold used by the authors for ICER was **£30,000 per QALY**. The base-case ICER computed from the analysis was **£28,600 to £32,800 per QALY** gained. Their cost-effectiveness judgment for abiraterone acetate is ***inconclusive***, given that the computed base-case ICER range bypassed the CE threshold. **[Ireland]** *National Centre for Pharmacoeconomics, 2012 [Economic Evaluation]* *Intervention: Abiraterone Acetate with prior docetaxel chemotherapy* *Comparator: Best supportive care* *Quality assessment: N/A* An economic evaluation study specific to Ireland setting used a survival-based decision analysis model with three health states (i.e., progression-free, progressive disease, death), with an annual discount rate of 4%, in order to compare abiraterone acetate with supportive care. The report did *not specify the time horizon for the base-case analysis* but noted that extending the model to a four-year time horizon had the largest impact in their univariate sensitivity analysis. The perspective used was that of a publicly-funded health care system (i.e., Irish Health Service Executive [HSE]). The cost-effectiveness threshold used by the authors for ICER was **€ 45,000/QALY and € 20,000/QALY**. The base-case ICERs computed from the analysis were: ● *For abiraterone acetate plus prednisolone vs prednisolone monotherapy*; **€135,454/QALY or €142,367** / life years gained (LYG) ● *For abiraterone acetate plus prednisolone vs mitoxantrone plus prednisolone*: **€160,388/QALY or €130,708**/LYG. ● *For patients who received one prior chemotherapy regimen:* ○ ICER for abiraterone acetate plus prednisolone vs prednisolone monotherapy: **€118,031/QALY or €116,110/LYG.** ○ ICER for abiraterone acetate plus prednisolone vs mitoxantrone plus prednisolone: **€144,485/QALY or €108,737/LYG** All ICER values exceed the cost- effectiveness threshold levels considered by the HSE. Thus, the NCPE concluded the drug as "***not cost-effective*** *for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior docetaxel-based chemotherapy*".

	The reviews cited used the high originator prices and are of limited use when considering whether these medicines would be cost-effective in resource-limited settings, when and where the medicines available at lower prices from generic suppliers. Their analysis did not include studies from low- to middle-income countries.

First- or second-line for patients who have metastatic castration-resistant prostate cancer (mCRPC)	***ENZALUTAMIDE*** Cost-effectiveness studies using the price from the originator product were reviewed by the WHO to assess the cost-effectiveness of enzalutamide compared to abiraterone acetate and best supportive care. One cost-effectiveness appraisal by the UK NICE was accepted in the application: **[UK]** *UK NICE, 2014 [Technical appraisal of CEA]* *Intervention: Enzalutamide as a second line drug after docetaxel* *Comparator: Abiraterone acetate and supportive care* *Quality assessment: N/A* An HTA review specific to the UK used a state-transition Markov cohort model which simulated 3 states (*i.e., stable disease, progressive disease, and death*), with an annual discount rate of 3.5% and a time horizon of 10 years, and used the perspective of a publicly-funded health care system (i.e., NHS and personal social services). The cost-effectiveness threshold used by the appraisal is a maximum acceptable ICER of £50,000 per QALY. Base-ICER computed by the Evidence Review Group (ERG) was £22,604 per QALY for the comparison between enzalutamide and abiraterone acetate, and £45,500 per QALY for the comparison between enzalutamide and best supportive care. In an incremental analysis conducted by ERG, abiraterone acetate was extendedly dominated by enzalutamide (that is, a QALY is attained at a higher cost with abiraterone acetate than with enzalutamide because the ICER for abiraterone acetate compared with best supportive care [£102,751 per QALY gained] is higher than that for enzalutamide compared with best supportive care). In addition, ERG performed a subgroup analysis on the following: • ***For patients who had received one course of chemotherapy***. The NICE Appraisal Committee determined an incremental cost–effectiveness ratio (ICER) of **£22,600 per quality-adjusted life year (QALY)** gained for enzalutamide compared with abiraterone acetate.The Committee accepted that this ICER was associated with uncertainty, but it was satisfied that it would remain lower than **£30,000 per QALY** gained on balance. • ***For patients who had received two or more chemotherapy courses***. ICER estimated by the Evidence Review Group was £48,000 per QALY gained. The Committee agreed that enzalutamide would remain ***cost effective*** when the correct patient access scheme for abiraterone acetate is taken into account. While the evidence above shows favorable results, it was conducted in a high-income country. The only aspect of the CE relevant to LMICs is the unit price of enzalutamide in India.

No CEA studies can be adopted because no CEA study included by the WHO is conducted in an Asian LMIC. Hence, scoping of CEA studies was done. The scoping review yielded 15 results, of which two studies were reviewed by the HTAC. ***These two studies, however, could not be adopted because these were conducted in a non-Asian UMIC setting.***

Table 4.2. Cost-effectiveness studies from scoping

Indication in the scoped studies	Remarks on Cost-effectiveness from WHO Review for Essential Medicines listing
Second-line for patients who have metastatic castration-resistant prostate cancer (mCRPC)	**[Mexico]** Gay, Schultz, & Braun, 2021 *[Cost-effectiveness evaluation]* *Intervention: Enzalutamide as a second line drug after docetaxel* *Comparator: Abiraterone acetate in combination with prednisone* A cost-effectiveness evaluation specific to Mexico used a three-health state Markov Model with an undisclosed discount rate and a time horizon of three years. The perspective used was that of a publicly-funded health care system (*i.e., Mexican Public Healthcare System*). A sensitivity analysis was performed which showed that the cost of drugs and length of the risk-sharing agreement were the most relevant variables. The willingness-to-pay threshold used by the authors for ICER was **MX$167,583**. For the base-case scenario, the results showed a 0.21-year increase in overall survival in favor of enzalutamide and an incremental cost of MX$3435. This represents an incremental cost-effectiveness ratio of **MX$16,197** per life-year gained. Enzalutamide is the more cost-effective alternative treatment for patients with mCRPC after progression on docetaxel.
Second-line for patients who have metastatic castration-resistant prostate cancer (mCRPC)	**[Costa Rica]** Obando et al., 2014 *[Cost-effectiveness evaluation]* *Intervention: Abiraterone acetate in combination with prednisone (A-P)* *Comparator: Cabazitaxel in combination with prednisone (C-P)* A cost-effectiveness evaluation specific to Costa-Rica used a three-health state cohort simulation Markov Model with an annual discount rate of 5% and a time horizon of 10 years. The perspective used was that of a publicly-funded health care system (*i.e. Public System of Health of Costa Rica*). A probabilistic sensitivity analysis was performed which evaluated uncertainty surrounding the parameters. A-P resulted in 0.79 QALY and 1.35 life years (LY) per patient, while C-P resulted in 0.71 QALY and 1.28 LY. The probabilistic sensitivity analysis showed that A-P was dominant and incurred more cost savings in most scenarios.

V. Recommendations

- **Abiraterone acetate**

  The **HTAC recommends the government financing of abiraterone acetate (250mg tablet)** in combination with **prednisone (PD) as first-line treatment or second-line treatment for metastatic castration-resistant prostate cancer (mCRPC) through its inclusion in the PNF** due to the following:

  - Abiraterone acetate in combination with PD is part of the standard of care for treatment of mCPRC as reported in the Philippine Clinical Practice Guideline for the Diagnosis and Management of Prostate Cancer developed by National Kidney and Transplant Institute (NKTI).

  - Evidence shows that the use of abiraterone acetate in combination with PD has better efficacy compared to placebo, prednisolone and bicalutamide in terms of prolonging the overall survival (3.9 to 4.2 months), progression-free survival (PFS) and reducing prostate-specific antigen (PSA) progression.

  - Abiraterone acetate in combination with PD has a favorable safety profile, given that it has lower incidence of grade > 3 adverse events. However, HTAC noted that it has a higher incidence of cardiac disorders, increased alanine aminotransferase and hypertension when compared to placebo.

  - Abiraterone acetate in combination with PD has lower associated medical cost and total cost per treatment compared to enzalutamide. The total cost of treatment regimen per patient for using abiraterone acetate in combination with prednisone will cost **₱779,447.58** while using enzalutamide will cost **₱984,040.00**. The government will incur **₱31.88 B** for implementing abiraterone acetate in combination with PD while enzalutamide will cost **₱40.25 B**. The total cost savings for implementing abiraterone acetate in combination with PD compared to enzalutamide is **₱8.37 B** based on 3-year budget impact analysis.

  - The cost-effectiveness of abiraterone acetate in combination with PD ***cannot be ascertained*** due to lack of evidence that could be adapted in the local setting.

- **Enzalutamide**

  The HTAC **does not recommend the government financing and inclusion of *enzalutamide (40 mg soft gel capsule)* for mCPRC** in the Philippine National Formulary (PNF). Although enzalutamide shows better efficacy compared to placebo, prednisolone, and bicalutamide as well as a favorable safety profile compared to placebo, the costing and budget impact analyses show that the use of enzalutamide is generally expensive. The total cost of treatment regimen per patient is **₱984,040.00** and the government will need to spend **₱40.25 B** to implement enzalutamide. On the other hand, the government may opt to use abiraterone acetate in combination with PD as a cheaper alternative for the treatment of patients with mCRPC.

  Moreover, the cost effectiveness of enzalutamide ***cannot be ascertained*** due to lack of evidence that could be adapted in the local setting.

Annex A: Sources of Cost Data

Data	Source	Agency/body	Disaggregation	Website
Cost item and value				
Public drug tender prices of DOH and DOH Hospitals	Drug Price Reference Index (DPRI)	DOH-Pharmaceutical Division	Geographic location, hospital	https://dpri.doh.gov.ph/
Wholesale, distribution and retail prices of essential drugs	Electronic Drug Price Monitoring System (EDPMS) and Drug Price Watch	DOH-Pharmaceutical Division	Geographic location, type of drug outlet	https://dpw.doh.gov.ph/
Hospital services billing	Philhealth case rates for medical and surgical procedures	Philhealth		https://www.philhealth.gov.ph/benefits/ Medical procedures: https://www.philhealth.gov.ph/circulars/2017/annexes/0019/AnnexA-MedicalCaseRates.pdf Surgical procedures: https://www.philhealth.gov.ph/circulars/2015/annexes/circ08_2014/Annex2_ListofProcedureCaseRatesRevision1.pdf
Philhealth Z-benefit packages	Database listing cost of catastrophic benefit packages reimbursed by PHIC	Philhealth		https://www.philhealth.gov.ph/benefits/

Salaries of health professionals	Salary Grade table of the Department of Health	DOH	Type of health professional	Available upon request
Health expenditure program	UHC Medium-term Health Expenditure Program	DOH	Health program, priority disease, expenditure classification	https://www.doh.gov.ph/sites/default/files/publications/MTEP%202019-2022%20Update%20for%20CY%202020%20Budget%20Preparation.pdf
Resource utilization/service use				
Coverage of essential primary care services	Field health Service Information system (FHSIS) National Demographic and Health Survey	DOH-Epidemiology Bureau	Age, gender, geographic location	https://www.doh.gov.ph/sites/default/files/publications/FHSIS_Annual_2018.pdf https://psa.gov.ph/sites/default/files/PHILIPPINE%20NATIONAL%20DEMOGRAPHIC%20AND%20HEALTH%20SURVEY%202017_new.pdf
Water and sanitation	National Demographic Health Survey	Philippine Statistics Authority (PSA)	Age, gender, geographic location, socioeconomic status	https://psa.gov.ph/sites/default/files/PHILIPPINE%20NATIONAL%20DEMOGRAPHIC%20AND%20HEALTH%20SURVEY%202017_new.pdf
Hospital services	Philhealth claims database	Philhealth	Age, gender, diagnosis (ICD-10), geographic location	Available upon request in PhilHealth
Hospital and pharmacy drug sales data	National sales audit (NSA)	IQVIA	Type of drug outlet; Company, innovator/generic; geographic location	Available upon request https://www.iqvia.com/locations/philippines
Public drug procurement data	Drug price reference index	DOH	Geographic location, hospital	https://dpri.doh.gov.ph/