

**PROPOSAL
FOR THE INCLUSION OF ENZALUTAMIDE
IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR
THE TREATMENT OF METASTATIC CASTRATION RESISTANT
PROSTATE CANCER**

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List of Tables and Figures

Table 1: Summary of relevant randomized clinical trials studying enzalutamide	9
Table 2: Characteristic of clinical trials included in the meta-analysis	10
Figure 1: Forest plot for the hazard ratio of the overall survival	11
Figure 2: Forest plot for the hazard ratio of the progression free survival	11
Table 3: Key Efficacy and Safety Information about Three Products Used for Treatment of mCRPC After Docetaxel Therapy (Reviewer Benefit-Risk Evaluation Table)	15
Table 4: Prices for Xtandi and Gross National Income in Different Countries	17
Table 5: US FDA drug master files (DMF) for the supply of enzalutamide APIs	30

1. Summary statement of the proposal for inclusion, change or deletion.

Enzalutamide (sold by Astellas under trade name Xtandi, sold by Glenmark under trade name Glenza) is indicated to treat metastatic castration-resistant prostate cancer (CRPC) and is a second generation competitive androgen receptor inhibitor. While there are other treatments used to treat CRPC, enzalutamide is far less invasive as it is administered via daily oral tablets, and has a low pill burden compared to the one other oral tablet CRPC treatment (abiraterone acetate).

The first registration was by Astellas, for Xtandi. The patent protection for Xtandi varies from country to country. At least one generic supplier, Glenmark, has entered the market.

With recent clinical trials reporting better prostate cancer control when enzalutamide is used in chemotherapy naive CRPC cases or in combination with other agents, it is expected that this drug will soon be prescribed to an even wider subset of patients. The listing of enzalutamide is being sought for the core Essential Medicines List.

2. Relevant WHO technical department and focal point (if applicable).

3. Name of the organization(s) consulted and/or supporting the application

Knowledge Ecology International (KEI)

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN: Enzalutamide

ATC Code: L02BB04

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Enzalutamide (originator trade name Xtandi) is sold in 40 mg capsules, and is prescribed for daily use for as long as the drug continues to be effective and tolerated. The typical dose of enzalutamide for the treatment of prostate cancer is 4 x 40 mg per day.

Enzalutamide is available from Astellas at very high prices, but also from several generic suppliers. Glenmark has introduced a generic version in India under the trade name Glenza. CIPLA sells enzalutamide under the trade name of CAPMIDE. Dr. Reddy's sells enzalutamide under the trade name Azel. Intas Pharmaceuticals sells enzalutamide under the trade name Enzamide. BDR Pharmaceuticals sells enzalutamide under the trade name Bdenza.

CIPLA offers Rs 4,800/

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

The request for inclusion is for the prostate cancer drug enzalutamide.

**7. Treatment details (requirements for diagnosis, treatment and monitoring).
The application should specify the proposed therapeutic dosage regimen and duration of treatment.**

Enzalutamide is indicated as first-line therapy for the treatment of patients with metastatic castration-resistant prostate cancer who have not received chemotherapy or who have previously received docetaxel and is also indicated for the treatment of non-metastatic castration-resistant prostate cancer.

Enzalutamide is sold in 40 mg capsules. The daily dose is four capsules (160 mg) orally once daily with or without food. If grade 3 or higher side effects occur or if the patient develops toxicity, enzalutamide should be stopped for 1 week or until symptoms subside to grade 2 or less. Notably, enzalutamide strongly interacts with CYP2C8 inhibitors, therefore if coadministration cannot be avoided, the dose of enzalutamide should be reduced to 80 mg once daily.

Enzalutamide is prescribed for daily use for as long as the drug continues to be effective and tolerated.

8. Information supporting the public health relevance.

Prostate cancer has not been linked to specific oncogenes and occurs through a combination of several genetic, environmental and lifestyle factors. Generally, the early stages of prostate cancer are slow growing and many go undiagnosed until a clinical autopsy. However, it is the second most common cancer in men and the fourth most common cancer overall.¹ In 2018, approximately 1.3 million men were diagnosed with prostate cancer.²

When patients are diagnosed with prostate cancer, if they are treated early and tumors are localized, the prognosis is often favorable. However, some patients will relapse which, in nearly all cases, leads to castration resistant prostate cancer (CRPC). At the CRPC stage, the disease is no longer responsive to androgen deprivation therapy (ADT), thus limiting the available treatment options with a greater disease burden. Access to second generation

¹ Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A. and Jemal, A. (2018), Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68: 394-424. doi:10.3322/caac.21492

² Ibid.

therapies such as enzalutamide becomes critical to extending the life of the patient, and allowing patients to live an improved quality of life.

9. Review of benefits: summary of evidence of comparative effectiveness.

Enzalutamide is a second generation competitive androgen receptor inhibitor. It antagonises the AR signaling by preventing the ligand from binding to the AR, and downstream events such as nuclear translocation and DNA binding.³ By acting directly on this pathway, enzalutamide interferes with a crucial element that contributes to cancer progression. Enzalutamide has a half-life of 5.8 days and is metabolized by CYP2C8 and CYP3A4 and the drug steady state is reached in 28 days.⁴

There are currently six treatments being used to treat CRPC. Enzalutamide has several advantages over the other treatments. Abiraterone acetate has a greater pill burden, and the other four treatments are invasive and require I.V. administration, leukapheresis, or the use of radiopharmaceuticals.

Enzalutamide and abiraterone acetate are the only daily oral tablets.

Enzalutamide has certain advantages over abiraterone acetate, including a lighter pill burden, a smaller daily dose of 160 milligrams (4 x 40mg) as opposed to 1000 milligrams (4 x 250mg), which may lead to lower per unit manufacturing costs for enzalutamide once there are additional generic manufacturers and greater economies of scale and competition. Enzalutamide also does not need to be taken in combination with prednisone.

For some patients, enzalutamide is better tolerated and has a more favorable toxicity profile than abiraterone acetate.

Quality of life is also more frequently improved and median time to deterioration is significantly longer with enzalutamide compared to placebo, as reported by patients in functional assessment questionnaires administered during clinical trials.⁵

In 2018 the US Food and Drug Administration (FDA) expanded the use of enzalutamide to first line treatment for both non-metastatic and metastatic castration-resistant prostate cancer (CRPC) based on a randomized, multicenter clinical trial (PROSPER, NCT020032924), that randomized 1,401 patients 2:1 to take either enzalutamide 160 mg orally once daily or placebo orally once daily.⁶ Currently enzalutamide (FDA approved,

³ Mostaghel EA, Montgomery B, Nelson PS. Castration-resistant prostate cancer: targeting androgen metabolic pathways in recurrent disease. *Urol Oncol.* 2009 May-Jun;27(3):251-7.

⁴ Ramadan WH, Kabbara WK, Al Basiouni Al Masri HS. Enzalutamide for patients with metastatic castration-resistant prostate cancer. *Onco Targets Ther.* 2015 Apr 17;8:871-6.

⁵ Rodriguez-Vida A *et al.* Enzalutamide for the treatment of metastatic castration-resistant prostate cancer. *Drug Des Devel Ther.* 2015 Jun 29;9

⁶ Hussain, M., Fizazi, K., Saad, F., Rathenborg, P., Shore, N., Demirhan, E. *et al.* PROSPER: A phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with

2012), abiraterone acetate (FDA approved, 2011), and docetaxel (trade name Taxotere, FDA approved, 2004) are the top three prescribed drugs in first line metastatic CRPC treatment.⁷ However, using docetaxel before enzalutamide has been shown to decrease the effectiveness of enzalutamide by a median overall survival of 15.8 months.⁸ Abiraterone acetate and enzalutamide are both oral therapeutics that target the androgen signaling axis, and although prospective head-to-head comparison clinical trials are still ongoing, retrospective analysis data have indicated that there is a clear clinical cross-resistance between the two drugs.⁹ In fact, in a study conducted by Schrader et al., it was reported that 48.6% of patients who previously took abiraterone acetate and docetaxel were completely resistant to enzalutamide.¹⁰ Based on the susceptibilities of individual patients, oncologists may want to prescribe enzalutamide over abiraterone acetate for its toxicity profile or to patients who cannot tolerate low-dose steroids.⁶

With recent and ongoing clinical trials reporting better prostate cancer control when enzalutamide is used in chemotherapy-naïve CRPC cases or in combination with other agents, it is expected that this drug will soon be prescribed to a wider subset of patients.^{11,12} In fact, experts say that in the next 3 years all CRPC patients will progress to enzalutamide or abiraterone acetate.¹⁴ In July 2018, the US FDA approved an expanded indication for enzalutamide to include the treatment of non-metastatic castration-resistant prostate cancer, making it the first and only FDA-approved oral treatment for both non-metastatic and metastatic CRPC.¹⁵

Identification of clinical evidence

nonmetastatic castration-resistant prostate cancer (M0 CRPC). *Journal of Clinical Oncology* 36, no. 6_suppl (February 2018) 3-3.

⁷ Flaig TW *et al.* Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. *Cancer Med.* 2015 Dec 29.

⁸ Crawford ED *et al.* Treating Patients with Metastatic Castration Resistant Prostate Cancer: A Comprehensive Review of Available Therapies. *J Urol.* 2015 Dec;194(6):1537-47.

⁹ Zhang T. *et al.* Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistant prostate cancer. *Expert Opin Pharmacother.* 2015 Mar;16(4):473-85.

¹⁰ Schrader AJ *et al.* Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *Eur Urol.* 2014 Jan;65(1):30-6.

¹¹ Scher HI *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med.* 2012 Sep.

¹² Lortol Y *et al.* Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol.* 2015 May.

¹³ Daniel Peter Petrylak, Charles G. Drake, Christopher Michael Pieczonka, John M. Corman, Jorge A. Garcia, Curtis Dunshee, Tim Van Mouwerik, Robert C. Tyler, Nancy N. Chang, and David Quinn. Overall survival and immune responses with sipuleucel-T and enzalutamide: STRIDE study. *Journal of Clinical Oncology* 2018 36:6_suppl, 246-246

¹⁴ Zhang T. *et al.* Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistant prostate cancer. *Expert Opin Pharmacother.* 2015 Mar;16(4):473-85.

¹⁵ Astellas. "U.S. FDA Approves XTANDI® (enzalutamide) for the Treatment of Men with Non-Metastatic Castration-Resistant Prostate Cancer (CRPC)." News Release. 13 July 2018. <https://newsroom.astellas.us/2018-07-13-U-S-FDA-Approves-XTANDI-R-enzalutamide-for-the-Treatment-of-Men-with-Non-Metastatic-Castration-Resistant-Prostate-Cancer-CRPC>

We searched systematic reviews and technology assessment reports, and meta-analyses of controlled clinical trials involving enzalutamide in at least one arm were searched on the Database of Abstracts of Reviews of Effectiveness. Additional searches for relevant reviews were undertaken in Clinical Evidence (CE), PubMed, and the Cochrane Database of Systematic Reviews. Unfortunately, there were no meta-analyses reporting exclusively on enzalutamide-containing trials. However, meta-analyses were found comparing enzalutamide, abiraterone acetate (although not head-to-head) and other therapies in various treatment exposure settings. We summarize below key randomized controlled trials (RTC) for enzalutamide.

Summary of available data

The phase III PROSPER trial supported the 2018 expanded indication for enzalutamide to non-metastatic CRPC. The phase III trial demonstrated that the use of enzalutamide plus androgen deprivation therapy (ADT), “significantly reduced the risk of developing metastasis or death compared to ADT alone in men with non-metastatic CRPC.”¹⁶

The results of the phase III PROSPER trial were published in the New England Journal of Medicine (NEJM) in 2018 and showed that among men with non-metastatic CRPC with a rapidly rising PSA level, treatment with enzalutamide led to a clinically meaningful and significant lower risk of death (71%) than placebo. Per the 2018 NEJM article:

“A total of 1401 patients (median PSA doubling time, 3.7 months) underwent randomization. As of June 28, 2017, a total of 219 of 933 patients (23%) in the enzalutamide group had metastasis or had died, as compared with 228 of 468 (49%) in the placebo group. The median metastasis-free survival was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (hazard ratio for metastasis or death, 0.29; 95% confidence interval, 0.24 to 0.35; $P<0.001$). The time to the first use of a subsequent antineoplastic therapy was longer with enzalutamide treatment than with placebo (39.6 vs. 17.7 months; hazard ratio, 0.21; $P<0.001$; such therapy was used in 15% vs. 48% of patients) as was the time to PSA progression (37.2 vs. 3.9 months; hazard ratio, 0.07; $P<0.001$; progression occurred in 22% vs. 69% of patients). At the first interim analysis of overall survival, 103 patients (11%) receiving enzalutamide and 62 (13%) receiving placebo had died. Adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo.”¹⁷

In 2020 the NEJM published a final analysis of the overall survival in the PROSPER trial. The final analysis of the PROSPER trial showed that treatment with enzalutamide was

¹⁶ Astellas. “U.S. FDA Approves XTANDI® (enzalutamide) for the Treatment of Men with Non-Metastatic Castration-Resistant Prostate Cancer (CRPC).” News Release. 13 July 2018. Retrieved January 15, 2019 from: <https://newsroom.astellas.us/2018-07-13-U-S-FDA-Approves-XTANDI-R-enzalutamide-for-the-Treatment-of-Men-with-Non-Metastatic-Castration-Resistant-Prostate-Cancer-CRPC>

¹⁷ Hussain, Maha; Fizazi, Karim; Saad, Fred; et al. “Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer.” New England Journal of Medicine. 28 June 2018. 378:2465-2474. doi: 10.1056/NEJMoa1800536

associated with a significant 27% lower risk of death than placebo in men with nonmetastatic, castration-resistant prostate cancer. According to the 2020 NEJM article:

“As of October 15, 2019, a total of 288 of 933 patients (31%) in the enzalutamide group and 178 of 468 (38%) in the placebo group had died. Median overall survival was 67.0 months (95% confidence interval [CI], 64.0 to not reached) in the enzalutamide group and 56.3 months (95% CI, 54.4 to 63.0) in the placebo group (hazard ratio for death, 0.73; 95% CI, 0.61 to 0.89; $P = 0.001$). The exposure-adjusted rate of adverse events of grade 3 or higher was 17 per 100 patient-years in the enzalutamide group and 20 per 100 patient-years in the placebo group. Adverse events in the enzalutamide group were consistent with those previously reported for enzalutamide; the most frequently reported events were fatigue and musculo-skeletal events.”¹⁸

The ENZAMET clinical trial (NCT02446405) was a phase III, randomized, open label clinical trial comparing testosterone suppression plus either open-label enzalutamide with a standard nonsteroidal antiandrogen therapy (standard-care group). The study found that enzalutamide was associated with significantly longer progression-free and overall survival than standard care in men with metastatic, hormone-sensitive prostate cancer receiving testosterone suppression. The enzalutamide group had a higher incidence of seizures and other toxic effects, especially among those treated with early docetaxel. According to the study, which was recently reported in the NEJM:

“A total of 1125 men underwent randomization; the median follow-up was 34 months. There were 102 deaths in the enzalutamide group and 143 deaths in the standard-care group (hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.86; $P = 0.002$). Kaplan–Meier estimates of overall survival at 3 years were 80% (based on 94 events) in the enzalutamide group and 72% (based on 130 events) in the standard-care group. Better results with enzalutamide were also seen in PSA progression-free survival (174 and 333 events, respectively; hazard ratio, 0.39; $P < 0.001$) and in clinical progression-free survival (167 and 320 events, respectively; hazard ratio, 0.40; $P < 0.001$). Treatment discontinuation due to adverse events was more frequent in the enzalutamide group than in the standard-care group (33 events and 14 events, respectively). Fatigue was more common in the enzalutamide group; seizures occurred in 7 patients in the enzalutamide group (1%) and in no patients in the standard-care group.”¹⁹

¹⁸ Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, Ferreira U, Efstathiou E, Madziarska K, Kolinsky MP, Cubero DIG, Noerby B, Zohren F, Lin X, Modelska K, Sugg J, Steinberg J, Hussain M; PROSPER Investigators. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2020 Jun 4;382(23):2197-2206. doi: 10.1056/NEJMoa2003892. Epub 2020 May 29. PMID: 32469184.

¹⁹ Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, Coskinas X, Frydenberg M, Hague WE, Horvath LG, Joshua AM, Lawrence NJ, Marx G, McCaffrey J, McDermott R, McJannett M, North SA, Parnis F, Parulekar W, Pook DW, Reaume MN, Sandhu SK, Tan A, Tan TH, Thomson A, Tu E, Vera-Badillo F, Williams SG, Yip S, Zhang AY, Zielinski RR, Sweeney CJ; ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med*. 2019 Jul 11;381(2):121-131. doi: 10.1056/NEJMoa1903835. Epub 2019 Jun 2. PMID: 31157964.

The AFFIRM clinical trial (NCT00974311) was a phase III randomized, double-blind, placebo-controlled, multicenter trial to study the efficacy and safety of enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC) who had previously taken docetaxel.²⁰ A total of 1,199 adult males, ranging from 41 to 92 years, were randomized in a 2:1 ratio, where 800 participants received a dose of 160mg of enzalutamide once a day, 399 participants received a placebo, and all continued on androgen deprivation therapy. The primary endpoint measured was overall survival (OS) and two secondary outcomes were progression-free survival (PFS) and PSA-level response (“reduction in the PSA level from baseline by 50% or more or 90% or more”).¹² OS was found to be 18.4 months for enzalutamide and 13.6 months for the control arm [Hazard ratio (HR) 0.63; 95% CI 0.53–0.75; $p < 0.001$]. PFS was 8.3 for enzalutamide versus 2.9 for the placebo [HR 0.40; 95% 0.35–0.47; $p < 0.001$]. 54% of patients in the treatment arm experienced 50% or greater decrease in PSA levels compared to only 2% in the control arm ($p < 0.001$). Overall there were few adverse events (AE), but grade ≥ 3 events relating to fatigue (6% vs 7%), diarrhea (1% vs $>1\%$), musculoskeletal pain (1% vs $>1\%$), headache (1% vs. 0%) and seizures (0.6% vs 0%) occurred slightly more often in the enzalutamide arm. However, AE causing death occurred in 3% in the enzalutamide arm and 4% in the placebo arm. The trial was stopped at the interim analysis having demonstrated an improved OS. The result from the AFFIRM trial formed the basis for the initial FDA approval.

The PREVAIL trial investigated enzalutamide in a first-line setting in mCRPC who had not yet received chemotherapy. This pivotal phase III, placebo controlled clinical trial, enrolled 1,717 patients that were randomized 1:1. As with AFFIRM, PREVAIL was halted after interim results were collected due to the benefits displayed by enzalutamide. Less deaths were reported in the treatment arm at 28% vs 35% for placebo [HR: 0.71, 95% CI: [0.60–0.84]; $p < 0.001$]. Based on the results from this trial, the FDA approved enzalutamide for use in first-line therapy for mCRPC.

Table 1: Summary of relevant randomized clinical trials studying enzalutamide

Trial	Arms	Study design	n	Primary outcome	PRO instruments used
AFFIRM ¹⁵	Enzalutamide vs placebo (mCRPC post-chemo)	Phase III	1,199	OS; mOS 18.4 months vs 13.6 months (HR: 0.63, $p < 0.001$)	FACT-P, BPI-SF
PREVAIL ¹⁶	Enzalutamide vs placebo (mCRPC pre-chemo)	Phase III	1,717	OS, radiographic PFS; deaths 28% vs 35% (HR: 0.71, $p < 0.001$)	FACT-P, EQ-5D, BPI-SF
STRIVE ¹⁷	Enzalutamide vs bicalutamide (CRPC)	Phase II	396	PFS; in mCRPC 16.5 vs 5.5 months (HR: 0.24, $p < 0.001$)	FACT-P
TERRAIN ¹⁸	Enzalutamide vs bicalutamide (mCRPC)	Phase III	375	PFS; 15.7 vs 5.8 months (HR: 0.44, $p < 0.0001$)	FACT-P, BPI-SF

Abbreviations: PRO, patient-related outcome; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; FACT-P, Functional Assessment of Cancer Therapy-Prostate; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; BPI-SF, Brief Pain Inventory – Short Form; mOS, median overall survival.

Source: Luo and Graff, 2016

Roviello et al. performed a meta-analysis by pooling data from eight studies looking at novel androgen receptor pathway targeted agents.²¹ Four trials contained enzalutamide in one

²⁰ Scher HI et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012 Sep 27;367(13):1187-97.

²¹ Roviello G, Sigala S, Sandhu S, Bonetta A, Cappelletti MR, Zanotti L, Bottini A, Sternberg CN, Fox SB, Generali D. Role of the novel generation of androgen receptor pathway targeted agents in the

arm, two trials investigated abiraterone acetate and two other trials investigated orteronel. Abiraterone acetate is a steroidal androgen synthesis inhibitor and acts on CYP17A1. Abiraterone acetate must be taken in combination with prednisone and together they are also indicated as treatment for mCRPC. Orteronel is a still experimental drug being developed by Takeda Pharmaceuticals and Millennium Pharmaceuticals. Orteronel is an androgen synthesis inhibitor similar to abiraterone acetate. Table 2 (below) summarizes the clinical trials used in this analysis.

Table 2: Characteristic of clinical trials included in the meta-analysis

Trials	Treatment arms	Cases	End-points	Setting	Jadad Score
AFFIRM [4]	Enzalutamide versus placebo	800 399	Primary: overall survival Secondary: time to prostatic antigen specific (PSA) progression, proportion of patients with a decrease in PSA of 50%, radiographic progression-free survival, and time to the first skeletal-related event	Post-chemotherapy	5
COU-AA-301 [3]	Abiraterone + prednisone versus placebo + prednisone	797 398	Primary: overall survival Secondary: time to PSA progression, radiographic progression-free survival, and time to the first skeletal-related event, PSA response rate ($\geq 50\%$ decline in PSA level from baseline)	Post-chemotherapy	5
COU-AA-302 [5]	Abiraterone + prednisone versus placebo + prednisone	546 542	Primary: radiographic progression-free survival and overall survival Secondary: times to opiate use for cancer-related pain, time to initiation of cytotoxic chemotherapy, time to a decline in ECOG performance status, and time to PSA progression, PSA response rate ($\geq 50\%$ decline in PSA level from baseline), rate of objective response according to RECIST criteria, and health-related quality of life, as measured by means of patients' reports of pain and functional status.	Chemotherapy-naïve	5
ELM-PC 4 [8]	Orteronel + prednisone versus placebo + prednisone	781 789	Primary: radiographic progression-free survival and overall survival Secondary: safety assessment, time to initiation of cytotoxic chemotherapy, frequency of skeletal related events, time to PSA progression, duration of PSA response, PSA response rate ($\geq 50\%$ and 90% decline in PSA level from baseline), rate of objective response according to RECIST criteria	Chemotherapy-naïve	5
ELM-PC 5 [7]	Orteronel + prednisone versus placebo + prednisone	734 365	Primary: overall survival Secondary: time to PSA progression, radiographic progression-free survival, PSA response rate ($\geq 50\%$ decline in PSA level from baseline) and pain response at 12 weeks, safety	Post-chemotherapy	5
PREVALE [6]	Enzalutamide versus placebo	872 875	Primary: radiographic progression-free survival and overall survival Secondary: time until the initiation of cytotoxic chemotherapy, the time until the first skeletal-related event, the best overall soft-tissue response, the time until PSA progression, and a decline in the PSA level of 50% or more from baseline. Prespecified exploratory end-points included quality of life, as measured with the use of the Functional Assessment of Cancer Therapy–Prostate (FACT-P) scale, and a decline in the PSA level of 90% or more from baseline.	Chemotherapy-naïve	5
TERRAIN [17]	Enzalutamide versus bicalutamide	183 189	Primary: progression-free survival Secondary: safety, investigator-review-based progression-free survival, time to PSA progression, PSA response by week 13, and best PSA response	Chemotherapy-naïve	4
STRIVE [18]	Enzalutamide versus bicalutamide	198 198	Primary: progression-free survival. Secondary: time to PSA progression, PSA response $\geq 50\%$, radiographic progression-free survival, best overall soft tissue response, time to a 10-point or greater decline of the global score of the FACT-P questionnaire, and PSA response of $\geq 90\%$	Chemotherapy-naïve	4

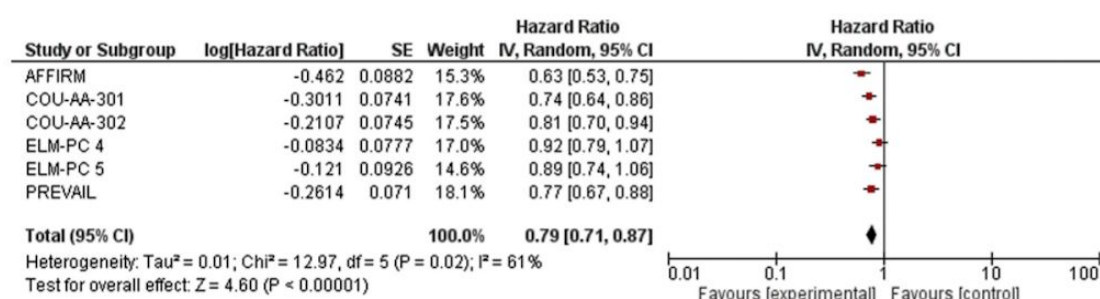
ECOG, Eastern Cooperative Oncology Group.

Source: Roviello et al.

management of castration-resistant prostate cancer: A literature based meta-analysis of randomized trials. Eur J Cancer. 2016 Jul;61:111-21.

Of the clinical trials that study enzalutamide, only AFFIRM and PREVAIL reported OS. Since the heterogeneity between the clinical trial was slightly above average ($I^2 = 60\%$), a random effects model was employed to calculate the hazard ratio (HR). The OS hazard ratios were similarly significant for enzalutamide and abiraterone (Figure 10-1). Orteronel reported OS HR, however, the hazard ratios were not significant.

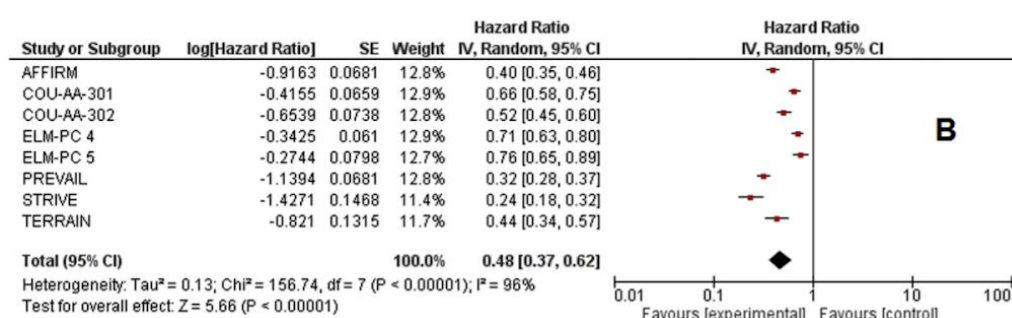
Figure 1: Forest plot for the hazard ratio of the overall survival



Source: Roviello et al.

As for the PFS, the HR ratios indicated that enzalutamide was favored over abiraterone acetate (Figure 2). Again, a random effects model was used since there was high heterogeneity among the trials ($I^2 = 96\%$). Furthermore, the HR for adverse events of grade 3 or higher were not significant for all clinical trials except AFFIRM, although AFFIRM presented only slightly less AE risk than the control arm.

Figure 2: Forest plot for the hazard ratio of the progression free survival



Source: Roviello et al.

Comparisons of enzalutamide and abiraterone acetate

Recent studies have compared the clinical efficacy; medication adherence, treatment patterns, and dose reductions; and the duration of treatment in patients taking enzalutamide and abiraterone acetate. This section summarizes three of those studies.

One study,²² funded by the Seoul National University Hospital Research Fund and with no conflict of interests declared, performed a network meta-analysis of randomized controlled trials (RCTs). This study included eight RCTs for men with mCRPC treated with one of the AR targeting agents: enzalutamide, abiraterone acetate, or orteronel. The primary endpoint was overall survival (OS), while the secondary end points were progression-free survival (PFS), prostate-specific antigen (PSA) responsiveness, time to PSA progression, time to first skeletal-related events (SRE), and adverse events (AEs). Pairwise meta-analysis and network meta-analysis were conducted to obtain direct and indirect evidence, respectively.

This study found that:

“[...] enzalutamide was the most efficacious drug (HR = 0.71), followed by abiraterone (HR = 0.78). Orteronel did not show a significant effect on OS (HR = 0.90). Enzalutamide was also the most efficacious drug for secondary endpoints, particularly PFS (HR = 0.56) and time to PSA progression (HR = 0.20). Additionally, AE risks did not differ between enzalutamide and control arms, suggesting that enzalutamide is safe for clinical use in mCRPC patients. Based on these pieces of evidence together, enzalutamide can be the most efficacious and safe agents for patients with mCRPC and abiraterone can be the second most efficacious drug. Conversely, orteronel had both the least efficacy and was associated with higher AEs. This is the key finding of our study.”

Another study,²³ funded by Janssen Scientific Affairs, conducted retrospective analyses using the Truven Health MarketScan research databases among patients with metastatic CRPC who initiated treatment with enzalutamide or abiraterone acetate between October 1, 2012, and December 31, 2014 (index date). The patients were followed for up to 12 months, and their baseline characteristics were assessed during the 6 months before the index date. Medication adherence was measured at 3, 6, 9, and 12 months postindex using medication possession ratios (MPRs), and dose reduction was measured using refill gaps and relative dose intensity over the entire observation period. Kaplan-Meier survival analyses and Cox proportional hazards models were used to assess the association between the initial treatment and the risk for dose reduction. The summary of the results are as follows:

“The study included 2591 and 807 patients who initiated treatment with abiraterone acetate and enzalutamide, respectively. At 6, 9, and 12 months postindex, the patients who initiated abiraterone acetate had higher MPRs than the patients who initiated enzalutamide. In addition, the patients who initiated abiraterone acetate had lower Kaplan-Meier rates of dose reduction across 4 measurements for dose reduction. All hazard ratios for treatment (abiraterone acetate vs enzalutamide) were

²² Kang, M., Jeong, C. W., Kwak, C., Ku, J. H., & Kim, H. H. (2017). Comparing the clinical efficacy of abiraterone acetate, enzalutamide, and orteronel in patients with metastatic castration-resistant prostate cancer by performing a network meta-analysis of eight randomized controlled trials. *Oncotarget*, 8(35), 59690-59697. doi:10.18632/oncotarget.17741

²³ Behl, A. S., Ellis, L. A., Pilon, D., Xiao, Y., & Lefebvre, P. (2017). Medication Adherence, Treatment Patterns, and Dose Reduction in Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Abiraterone Acetate or Enzalutamide. *American health & drug benefits*, 10(6), 296-303.

significantly lower than 1 (range, 0.57-0.80), indicating a lower risk for dose reduction associated with abiraterone acetate.”

This study concluded that patients who initiated abiraterone acetate therapy had higher medication adherence and lower risk for dose reduction than those who initiated enzalutamide therapy. Improved medication adherence may be associated with longer duration of treatment, which in turn may lead to better survival.

Another study,²⁴ funded by Janssen Scientific Affairs, used the Truven Health MarketScan Research Databases from March 2012 to December 2014 to identify males with prostate cancer initiated on abiraterone acetate (AA) or enzalutamide (ENZ) (index therapy). Baseline characteristics were assessed during the 6 months pre-index. Inverse probability of treatment weights (IPTWs) were used to reduce baseline confounding. Treatment duration spanned from the index date to the earliest of treatment discontinuation (defined as a > 60-day gap in treatment), 24 months post-index, health plan disenrollment, or end of data. Weighted Kaplan-Meier and Cox proportional hazard models were used to compare the combined duration of mCRPC treatments (AA, ENZ, chemotherapy, sipuleucel-T, and radium 223) and any prostate cancer treatments (mCRPC, hormonal, and corticosteroid treatments) between patients initiated on either AA or ENZ. The results of this study were summarized as follows:

“A total of 2,591 patients initiated on AA and 807 patients initiated on ENZ were selected for the study. Patients’ characteristics were generally well balanced after IPTW. At 3 months, patients initiated on AA were associated with fewer discontinuations of mCRPC treatments (hazard ratio [HR] = 0.73, P = 0.004) or of any prostate cancer treatments (HR = 0.61, P = 0.002), compared with patients initiated on ENZ. This result was maintained at 6, 9, 12, 18, and 24 months for mCRPC treatments (HR = 0.75, P < 0.001) and for any prostate cancer treatments (HR = 0.69, P < 0.001). Median duration of mCRPC treatments was 4.1 months longer for patients initiated on AA compared with those initiated on ENZ (18.3 vs. 14.2 months, P < 0.001) and similarly, the median duration of any prostate cancer treatment was longer for patients initiated on AA compared with those initiated on ENZ (not reached vs. 22.2 months, P < 0.001).”

According to the study, these results can be interpreted as suggesting that patients initiated on abiraterone acetate, compared with those initiated on enzalutamide, had a longer combined duration of mCRPC or prostate cancer treatments.

More recently, a study funded by Janssen, Astellas, and several other organizations randomly assigned patients to receive either abiraterone acetate 1000 mg orally once daily plus prednisone 5 mg orally twice daily until PSA progression followed by crossover to enzalutamide 160 mg orally once daily (group A), or the opposite sequence (group B). The trial is registered with ClinicalTrials.gov (NCT02125357). According to the study,

²⁴ Dominic Pilon, Ajay S. Behl, Lorie A. Ellis, Bruno Emond, Patrick Lefebvre, and Nancy A. Dawson. Duration of Treatment in Prostate Cancer Patients Treated with Abiraterone Acetate or Enzalutamide. *Journal of Managed Care & Specialty Pharmacy* 2017 23:2, 225-235

enzalutamide showed activity as a second-line novel androgen receptor pathway inhibitor, whereas abiraterone acetate did not, leading to a longer time to second PSA progression for the sequence of abiraterone followed by enzalutamide than with the opposite treatment sequence. According to the study, which was Published on the Lancet Oncology:

“Between Oct 21, 2014, and Dec 13, 2016, 202 patients were enrolled and randomly assigned to either group A (n=101) or group B (n=101). At the time of data cutoff, 73 (72%) patients in group A and 75 (74%) patients in group B had crossed over. Time to second PSA progression was longer in group A than in group B (median 19·3 months [95% CI 16·0–30·5] vs 15·2 months [95% CI 11·9–19·8] months; hazard ratio 0·66, 95% CI 0·45–0·97, p=0·036), at a median follow-up of 22·8 months (IQR 10·3–33·4). PSA responses to second-line therapy were seen in 26 (36%) of 73 patients for enzalutamide and three (4%) of 75 for abiraterone (χ^2 p<0·0001). The most common grade 3–4 adverse events throughout the trial were hypertension (27 [27%] of 101 patients in group A vs 18 [18%] of 101 patients in group B) and fatigue (six [10%] vs four [4%]). Serious adverse events were reported in 15 (15%) of 101 patients in group A and 20 (20%) of 101 patients in group B. There were no treatment-related deaths.”²⁵

10. Review of harms and toxicity: summary of evidence of safety.

Enzalutamide is approved for the treatment of three indications, (1) mCRPC in patients who have previously taken docetaxel, (2) mCRPC in patients who have not previously undergone chemotherapy, and most recently, (3) patients with non-metastatic CRPC. Discussions of the safety, toxicity, and adverse events (AE) follow below.

Indication 1: Metastatic castration-resistant prostate cancers in patients who have previously taken docetaxel

As previously discussed, in the AFFIRM trial of patients with mCRPC who had previously taken docetaxel, there were overall few adverse events (AE), but grade ≥ 3 events relating to fatigue (6% vs 7%), diarrhea (1% vs >1%), musculoskeletal pain (1% vs >1%), headache (1% vs. 0%) and seizures (0.6% vs 0%) occurred slightly more often in the enzalutamide arm. However, AE causing death occurred in 3% in the enzalutamide arm and 4% in the placebo arm.

In the key phase III trial (CRPC2) discussed in the medical review for the indication for which enzalutamide received its first approved indication from the US FDA, more patients from the placebo arm withdrew from the study due to adverse events than the enzalutamide arm.²⁶

²⁵ Khalaf, Daniel J et al. (2019) Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. The Lancet Oncology, Volume 20, Issue 12, 1730 - 1739

²⁶ FDA. Medical Review in support of US Food and Drug Administration approval of Xtandi (enzalutamide). Application No.: 203415. Approved August 2012. Retrieved January 15, 2019 from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203415Orig1s000MedR.pdf

Table 3 (below) from the medical review of the US FDA initial approval of enzalutamide compares the safety and efficacy of enzalutamide with two other products that treat mCRPC.

Table 3: Key Efficacy and Safety Information about Three Products Used for Treatment of mCRPC After Docetaxel Therapy (Reviewer Benefit-Risk Evaluation Table)

	<i>Cabazitaxel</i>	<i>Abiraterone</i>	<i>Enzalutamide (MDV3100)</i>
<i>Approval Year</i>	2010	2011	
<i>Drug Class</i>	<i>Cytotoxic</i>	<i>Hormonal</i>	<i>Hormonal</i>
<i>Trial Demonstrating Clinical Benefit</i>	<i>EFC6193</i>	<i>COU-AA-301</i>	<i>CRPC2</i>
<i>Study Disease Setting</i>	<i>mCRPC s/p Docetaxel</i>	<i>mCRPC s/p Docetaxel</i>	<i>mCRPC s/p Docetaxel</i>
<i>Study Control*</i>	<i>Mitoxantrone</i>	<i>Placebo</i>	<i>Placebo</i>
<i>Study Size (# to treatment arm)</i>	755 (378)	1195 (797)	1199 (800)
<i>Survival Difference** HR (95% CI)</i>	0.70 (0.59-0.83)	0.65 (0.543, 0.768)	0.63 (0.53, 0.75)
<i>Improvement in Median OS (mos)</i>	2.4	3.9	4.8
<i>Key Toxicity Profile***</i>			
<i>Infusion Reaction/ Boxed Warnings</i>	Yes	N/A	N/A
<i>Severe Toxicity (Grade 3/4)</i>			
<i>Neutropenia (%)</i>	82%	NS	1%
<i>Febrile Neutropenia (%)</i>	7%	NS	NS
<i>Infection or UTI (%)</i>	2%	2%	1%
<i>Fluid Retention/Edema (%)</i>	<1%	2%	1%
<i>Hepatic ALT/AST (%)</i>	1%	2%	0.3%
<i>Seizure (%)</i>	NS	NS	1%
<i>Adverse Reaction of Interest (Grade 3/4)</i>			
<i>Hypokalemia (%)</i>	NS	5%	NS
<i>Hypertension (%)</i>	NS	1%	2%
<i>Adrenocortical Insufficiency</i>	NS	<1%	NS
<p>* Use of glucocorticoids varied among the trials</p> <p>** Compared to Study Control in each trial. Inherent bias prevents from inter-trial comparisons.</p> <p>*** Based on information from the active treatment arm only.</p> <p>N/A denotes "not applicable"</p> <p>NS denotes "not specified", meaning not found in relevant product's label or the review.</p>			

Indication 2: Metastatic castration-resistant prostate cancer in patients who have not previously undergone chemotherapy

In the PREVAIL trial of mCRPC treatment-naïve patients discussed in the previous section, less deaths were reported in the treatment arm at 28% vs 35% for placebo [HR: 0.71, 95% CI: [0.60–0.84]; p<0.001].

Indication 3: Non-metastatic castration-resistant prostate cancer

As observed in the PROSPER trial for the 2018 expanded indication of the use of enzalutamide for the treatment of non-metastatic CRPC:

"At the first interim analysis of overall survival, 103 patients (11%) receiving enzalutamide and 62 (13%) receiving placebo had died. Adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo."²⁷

As noted in a comparison of clinical trials of enzalutamide, abiraterone acetate, and orteronel by Kang et al.:

"...AE risks did not differ between enzalutamide and control arms, suggesting that enzalutamide is safe for clinical use in mCRPC patients. Based on these pieces of evidence together, enzalutamide can be the most efficacious and safe agents for patients with mCRPC and abiraterone can be the second most efficacious drug."²⁸

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

When sourced from the originators (Xtandi for enzalutamide and Zytiga for abiraterone acetate), both oral drugs are expensive. Many of the cost-benefit studies have been done using the prices from originators. Both drugs are now also available from generic suppliers, and as competition among generic suppliers expands, prices should decline considerably.

At the high originator prices, there are many studies of the cost-effectiveness of enzalutamide compared to alternatives, including ones that are also expensive (see section on cost-effectiveness studies below). The studies cited may be of limited use when considering if enzalutamide would be cost-effective in resource setting, when and where the drug is available at lower prices from generic suppliers.

The WHO needs to consider the cost-effectiveness for both cases: when the drugs are expensive (from the originator), and when the drugs are less expensive (from generic suppliers), including looking at reasonable scenarios for generic prices falling over time.

Costs of manufacturing enzalutamide

²⁷ Hussain, Maha; Fizazi, Karim; Saad, Fred; et al. "Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer." *New England Journal of Medicine*. 28 June 2018. 378:2465-2474. doi: 10.1056/NEJMoa1800536

²⁸ Kang, M., Jeong, C. W., Kwak, C., Ku, J. H., & Kim, H. H. (2017). Comparing the clinical efficacy of abiraterone acetate, enzalutamide, and orteronel in patients with metastatic castration-resistant prostate cancer by performing a network meta-analysis of eight randomized controlled trials. *Oncotarget*, 8(35), 59690-59697. doi:10.18632/oncotarget.17741

In 2016, Canada-based Biolyse Pharma offered to sell generic enzalutamide to the US Medicare program for \$3 for a 40mg tablet, or \$12 for a daily dose of four tablets. But generic prices could fall much further, given API costs.

In previous years, before generic entry, some publicly quoted prices for the active pharmaceutical ingredient enzalutamide were in the range of \$6,000 to \$13,000 per kilo. At the \$6,000 per kilo figure, the cost of the API for one 40 milligram capsule of enzalutamide would be \$0.24 (API cost of \$.006 per mg). API prices would fall over time, as generic producers enter the market.

Table 5 (below) provides an overview of recent prices for Xtandi in a range of countries.

Table 4: Prices for Xtandi and Gross National Income in Different Countries

Country	Date	Price per 40mg capsule in local currency	URL	Currency exchange rate, date of quote	Price per 40mg capsule in USD	Notes	GNI per capita US\$ (2019, World Bank) Atlas method, current USD
United States	Nov 17, 2020	11,918.16 / 120	Source: Redbook	1.00	\$99.32	WAC	\$65,760
United States	Nov 17, 2020	14,301.79 / 120	Source: Redbook	1.00	\$119.18	AWP	\$65,760
United States	Nov 16, 2020	7,403.32 / 120	Source	1.00	\$61.69	VA FSS price (V797D-30296)	\$65,760
United States	Nov 17, 2020	91.48	Source	1.00	\$91.48	Medicare Part D, average spending per unit (2018)	\$65,760
Denmark	Nov 16, 2020	29,063.25 / 112	Source	.16	\$41.51	Price per packing	\$63,240
Iceland	Nov 16, 2020	563,139.00 / 112	Source	.0073	\$36.70	Maximum retail price	\$72,850
Germany	Nov 17, 2020	3,336.07 / 112	Source	1.19	\$35.45		\$48,520
Finland	Nov 16, 2020	3,404.12 / 112	Source	1.19	\$36.17		\$49,580
Switzerland	Nov 16, 2020	4,011.40 / 112	Source	1.98	\$42.61	Price to public	\$85,500
The Netherlands	Nov 17, 2020	119.22 / 4	Source	1.19	\$35.47		\$53,200
United Kingdom	Nov 17, 2020	2,734.67 / 112	Source	1.33	\$32.47		\$42,370
France	Nov 16,	2,974.84 / 112	Source	1.19	\$31.61	Price	\$42,400

	2020					excluding dispensing fee	
Norway	Nov 16, 2020	26,045.67 / 112	Source	.11	\$25.58	Price to pharmacy	\$82,500
South Korea	Nov 17, 2020	22,850.00	Source	.00090	\$20.57		\$33,720
Australia	Nov 17, 2020	3552.60 / 112	Source	.73	\$23.16	DPQM, subject to 'special pricing arrangements' meaning actual price is lower	\$54,910
Italy	Nov 17, 2020	2,398 / 112	Source: AIFA	1.19	\$25.48		\$34,460
Canada	Nov 16, 2020	29.20	Source	.76	\$22.19	Exceptional Access Program (Ontario)	\$46,370
Japan	Nov 17, 2020	2,397.70	Source	.0096	\$23.02		\$41,690
India, CIPLA	Dec 7, 2020	6,440 / 28	Package price	0.01346	\$3.12		\$2,130
India, CIPLA	Dec 7, 2020	4,800 / 28	Source	0.01346	\$2.31		\$2,130
India, Hetro	Dec 8, 2020	21,000 / 112	Source	0.01346	\$2.52		\$2,130

The price for the APIs for enzalutamide will fall over time, dramatically. Andrew M Hill, Melissa J Barber, Dzintars Gotham and others have recently published a series of papers reporting the costs of active pharmaceutical ingredients for various drugs, including several drugs for cancer.²⁹ In the 2018 BMJ paper on the WHO EML drugs, the authors reported API prices for 21 antineoplastic and immunosuppressive drugs in the WHO EML. Three products were reported to have API prices higher than \$6,000 per kilo: methotrexate (\$77,181/kg), anastrozole (\$48,669/kg), and etoposide (\$8,463/kg). The two products with the highest API prices were sold with only 2.5/mg or 1/mg or API per tablet. The remaining 18 products had API prices from \$34/kg to \$2,284/kg. These included such products as tamoxifen (\$271/kg), capecitabine (\$393/kg), prednisolone (\$962/kg) and imatinib (\$2,284/kg).

²⁹ For example, Hill A, Redd C, Gotham D, et al Estimated generic prices of cancer medicines deemed cost-ineffective in England: a cost estimation analysis BMJ Open 2017;7:e011965. doi: 10.1136/bmjopen-2016-011965; Hill AM, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. BMJ Glob Health. 2018;3(1):e000571. Published 2018 Jan 29. doi:10.1136/bmjgh-2017-000571

We have seen prices for several generic versions from Indian suppliers, with a range of prices, with prices in the \$57 to \$70 thousand per kilo range of API, which we see as evidence that there is considerable room for decreasing prices in the future.

Cost-effectiveness Studies

United Kingdom

The National Institute for Health and Care Excellence (NICE) published an evaluation of the cost benefit analysis in 2014.

Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. Technology appraisal guidance [TA316] Published date: 23 July 2014

This guidance was reevaluated in 2016 and 2017. The 2017 evaluation stated: “We found nothing new that affects the recommendations in this guidance.”³⁰

According to the “Technology appraisal guidance [TA316]”, published July 23, 2014:

Enzalutamide is recommended as an option for treating hormone-relapsed metastatic prostate cancer in adults, only if:

1. their disease has progressed during or after docetaxel-containing chemotherapy and
2. they have not had treatment with abiraterone and the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.

The Committee agreed that enzalutamide should be compared with abiraterone for patients who had received 1 course of chemotherapy, and with best supportive care for patients who had received 2 or more courses of chemotherapy.

For patients who had received 1 course of chemotherapy, the Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an ICER of £22,600 per QALY gained for enzalutamide compared with abiraterone. The Committee accepted that this ICER was associated with uncertainty but, on balance, it was satisfied that it would remain below £30,000 per QALY gained. The Committee noted that taking into account the correct patient access scheme for abiraterone would not change its conclusion.

For patients who had received 2 or more courses of chemotherapy, the Committee noted that the ICER estimated by the manufacturer for enzalutamide compared with best supportive care was £45,500 per QALY gained and that the ERG’s ICER was

³⁰ Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. Technology appraisal guidance [TA316] Published July 2014. <https://www.nice.org.uk/guidance/ta316>

£48,000 per QALY gained. The Committee agreed that enzalutamide would be considered an end-of-life treatment as defined by NICE for this subgroup and that the magnitude of the additional weight that would need to be assigned to the QALY benefits would justify enzalutamide being recommended as a cost-effective use of NHS resources. Because the Committee had not seen evidence for patients who had received abiraterone as 1 of the 2 or more courses of chemotherapy, it agreed that the evidence it had considered could not be generalised to patients who had received abiraterone.³¹

The Committee did not see sufficient evidence to make any recommendations on the clinical- and cost-effectiveness of sequential use of enzalutamide and abiraterone acetate.

Ireland

Cost Effectiveness of enzalutamide (Xtandi) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, June 2015.

The NCPE evaluation stated:

“Following NCPE assessment of the company submission, enzalutamide is not considered cost effective for this indication and therefore is not recommended for reimbursement at the submitted price.”³²

The December 2015 guidance has approved reimbursement following confidential price negotiations.³³

Canada

Cost-Utility Analysis of Enzalutamide for Patients with Previously Treated Metastatic Castration-Resistant Prostate Cancer (MCRPC). C. Vicente, V. Babashov, F. Husein, F. Saad, S. Naidoo, S. Holmstrom DOI: <http://dx.doi.org/10.1016/j.jval.2014.03.521>

³¹ Ibid.

³² Cost Effectiveness of enzalutamide (Xtandi) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, June 2015. Retrieved January 15, 2019 from: <http://www.ncpe.ie/wp-content/uploads/2014/12/Final-enzalutamide-LM-Web-Summary-June-2015.pdf>

³³ National Centre for Pharmacoeconomics. NCPE Ireland. Enzalutamide (Xtandi®) on or after chemotherapy. Retrieved January 15, 2019 from: <http://www.ncpe.ie/drugs/enzalutamide-xtandi/>

Objectives: mCRPC is a terminal disease, with a median survival of approximately 1 to 2 years. The AFFIRM study demonstrated that enzalutamide is highly efficacious, prolonging overall survival and progression-free survival compared to placebo in patients with mCRPC previously treated with docetaxel-based chemotherapy. The purpose of this analysis is to assess from the Canadian perspective the cost-effectiveness of enzalutamide 160 mg once-daily compared with abiraterone acetate (AA) (+ prednisone) and intravenous (IV) cabazitaxel in mCRPC patients previously treated with docetaxel-based chemotherapy. Methods: A Markov model was developed to capture time spent by patients in various health states, including progression, progression free survival (PFS) and death. Results were reported as incremental costs per additional quality adjusted life-years (QALY) gained over a 10-year period. Transition probabilities were derived from patient-level data from AFFIRM and an indirect treatment comparison from available published literature. The base case analysis focused on direct medical costs from the perspective of the Canadian Ministry of Health (MoH), with the second analysis focusing on the societal perspective. Cost data for 2013, obtained from a variety of sources were reported as Canadian Dollars. A 5% discount rate was applied to both costs and patient outcomes. Multiple sensitivity analyses were undertaken to test the robustness of the model Results: From the MoH perspective, enzalutamide had an incremental cost-utility ratio (ICUR) of \$42,325 and \$43,105 per additional QALY gained compared to AA and cabazitaxel, respectively. Results were similar from the societal perspective. Results were robust over a wide range of one-way and probabilistic sensitivity analyses. In greater than 85% of iterations the incremental cost-effectiveness ratio ICER was below a willingness-to-pay threshold of \$100,000 per QALY for the comparison versus either AA or cabazataxel. Conclusions: Enzalutamide is a cost-effective treatment compared to AA and cabazitaxel in mCRPC patients previously treated with docetaxel-based chemotherapy.³⁴

United States of America

One 2014 study by Leslie Wilson et al. for the US context, which features the highest prices in the world for Astellas-branded Xtandi, calculated the cost-effectiveness of three metastatic castration-resistant prostate cancer (mCRPC) treatments -- Zytiga (abiraterone acetate), Xtandi (enzalutamide), and Jevtana (cabazitaxel) -- and found that the price of enzalutamide was the single limiting factor rendering enzalutamide less cost-effective than abiraterone acetate. This study was detailed in the Journal of Oncology Pharmacy Practice:

L. Wilson et al. New therapeutic options in metastatic castration-resistant prostate cancer: [Can cost-effectiveness analysis help in treatment decisions?](#) Journal of Oncology Pharmacy Practice 2014, Vol. 20(6) 417–425.

³⁴ Cost-Utility Analysis of Enzalutamide for Patients with Previously Treated Metastatic Castration-Resistant Prostate Cancer (MCRPC). C. Vicente, V. Babashov, F. Husein, F. Saad, S. Naidoo, S. Holmstrom DOI: <http://dx.doi.org/10.1016/j.jval.2014.03.521>

According to the authors' incremental cost-effectiveness calculations based upon 2012 prices, enzalutamide would be the preferred treatment, if prices were decreased:

Results: Abiraterone was the most cost-effective of the treatments (\$123.4 K/quality-adjusted life year) compared to placebo, enzalutamide was \$437.6 K/quality-adjusted life year compared to abiraterone, and cabazitaxel was \$351.9 K/quality-adjusted life year compared to enzalutamide. Enzalutamide and cabazitaxel were not cost-effective compared to placebo at \$154.3 K/quality-adjusted life year and \$163.2 K/quality-adjusted life year, respectively. Acceptability curves showed abiraterone was cost-effective 29.3% of the time with a willingness to pay threshold of \$100 K. The model was sensitive to changes in cost of the drugs, life expectancy, and survival rate. Sensitivity analysis shows that enzalutamide can become the most cost-effective option if the price of the medication decreased by 26% and other drug costs remained the same. [emphasis added]³⁵

Niranjan Kathe, M.S., Corey Hayes, Pharm D MPH, Anand Shewale, M.S. and Bradley Martin, Pharm D PhD, University of Arkansas for Medical Sciences, Little Rock, AR. COST EFFECTIVENESS OF THERAPIES FOR CASTRATION RESISTANT METASTATIC PROSTATE CANCER, 37th Annual Meeting of the Society for Medical Decision Making, PS1-4 , Sunday, October 18, 2015, Poster Board # PS1-4³⁶

The study by Niranjan et al. concluded:

Result: In the base case analysis, cabazitaxel therapy was the most expensive (\$139,978), followed by enzalutamide (\$133,834), abiraterone while (\$120,260), mitoxantrone (\$93,255), prednisolone (\$82,930). Quality adjusted life expectancy was highest with cabazitaxel (0.76 QALY), followed by abiraterone (0.70 QALY), mitoxantrone (0.58 QALY), enzalutamide (0.56 QALY) and prednisolone (0.43 QALY). Mitoxantrone was found to be the most cost effective treatment (\$51,524.53/QALYs) compared to prednisolone. When compared to mitoxantrone abiraterone and cabazitaxel have high incremental cost effectiveness ratios (\$220,803/QALY and \$353,203/QALY respectively) while enzalutamide was dominated. At a willingness to pay of \$100,000/QALY, the cost effectiveness acceptability curves showed that mitoxantrone and abiraterone were cost effective 23.4% and 24.6% times respectively. One-way sensitivity analysis showed that abiraterone had an ICER below \$100,000/QALY when the price of abiraterone reduced by 30.1%.

Conclusion: Treatment of mCRPC with recently developed therapies can extend the survival, however, the gains in survival are accompanied by significant costs with

³⁵ L. Wilson et al. New therapeutic options in metastatic castration-resistant prostate cancer: Can cost-effectiveness analysis help in treatment decisions? Journal of Oncology Pharmacy Practice 2014, Vol. 20(6) 417–425

³⁶ <https://smdm.confex.com/smdm/2015mo/webprogram/Paper9446.html>

abiraterone, cabazitaxel and enzalutamide. At 2015 prices, mitoxantrone which has a lower side effect profile appears would be cost effective at conventional willingness to pay thresholds.³⁷

Vicente, C et al. Cost-Utility Analysis Of Enzalutamide For Patients With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer (Mcrpc) After Failure Of Androgen Deprivation Therapy (Adt). Value in Health, Volume 18, Issue 7, A474. (November 2015).

The study by Vicente et al. stated:

NMA results suggested no difference between enzalutamide and ABI+P for overall survival, but indicated that enzalutamide is superior to ABI+P for rPFS (hazard ratio 0.35; credible interval 0.27, 0.46). The improvement in rPFS translated into a longer mean duration of stable disease with enzalutamide (36.7 months) than with ABI+P (16.4 months), and greater total QALYs (enzalutamide 2.65; ABI+P 2.23). From the Canadian MoH perspective, enzalutamide had an incremental cost-effectiveness ratio (ICER) of \$92,690 per additional QALY gained versus ABI+P. The ICER was robust over a wide range of sensitivity analyses. In the probabilistic sensitivity analysis, the mean ICER was \$110,036 per QALY gained versus ABI+P, with >60% of iterations falling below a willingness-to-pay threshold of \$100,000 per QALY gained.

Conclusions

Enzalutamide is considered a cost-effective treatment option compared to ABI+P in patients with chemotherapy-naïve mCRPC after failure of ADT.³⁸

Three of the authors in this study were affiliated with Astellas at the time of publication.

Avxentyev, NA et al., Pharmacoeconomic Analysis of Enzalutamide and Abiraterone for Treatment of Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer, Value in Health, Volume 20, Issue 9, A436. (October-November 2017)

The study by Avxentyev et al. concluded:

Enzalutamide was found to be a cost-saving option compared to abiraterone. Monthly medication costs for enzalutamide were \$3760 per patient, 11.7% less than for abiraterone. The 8-year discounted total medical costs for enzalutamide and abiraterone were \$114,307 and \$121,272 per patient, respectively, indicating that the 8-year health budget could be cut by \$696,500 per 100 mCRPC patients through

³⁷ Niranjana Kathe, M.S., Corey Hayes, Pharm D MPH, Anand Shewale, M.S. and Bradley Martin. Presented at the 37th Annual Meeting of the Society for Medical Decision Making. October 18 - 21, 2015.

³⁸ Vicente, C et al. Cost-Utility Analysis Of Enzalutamide For Patients With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer (Mcrpc) After Failure Of Androgen Deprivation Therapy (Adt). Value in Health, Volume 18, Issue 7, A474. (November 2015).

treatment with enzalutamide. Enzalutamide was also found to be cost-effective compared to abiraterone when both were compared against chemotherapy alone.

Conclusions

Enzalutamide is a cost-saving and cost-effective option compared to abiraterone and should be recommended for inclusion into the VEDL in Russia.³⁹

Avxentyev, N.A. et al., Pharmacoeconomic Evaluation Of Enzalutamide For The Treatment Of Post-chemotherapy Patients With Metastatic Castration-resistant Prostate Cancer In Russia, Value in Health, Volume 21, S29. 2018.

This study by Avxentyev et al. on patients in Russia found:

Use of enzalutamide, abiraterone and cabazitaxel resulted in 1.04, 0.94 and 0.96 quality-adjusted life years respectively. Monthly medication costs for enzalutamide were US\$2973 per patient, 15% less for abiraterone and 49% less than for cabazitaxel. Five-year total medical costs were US\$53,959, US\$53,975 and US\$71,836 per patient for enzalutamide, abiraterone and cabazitaxel, respectively. The smaller difference in total medical costs resulted from longer progression-free survival on enzalutamide compared to abiraterone or cabazitaxel. If included in GDRP, enzalutamide results in the lowest budget impact. . . .⁴⁰

This study was funded by Astellas Pharma Inc and Pfizer Inc, as disclosed by the authors in one of their presentations of this study.⁴¹

Devlin, N et al. Health-Related Quality Of Life (HrQoL) Benefits Of Enzalutamide In Patients With Metastatic Castration-Resistant Prostate Cancer (Mcrpc): An In-Depth Analysis Of Eq-5d Data From The Prevail Trial, Value in Health, Volume 18, Issue 7, A475. (November 2017).

The study by Devlin et al. stated:

HRQOL deterioration (indicated by decreases in EQ-5D Index and VAS scores) was more gradual with enzalutamide versus placebo; reductions were significantly ($p < 0.05$) smaller with enzalutamide in EQ-5D Index up to Week 37 and in EQ-VAS up to Week 61 (except Week 49). Benefits of enzalutamide were primarily in the Pain/Discomfort dimension, with significant between-group differences ($p < 0.05$)

³⁹ Avxentyev, NA et al., Pharmacoeconomic Analysis of Enzalutamide and Abiraterone for Treatment of Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer, Value in Health, Volume 20, Issue 9, A436. (October-November 2017)

⁴⁰ Avxentyev, N.A. et al., Pharmacoeconomic Evaluation Of Enzalutamide For The Treatment Of Post-chemotherapy Patients With Metastatic Castration-resistant Prostate Cancer In Russia, Value in Health, Volume 21, S29. 2018.

⁴¹ Avxentyev, N.A. et al., Pharmacoeconomic Evaluation Of Enzalutamide For The Treatment Of Post-chemotherapy Patients With Metastatic Castration-resistant Prostate Cancer In Russia. Scientific Presentations Database. Retrieved January 15, 2019 from: <https://tools.ispor.org/ScientificPresentationsDatabase/Presentation/88583>

through to Week 37. PCHC analysis showed a higher percentage of enzalutamide patients reporting improvements on EQ-5D dimensions up to Week 49 and a higher proportion of placebo patients reporting worsening up to week 25. Time to event analysis showed superiority of enzalutamide on time to shift from full health (state 11111) and time to first worsening on the Pain/Discomfort and Anxiety/Depression dimensions. At Week 61, of patients originally randomised to enzalutamide, 20.1% reported being in full health (state 11111), 28.2% reported no pain or discomfort, and 43.1% reported no anxiety/depression compared with 5.1%, 6.5%, and 10.2%, respectively, of placebo patients.

Conclusions

In PREVAIL, as well as improving overall survival versus placebo, enzalutamide showed HRQOL benefits captured through EQ-5D Index and VAS scores, including benefits in the Pain and Discomfort dimension of EQ-5D, and reporting being in full health, having no pain/discomfort, or no anxiety/depression.⁴²

Two of the authors in this study were affiliated with Astellas at the time of publication.

Aguirre, A et al., Cost Per Median Overall Survival Associated with Abiraterone Acetate and Enzalutamide For Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer in Colombia, Value in Health, Volume 20, Issue 9, A876 - A877. (October-November 2017)

The study by Aguirre et al. concluded:

The results demonstrated that AA+P has a lower cost per monthly median OS than enzalutamide (\$846.00 vs. 1,573.00; 46% reduction), based on the following assumptions: exchange rate USD 1 = COP 2967, median treatment duration of 14 months for AA+P and 18 months for enzalutamide, median OS of 34.7 months for AA+P and 35.3 months for enzalutamide, and EFP per 30-day supply of \$2,096.57 for AA+P versus \$3,084.11 for enzalutamide. Sensitivity analyses showed that accounting for recommended treatment-related monitoring costs or assuming identical treatment durations for AA+P and enzalutamide (18 months) resulted in costs per median OS month 31% to 44% lower for AA+P than for enzalutamide. Costs per month of chemotherapy avoided were \$1,165.00 for AA+P and \$1,983.00 for enzalutamide, while costs per month to achieve median rPFS were \$1,779.00 for AA+P and \$2,776.00 for enzalutamide.

Conclusions

Costs per monthly median OS, along with costs of other Phase 3 trial outcomes, were lower for AA+P than for enzalutamide. The findings were robust to sensitivity

⁴² Devlin, N et al. Health-Related Quality Of Life (Hrql) Benefits Of Enzalutamide In Patients With Metastatic Castration-Resistant Prostate Cancer (Mcrpc): An In-Depth Analysis Of Eq-5d Data From The Prevail Trial, Value in Health, Volume 18, Issue 7, A475. (November 2017).

analyses. These results have important implications for population health decision makers evaluating the relative value of therapies for mCRPC patients.⁴³

The two authors in this study were affiliated with Janssen at the time of publication.

Gay J, Schultz N, Braun, Cost-Effectiveness Evaluation of Enzalutamide and Abiraterone for the Treatment of Metastatic Castration-Resistant Prostate Cancer Patients Progressing after Docetaxel in the Mexican Public Healthcare System. Value in Health, 21. S29-30. (2018)

The study by Gay, Schultz, and Braun (note that Schultz and Braun are employees of Astellas) stated:

Objectives: Enzalutamide (ENZA) and abiraterone acetate plus prednisone (ABI) are approved oral treatments for patients with metastatic castration-resistant prostate cancer (mCRPC) after progression on docetaxel in the Mexican public healthcare (PHC) system. Financial schemes have been proposed to facilitate access to these new treatment options. This analysis evaluated the cost-effectiveness of ENZA and ABI for patients with mCRPC progressing after docetaxel treatment in the Mexican PHC system.

Methods: A three health-state Markov model was developed in which “free of progression”, “progression”, and “death” were defined as health states. Safety and efficacy inputs of ENZA and ABI were obtained from a published meta-analysis and the clinical trials AFFIRM (for ENZA) and COU-AA-301 (for ABI). Cost per month in each health state considered direct medical costs from local sources of the Mexican Social Security Institute (IMSS), and included the cost of treatment and adverse event management. A risk-sharing agreement was modeled, eliminating the cost of ENZA for patients with treatment failure before 12 months of treatment. A 3-year time horizon was utilized and a deterministic sensitivity analysis was performed to identify the most relevant variables.

Results: For the base-case scenario, the results showed a 0.21-year increase in overall survival in favor of ENZA and an incremental cost of MX\$3435. This represents an incremental cost-effectiveness ratio (MX\$/life-year gained) of MX\$16,197, which is considered cost-effective at the willingness-to-pay threshold of MX\$167,583. The sensitivity analysis showed that the cost of drugs and length of the risk-sharing agreement were the most relevant variables.

Conclusions: From the IMSS perspective in Mexico, ENZA is a cost-effective alternative treatment for patients with mCRPC after progression on docetaxel. The introduction of financial schemes to purchase innovative technologies seems a highly

⁴³ Aguirre, A et al., Cost Per Median Overall Survival Associated with Abiraterone Acetate and Enzalutamide For Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer in Colombia, Value in Health, Volume 20, Issue 9, A876 - A877. (October-November 2017)

promising method of improving access to modern and more effective drugs for cancer patients in the Mexican PHC system.⁴⁴

Rachael McCool, Kelly Fleetwood, Julie Glanville, Mick Arber, Howard Goodall, Shevani Naidoo, [Systematic Review and Network Meta-Analysis of Treatments for Chemotherapy-Naive Patients with Asymptomatic/Mildly Symptomatic Metastatic Castration-Resistant Prostate Cancer](#), Value in Health, Vol. 21, Issue 10, p1259–1268, May 3, 2018.

Conclusions

For rPFS, the NMA suggests that enzalutamide is superior to abiraterone/prednisone and sipuleucel-T. There is no evidence of a statistically significant difference in OS between enzalutamide and abiraterone/prednisone, sipuleucel-T, or radium-223. Given the limitations in network construction and underlying assumptions made to complete these analyses, results should be interpreted with caution.

One of the authors in this study was affiliated with Astellas at the time of publication.

J De La Cruz-Vargas, N Chavez-Villanueva, E Guerrero, A Aguirre, G Ojeda-Botteri, [Cost Treatment Comparison of Abiraterone Acetate Plus Prednisone in the Pre-Chemotherapy Setting Followed by Enzalutamide in the Post-Chemotherapy Setting Versus the Opposite Treatment Sequence in Metastatic Castration-Resistant Prostate Cancer Patients With Non-Visceral Metastases in Peru](#), Value in Health, Vol. 21, S24, May 2018.

Three of the authors in this study were affiliated with Janssen at the time of publication.

N.A. Avxentyev, E.V. Derkach, A.S. Makarov, [PCN91 - PHARMACOECONOMIC EVALUATION OF ENZALUTAMIDE FOR THE TREATMENT OF POST-CHEMOTHERAPY PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER IN RUSSIA](#), Value in Health, Vol. 21, S29, October 2018.

This study was funded by Astellas Pharma Inc and Pfizer Inc.

H Metin, K McQuarrie, P Thilakarathne, J Diels, T Ito, T Li, G Sulur, KN Chi, and others, [Benefit Of Abiraterone Acetate Plus Prednisone \(AA+P\) Added To Androgen Deprivation Therapy \(ADT\) In Patients With High-Risk, Newly Diagnosed Metastatic Hormone-Sensitive Prostate Cancer \(MHSPC\): Post Hoc Analysis Of EQ-5D-5L From The Latitude Study](#), Value in Health, Vol. 21, S38, May 2018.

Seven of the authors in this study were affiliated with Janssen at the time of publication.

⁴⁴ Gay J, Schultz N, Braun, Cost-Effectiveness Evaluation of Enzalutamide and Abiraterone for the Treatment of Metastatic Castration-Resistant Prostate Cancer Patients Progressing after Docetaxel in the Mexican Public Healthcare System. Value in Health, 21. S29-30. (2018)

J Lam, C Yang, C Kaiser, W Wong, [Real-World Treatment Patterns And Care Pathways In Metastatic Castration Resistant Prostate Cancer](#), Value in Health, Vol. 21, S41, May 2018.

Three of the authors in this study were affiliated with Genentech at the time of publication.

J. Hu, A. Aprikian, M. Vanhuyse, A. Dragomir, [PCN248 - USE OF CANCER DRUGS IN THE END-OF-LIFE IN MEN DYING OF CASTRATION-RESISTANT PROSTATE CANCER: POPULATION-BASED STUDY](#), Value in Health, Vol. 21, S56, October 2018

J Scott, R Concepcion, D Garofalo, S Verma-Kurvari, B Xu, J Montgomery, [Real-World Data Analysis Of Metastatic Castration-Resistant Prostate Cancer \(MCRPC\) Treatment Decisions With The Introduction Of Newer Treatment Options](#), Value in Health, Vol. 21, S43, May 2018.

PA Alfonso Quiñones, M Carrasquilla-Sotomayor, NJ Alvis-Zakzuk, ME Romero Prada, N Alvis-Guzmán, LM Huerfano, [Efficacy and Safety Analysis of Radium-223 in Patients with Prostate Cancer Castration-Resistant and Bone Metastasis](#), Value in Health, Vol. 21, S16–S17, May 2018.

B Wu, S Li, O Tunceli, C Pericone, Z Ding, A Behl, K Mangla, N Dawson, [Cost of Care for Patients with Metastatic Castration-Resistant Prostate Cancer in US Commercially Insured and Medicare Supplement Plans](#), Value in Health, Vol. 21, S28, May 2018.

Six of the authors in this study were affiliated with Janssen at the time of publication.

Z. Zhou, X. Hu, [PCN153 - COST-EFFECTIVENESS ANALYSIS OF APALUTAMIDE FOR TREATMENT IN NON- METASTASIS CASTRATION-RESISTANT PROSTATE CANCER](#), Value in Health, Vol. 21, S40–S41, October 2018.

12. Summary of regulatory status and market availability of the medicine.

Enzalutamide is approved worldwide and in various jurisdictions such as:

US (FDA)

Enzalutamide is licensed in the USA for the treatment of:

- “castration-resistant prostate cancer (CRPC);
- metastatic castration-sensitive prostate cancer (mCSPC).”

EU (EMA)

Enzalutamide is licensed in the EU for the treatment of:

- high-risk non-metastatic castration-resistant prostate cancer (CRPC);

- metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated; and
- metastatic castration resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

Australia (TGA)

Enzalutamide is licensed in Australia for the treatment of:

- non-metastatic castration-resistant prostate cancer;
- metastatic castration resistant prostate cancer following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated; and
- metastatic castration-resistant prostate cancer who have previously received docetaxel.

Japan (PMDA)

Enzalutamide is approved in Japan for the treatment of:

- metastatic hormone-sensitive prostate cancer (mHSPC); and
- castration-resistant prostate cancer (CRPC).

Canada (Health Canada)

Enzalutamide is approved in Canada for the treatment of:

- metastatic castration-sensitive prostate cancer (mCSPC);
- non-metastatic castration-resistant prostate cancer (NM-CRPC).

In Canada enzalutamide is also, “indicated in the setting of medical or surgical castration for the treatment of metastatic castration-resistant prostate cancer (CRPC) in patients who:

- are chemotherapy-naïve with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy.
- have received docetaxel therapy.”

International availability - sources, if possible manufacturers and trade names

The patents on enzalutamide include a “paid-up license” for the United States government to “practice or have practiced for or on behalf” the inventions “throughout the world.”

In 2016, Biolyse Pharma, a Canadian drug manufacturer, asked the US government for the right to use this license to supply the drug to patients in developing countries, where price is a barrier to access. The NIH was asked to respond, and rejected this request. However, this decision can be revised at any time. The NIH indicated that its decision was partly a consequence of a lack of general policy on such requests, something that may be remedied in the future.

Biolyse has also indicated that it will be asking the Canadian government to grant a compulsory license under a Canadian compulsory licensing program for export to countries that lack sufficient capacity to manufacture.

In India, the patent on enzalutamide was rejected on November 8, 2016, in a challenge brought by 1) Fresenius Kabi Oncology Limited, 2) BDR Pharmaceutical International Pvt. Ltd., 3) Umesh Shah, 4) Sheela Pawar, and 5) Indian Pharmaceuticals Alliance (IPA) against the Regent of the University of California.

The sole generic version of enzalutamide is sold by Glenmark, selling a version under the trade name of Glenza. The number of India-based firms selling enzalutamide will increase if the patent status in India, which is currently litigated by the University of California, is resolved.

As of the third quarter of 2018, nine companies have US FDA drug master files (DMF) for the supply of enzalutamide APIs.

Table 5: US FDA drug master files (DMF) for the supply of enzalutamide APIs

DMF#	STATUS	TYPE	SUBMIT DATE	HOLDER	SUBJECT
29062	A	II	3/23/2015	SAI LIFE SCIENCES LTD	4-((2-CYANOPROPAN-2-YL)AMINO)-2-FLUORO-N-METHYLBENZAMIDE (ENZALUTAMIDE INTERMEDIATE)
29117	A	II	3/31/2015	DR REDDYS LABORATORIES LTD	ENZALUTAMIDE
29872	A	II	5/24/2016	TEVA PHARMACEUTICAL INDUSTRIES LTD	ENZALUTAMIDE
30010	A	II	11/28/2015	MYLAN LABORATORIES LTD	ENZALUTAMIDE
30260	A	II	3/17/2016	SHILPA MEDICARE LTD	ENZALUTAMIDE
30279	A	II	2/29/2016	MSN LABORATORIES PRIVATE LTD	ENZALUTAMIDE [ROUTE CODE "E1"]
30304	A	II	3/29/2016	CADILA HEALTHCARE LTD	ENZALUTAMIDE
30644	A	II	7/9/2016	SCINOPHARM TAIWAN LTD	ENZALUTAMIDE
31196	A	II	12/30/2016	LAURUS LABS LTD	ENZALUTAMIDE

KEI anticipates that API costs will decline to \$300/kg to \$900/kg over time, in line with prices for tamoxifen (\$271/kg), capecitabine (\$393/kg) and prednisolone (\$962/kg).

A decline of that magnitude would result in API costs of \$0.012 to \$0.036 per 40mg capsule, or \$0.048 to \$0.144 per day for enzalutamide.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia).

The application should address whether the proposed medicine is included in at least one of the following Pharmacopoeia:

- *The British Pharmacopoeia*
- *The International Pharmacopoeia*
- *The United States Pharmacopoeia*
- *The European Pharmacopoeia*

14. Comprehensive reference list and in-text citations.

The application should be clearly referenced with in-text citations using the Vancouver style. Where possible, a copy of the electronic reference library files should be provided in EndNote™.