January 14, 2016

The Honorable Sylvia Mary Mathews Burwell
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201
Via: Sylvia.Burwell@hhs.gov

Francis Collins, M.D., Ph.D.
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
Via: Francis.Collins@nih.hhs.gov

The Honorable Ashton Carter
Secretary
Department of Defense
1400 Defense Pentagon
Washington, D.C. 20301-1400
Via: ashton.b.carter.civ@mail.mil; whs.pentagon.esd.mbx.cmd-correspondence@mail.mil

Dear Secretaries Burwell and Carter and Director Collins:

Introduction

Knowledge Ecology International is a non-profit organization with offices in Washington, DC and Geneva, Switzerland. The Union for Affordable Cancer Treatment (UACT) is a non-profit cancer patient group. More about each group is available on their respective web pages: http://keionline.org and http://cancerunion.org.

This letter is a request that the U.S. federal government use its rights in patents for the prostate cancer drug (enzalutamide), marketed under the brand name of Xtandi by Japan-based Astellas

Pharma. This is a product that has an average wholesale price (AWP) of $129,269 per year,[1] and which is far more expensive in the United States than in other countries.

Specifically, we ask the Department of Health and Human Services (DHHS), National Institutes of Health (NIH), and/or the Department of Defense (DoD) to use its royalty-free rights in the relevant patents, or to grant this request for march-in rights. The relevant patents include, but are not limited to, the three patents listed in the FDA Orange Book for Xtandi (7709517, 8183274, and 9126941), all of which were granted to the Regents of the University of California, a public institution. All three inventions were made with the support of the United States government under National Institutes of Health SPORE grant number 5 P50 CA092131 and Department of Defense (Army) grant number W81XWH-04-1-0129.

The statutory basis for the request includes 35 U.S.C. § 202(c)(4), for the royalty-free rights in the patents, and 35 U.S.C. § 203(a)(1-3), noting that the term "practical application" of an invention in 35 U.S.C. § 203(a)(1) is defined by 35 U.S.C. § 201(f) to require that the benefits of an invention are "available to the public on reasonable terms." It is our contention that the pricing of Xtandi is excessive and discriminatory as regards U.S. citizens.

Xtandi is an expensive drug everywhere, indeed so expensive that access is extremely limited in many countries. But, based upon our research, the prices in the United States are far higher than any other country in the world, despite the fact that the critical research benefited from U.S. taxpayer funded grants from the NIH and DoD.

More generally, we ask the U.S. federal government to adopt the policy that the federal government will use its royalty free rights, or grant licenses under federal march-in rights, when prices in the United States are excessive, and/or higher than they are in high income foreign countries, and to apply that policy in this case for patents on enzalutamide.

Such an approach would be in accord with the policy and objective of the Bayh-Dole Act as stated in 35 U.S.C. § 200, to "protect the public against nonuse ***and*** the unreasonable use of inventions…" [emphasis added].

The analysis in this document includes the following topics and tables.

1. Prices for Xtandi are much higher in the United States than in other high income countries,
2. The high prices for Xtandi create hardships on U.S. patients,
3. The cost of Xtandi to Medicare,
4. Astellas and Medivation projections of Xtandi sales,
5. The role of the U.S. government in funding research on Xtandi,
6. Enzalutamide is an important cancer drug,

[1] $88.48 per 40 mg unit, four times a day, 365.25 days per year.

7. The University of California at Los Angeles (UCLA) interest in the patents,
8. Orange Book patent claims for Xtandi,
9. Non-patent exclusivity,
10. Generic supply,
11. Xtandi R&D investments through the 2012 approval for the lead indication,
12. Clinical trials on enzalutamide, including trials subsequent to 2012 NDA,
13. Licensing terms, including reasonable royalty,
14. Funding of research to further develop enzalutamide,
15. Standard for determining the Xtandi prices are unreasonable.
16. Conclusion

Tables:

1. Prices for Xtandi are much higher in the United States than in other high income countries.

Xtandi is sold in 40 mg capsules or tablets, and is prescribed for daily use for as long as the drug continues to be effective and tolerated. The typical dose of Xtandi for the treatment of prostate cancer is 4 x 40 mg per day.

The U.S. average wholesale price (AWP), according to *Redbook* data published April 2015, was $88.48 per 40 milligram capsule, which amounts to $353.92 per day, or $129,269.28 per year (365.25 day year). The average price for Medicare in 2014 was $69.41 per capsule,[2] or $101,408.01 for a full year's treatment.

Astellas Pharma, a Japanese-owned drug company, is exploiting the weak response of the United States to excessive pricing of drugs, and is charging U.S. consumers and third-party payers roughly two to four times as much as the prices in other high income countries. For example, in Norway, a country with a per capita income of $103,630 in 2014, the price is $32.43 per 40 mg capsule, just 47 percent of the US Medicare price, and 39 percent of the Redbook AWP for the U.S. private sector.

In Australia, the price is $23.46 per capsule, roughly one third of the U.S. Medicare price. In Quebec, Canada, the price is $20.12 per capsule, just 29 percent of the U.S. Medicare price, and 24 percent of the U.S. AWP.

Astellas Pharma, the company that holds the rights to market Xtandi, is a member of the Japan-based Mitsubishi UFJ Financial Group (MUFJ) keiretsu. Note that in Japan, the price per 40 mg unit of this UCLA-invented drug is $26.37, less than one-third of the U.S. AWP.

In our opinion, it is unreasonable, and indeed outrageous, that prices are higher in the United States than in foreign countries, for a drug invented at UCLA using federal government grants.

[2] See Centers for Medicare and Medicaid Services Medicare Drug Spending Dashboard, available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Dashboard/Medicare-Drug-Spending/Drug_Spending_Dashboard.html

Table 1.1: Prices for Xtandi 40mg capsule/tabs, in the United States and 13 high income countries.

Country	Price per unit, national currency		EX Rate (Jan. 6, 2016)	Price per unit, USD	Percent of 2015 AWP	2014, GNI Per Capita, Atlas Method, USD
USA, April 2015 AWP	88.48	USD	1	$88.48	100%	$55,200
USA, 2014 Medicare	69.41	USD	1	$69.41	78%	$55,200
Australia	33.04	AUD	0.71	$23.46	27%	$64,540
Belgium	29.15	EUR	1.08	$31.48	36%	$47,260
Canada, Quebec	28.35	CAN	0.71	$20.12	23%	$51,630
France	24.75	EUR	1.08	$26.73	30%	$42,960
Germany, public insurance	34.19	EUR	1.08	$36.93	42%	$47,640
Italy, procurement price	24.08	EUR	1.08	$26.01	29%	$34,270
Japan	3,138.80	Yen	0.0084	$26.37	30%	$42,000
The Netherlands	29.15	EUR	1.08	$31.48	36%	$51,890
Norway	294.78	NOK	0.11	$32.43	37%	$103,630
Spain	29.98	EUR	1.08	$32.38	37%	$29,440
Sweden	224.705	SEK	.12	$26.96	30%	$61,610
Switzerland	35.82	CHF	0.99	$35.46	40%	$88,120*
UK	24.42	GBP	1.46	$35.65	40%	$43,430

*Only 2013 was available for Switzerland.

2. The high prices for Xtandi create hardships on U.S. patients.

Recent clinical studies indicate that treatment delays may be harmful to patients. While the drug is relatively new, clinicians are now recommending that doctors prescribe Xtandi before prescribing other drugs that target the same androgen axis, to prevent the development of drug resistance.

Since 2014, the FDA has expanded the use of Xtandi to first line treatment for metastatic castration-resistant prostate cancer (mCRPC) based on the phase III PREVAIL clinical trial. Currently Xtandi (FDA approved, 2012), Zytiga (FDA approved, 2011), and Taxotere (FDA approved, 2004) are the top three prescribed drugs in first line metastatic CRPC treatment.[3] However, using Taxotere before Xtandi has been shown to decrease the effectiveness of Xtandi

[3] 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.

by a median overall survival of 15.8 months.[4] Zytiga and Xtandi 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.[5] In fact, in a study conducted by Schrader *et al.*, it was reported that 48.6% of patients who previously took Zytiga and Taxotere were completely resistant to Xtandi.[6] Based on the susceptibilities of individual patients, oncologists may want to prescribe Xtandi over Zytiga for its toxicity profile or to patients who cannot tolerate low-dose steroids.[6] If insurance companies were to restrict the use of Xtandi in favor of Zytiga or Taxotere, it would likely prove detrimental to the survival of those patients.

As a direct result of the high price charged by Astellas, U.S. insurance companies and other third party payers have predictably restricted access to Xtandi. Insurers discourage prescribers by requiring restrictive prior authorizations that prevent use of Xtandi before a patient has failed other treatments. UnitedHealthcare, for example, noted in a memorandum that "Supply limits and/or Step Therapy may be in place."[7]

Table 2.1 shows information from insurance formularies from across the United States, including whether prior authorization is required and what tier the insurer has placed the drug on in their formulary. Higher tiers generally indicate higher copays and restricted access, and insurers generally use 3- or 5-tier systems. (See the next section for a discussion of Medicare spending on Xtandi.)

Table 2.1: Prior authorization requirements and formulary tiers for seven insurers providing reimbursements for Xtandi/enzalutamide.

Payer	Formulary	Tier	Prior Authorization
Rocky Mountain Health Plans	Good Health Formulary[8]	3	Yes
Kaiser Permanente	Exchange Formulary[9]	4	No
Aetna	Three Tier Open Individual Formulary[10]	3	Yes: step therapy
Cigna	Prescription Drug List[11]	5	Yes

[4] 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.
[5] Zhang T. *et al.* Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistantprostate cancer. Expert Opin Pharmacother. 2015 Mar;16(4):473-85.
[6] Schrader AJ *et al*. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. Eur Urol. 2014 Jan;65(1):30-6.
[7] https://goo.gl/PFtBkf
[8] http://www.rmhp.org/docs/default-source/resources/good_health_formulary.pdf?sfvrsn=10
[9] https://healthy.kaiserpermanente.org/static/health/pdfs/formulary/mid/mid_exchange_formulary.pdf
[10] https://goo.gl/Z31uvf
[11] http://www.cigna.com/individuals-families/prescription-drug-list?consumerID=cigna&indicator=IFP

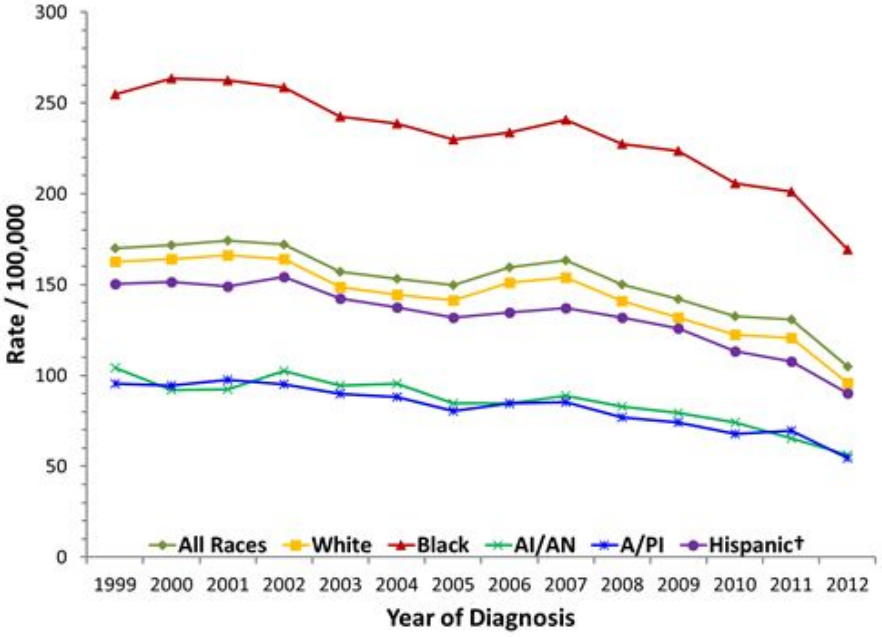
BlueCross BlueShield	Federal Employee Program[12]	4	Yes
Montana Health CO-OP	2015 CoventryOne Prescription Drug List[13]	4	Yes
Anthem BlueCross	Select Drug List 4-Tier Formulary[14]	4	Yes

There is also a racial disparity in the incidence, mortality, and treatment of prostate cancer. NIH and DoD should be concerned that the high price of Xtandi may be contributing to systemic racial discrimination in medical care in the United States. Data collected by the Centers for Disease Control shows that African American men have higher incidence and mortality rates than all other populations. Around two times more African American men have prostate cancer than white men (graph 2.1), and around 2.5 times more African American men die from the disease compared to white men (graph 2.2).[15] In addition, African American men are more likely to have a more aggressive form of prostate cancer. Researchers believe that this racial disparity is the result of sociobiological factors that affect people of African descent.

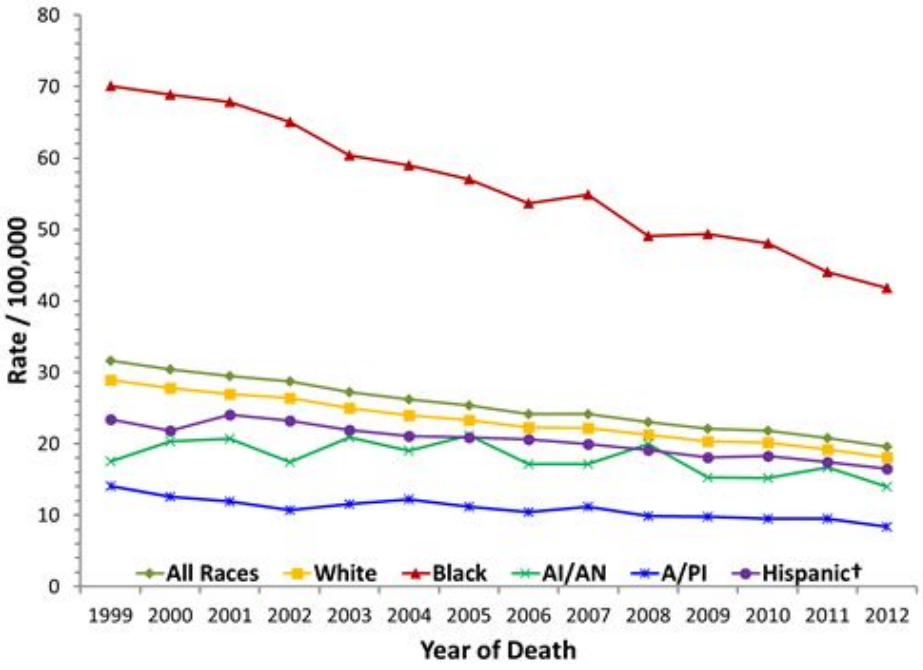
Beyond sociobiological effects on incidence, mortality, and severity of prostate cancer, African American men face systemic discrimination that affects their access to and quality of treatment. One recent study has found that African-American men on Medicare being treated for nonmetastatic prostate cancer experienced treatment delays, and had more postoperative emergency room visits and readmissions compared to white men.[16] “This might be a form of institutional discrimination based on socioeconomic status resulting in racially disparate outcomes,” wrote Dr. Otis Brawley, chief medical officer of the American Cancer Society, commenting on that study.[17]

[12] https://media.fepblue.org/-/media/PDFs/Brochures/FEP_AbbreviatedFormulary_100715.pdf
[13] http://www.mhc.coop/wp-content/uploads/docs/MHC-Covered-Drugs.pdf
[14] https://fm.formularynavigator.com/MemberPages/pdf/2016CASelectHIX_7006_Full_1576.pdf
[15] See CDC, “Prostate Cancer Rates by Race and Ethnicity,” available at http://www.cdc.gov/cancer/prostate/statistics/race.htm.
[16] Schmid M et al. Racial differences in the surgical care of Medicare beneficiaries with localized prostate cancer. JAMA Onc. 2015 Oct. doi:10.1001/jamaoncol.2015.3384
[17] Brawley OW. The meaning of race in prostate cancer treatment. JAMA Onc. 2015 Oct. doi:10.1001/jamaoncol.2015.3615

Graph 2.1: "Prostate Cancer Incidence Rates by Race and Ethnicity, U.S., 1999–2012"[18]



Graph 2.2: "Prostate Cancer Death Rates by Race and Ethnicity, U.S., 1999–2012"[19]



[18] See CDC, "Prostate Cancer Rates by Race and Ethnicity," available at http://www.cdc.gov/cancer/prostate/statistics/race.htm, which contains additional notes on the data/methodologies used to create graphs 1 and 2 in this letter.
[19] See CDC, "Prostate Cancer Rates by Race and Ethnicity," available at http://www.cdc.gov/cancer/prostate/statistics/race.htm.

Veterans who served in Vietnam and the Korean demilitarized zone, who may have been exposed to Agent Orange, are also at higher risk for more aggressive forms of prostate cancer, according to a study conducted by the Department of Veterans Affairs and Oregon Health and Science University.[20]

3. The cost of Xtandi to Medicare.

According to the Centers for Medicare and Medicaid Services, total Medicare spending on Xtandi grew dramatically from under $35 million in 2012 to nearly $447 million in 2014. The increase in outlays from 2013 to 2014 was 93 percent. Part of that growth was due to a 9 percent price increase from 2012 to 2014, a period in which the Consumer Price Index (CPI) grew a mere 3 percent. There was also a steep increase in the number of patients, from 2,143 in 2012, to 7,329 in 2013, and 11,800 in 2014.

Table 3.1: Xtandi/Enzalutamide/Medicare Part D, 2012 to 2014

Year	Total Spending	Beneficiary Cost Share	Beneficiary Count	Total Annual Spending Per User	Avg Cost Per Unit	Claim Count
2012	$34,898,755.93	$2,359,870.77	2,143	$16,285.00	$63.72	4,519
2013	$231,503,731.19	$13,276,790.11	7,329	$31,587.36	$64.85	29,572
2014	$447,311,084.46	$24,567,059.52	11,800	$37,907.72	$69.41	53,980

For prostate cancer, the average age at diagnosis is 66 years. At present, approximately 14 percent of the population is 65 or over, but in five years this will increase to 16 percent, and by 2030 is expected to exceed 19 percent. As the population continues to age, we can reasonably predict that Medicare expenditures on Xtandi will continue to climb.

4. Astellas and Medivation projections of Xtandi sales.

According to the Astellas 2015 annual report,[21] the United States market will represent 61.16 percent of all global sales of Xtandi, for the fiscal year ending March 31, 2016. Note that in the U.S., sales of Xtandi increased 77 percent from FY2013 (April 1, 2013 to March 31, 2014) to FY2014 (April 1, 2014 to March 31, 2015), and are projected to increase 51 percent from FY2014 to FY2015. This is a steep increase in use for a costly drug.

[20] Ansbaugh N et al. Agent Orange as a risk factor for high-grade prostate cancer. Cancer. 2013 Jul; 119(13):2399-2404. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4090241/.
[21] Astellas Annual Report 2015, available at https://www.astellas.com/en/ir/library/pdf/2015AR_en_1007-2.pdf.

Table 4.1: Actual and projected Xtandi sales, FY2013 to FY2015[22]

Country/Region	FY2013	FY2014	FY2015 (projected)
Japan		$125,147,037	$193,179,990
U.S.	$441,000,000	$779,000,000	$1,180,000,000
Percent Change in Sales, U.S.		77%	51%
Other Americas	$8,000,000	$24,000,000	$35,000,000
Europe, Middle East, and Africa	$75,255,950	$259,095,485	$505,289,950
Asia/Oceania		$5,039,478	$15,958,347
Global	$524,255,950	$1,192,282,001	$1,929,428,288
Percent U.S. Sales to Global	84%	65%	61%

Astellas developed Xtandi in collaboration with Medivation. The Medivation 2015 SEC 10-K filing reports actual Xtandi sales in the United States for calendar years 2012 to 2014.

Medicare's share of sales have increased sharply since 2012. In 2014 they accounted for 66 percent of Xtandi's overall U.S. sales, and 42 percent of global sales. The United States is the largest spender on Xtandi, and most of that money is coming from taxpayers and the insurance payments of aging Americans.

Table 4.2: Actual Xtandi sales, U.S., 2012 to 2014[23]

Calendar Year	2012	2013	2014
Xtandi U.S. Sales	$71,504,000	$392,415,000	$679,805,000
Percent Change in U.S. Sales		449%[24]	73%
Xtandi Non-U.S. Sales		$52,800,000[25]	$381,100,000
Medicare Total Spending	$34,898,755.93	$231,503,731.19	$447,311,084.46
Medicare Share of U.S. Sales	49%	59%	66%
Medicare Share of Global Sales	49%	52%	42%

[22] Astellas defines its fiscal year as April 1 to March 31, beginning in the year indicated. Monetary amounts were converted to USD from regional currencies, as necessary.
[23] Medivation 2015 Form 10-K, available at http://files.shareholder.com/downloads/MDV/1291225255x0xS1193125-15-62576/1011835/filing.pdf.
[24] Note: Xtandi was approved on August 12, 2012, which accounts for low sales.
[25] Note: Xtandi was first approved outside the U.S. in June 2013, which accounts for low sales.

5. The role of the U.S. government in funding research on Xtandi.

As noted above, all three patents in the Orange Book for Xtandi disclose the fact that the inventions were made with the support of the United States government under National Institutes of Health SPORE grant number 5 P50 CA092131 and Department of Defense (Army) grant number W81XWH-04-1-0129.

In addition to the grants listed in these three patents, the development of this drug benefited from additional research subsidies from the federal government and charitable foundations, including grants for clinical testing of the drug. For example, a 2009 paper in *Science* reporting on the development of MDV3100 (the development name for enzalutamide)[26] acknowledged funding from the Prostate Cancer Foundation, the National Cancer Institute, the DOD PC051382 Prostate Cancer Research Program Clinical Consortium Award, and support from the Charles H. Revson Foundation. Likewise, a 2010 paper in *the Lancet r*eporting on a critical Phase 1-2 trial acknowledges the financial support of Medivation, but also the Prostate Cancer Foundation, National Cancer Institute, the Howard Hughes Medical Institute, Doris Duke Charitable Foundation, and Department of Defense Prostate Cancer Clinical Trials Consortium.[27]

6. Enzalutamide is an important cancer drug.

In the United States today there are nearly 3 million men suffering from prostate cancer, with over 220,000 new cases in 2015 alone, and 27,540 deaths. It is the third most common form of cancer in the U.S.

When patients are treated early and tumors are localized, the prognosis is often favorable. However, some patients will relapse, leading in nearly all cases 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 Xtandi/enzalutamide, a non-steroidal second generation androgen receptor agonist, becomes critical to extending the life of the patient, and allowing patients to live an improved quality of life.

There are currently six treatments being used to treat CRPC. Xtandi/enzalutamide has several advantages over the other treatments. Four of the treatments are invasive and require I.V. administration, leukapheresis, or the use of radiopharmaceuticals. Xtandi/enzalutamide and Zytiga are the only daily oral tablets. However Xtandi/enzalutamide's pill burden is lighter since

[26] Tran C *et al.* Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science. 2009. May. 8;324(5928):787-90.

[27] Scher HI *et al.* Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study, Lancet. 2010 Apr 24;375(9724):1437-46. doi: 10.1016/S0140-6736(10)60172-9.

it does not need to be taken in combination with prednisone. As such, Xtandi/enzalutamide is well tolerated and has more favorable toxicity profile.

Quality of life was also more frequently improved and median time to deterioration was significantly longer with Xtandi/enzalutamide compared to placebo, as reported by patients in functional assessment questionnaires administered during clinical trials.[28]

With recent and ongoing clinical trials reporting better prostate cancer control when Xtandi/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 wider subset of patients.[29,30,31] In fact experts say that in the next 3 years all CRPC will progress to Xtandi or Zytiga.[32]

Xtandi/enzalutamide is also being tested for other types of cancer, including clinical trials for breast cancer (triple negative[33], her2+[34]), hepatocellular carcinoma[35], bladder cancer[36], ovarian or fallopian tube cancer,[37] pancreatic cancer[38] and Mantle Cell Lymphoma[39].

7. The University of California at Los Angeles (UCLA) interest in the patents

According to the Medivation's 2014 10-K report to the Securities and Exchange Commission (SEC), the University of California at Los Angeles (UCLA) licensed the patents for the drug to Medivation in exchange for an annual payment of $2.8 million, a 4 percent royalty on global net sales of the drug, and in addition a 10 percent share of Medivation's sublicensing income

[28] Rodriguez-Vida A *et al.* Enzalutamide for the treatment of metastatic castration-resistant prostate cancer.Drug Des Devel Ther. 2015 Jun 29;9
[29] Scher HI *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep.
[30] Loriot Y *et al*. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol. 2015 May.
[31] STRIDE results presented at 2015 American Society of Clinical Oncology annual meeting, Clinicaltirals.gov:NCT01981122.
[32] Zhang T. *et al.* Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistantprostate cancer. Expert Opin Pharmacother. 2015 Mar;16(4):473-85.
[33] NCT01889238.
[34] NCT02091960.
[35] NCT02528643, NCT02642913. Hepatocellular carcinoma (HCC, also called malignant hepatoma) is the most common type of liver cancer, often secondary to a viral hepatitis infection (hepatitis B or C) or cirrhosis.
[36] NCT02605863, NCT02300610.
[37] NCT02300610.
[38] NCT02138383.
[39] NCT02489123. Mantle cell lymphoma (MCL) is a rare, B-cell NHL that most often affects men over the age of 60.

derived from the Astellas Collaboration Agreement.[40] The Astellas Collaboration Agreement has separate terms for U.S. and non-U.S. sales, as described below:

Medivation 2014 10-K

p.121:

(c) License Agreement with UCLA

Under an August 2005 license agreement with UCLA, the Company's subsidiary Medivation Prostate Therapeutics, Inc. holds an exclusive worldwide license under several UCLA patents and patent applications covering XTANDI and related compounds. Under the Astellas Collaboration Agreement, the Company granted Astellas a sublicense under the patent rights licensed to it by UCLA.

The Company is required to pay UCLA (a) an annual maintenance fee, (b) $2.8 million in aggregate milestone payments upon achievement of certain development and regulatory milestone events with respect to XTANDI (all of which has been paid as of December 31, 2014), (c) ten percent of all Sublicensing Income, as defined in the agreement, which the Company earns under the Astellas Collaboration Agreement, and (d) a four percent royalty on global net sales of XTANDI, as defined.

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(c) Collaboration Revenue

Collaboration revenue consists of three components: (a) collaboration revenue related to U.S. XTANDI sales; (b) collaboration revenue related to ex-U.S. XTANDI sales; and (c) collaboration revenue related to upfront and milestone payments.

[...]

Collaboration Revenue Related to U.S. XTANDI Sales

Under the Astellas Collaboration Agreement, Astellas records all U.S. XTANDI sales. The Company and Astellas share equally all pre-tax profits and losses from U.S. XTANDI sales. Subject to certain exceptions, the Company and Astellas also share equally all XTANDI development and commercialization costs attributable to the U.S. market, including cost of goods sold and the royalty on net sales payable to UCLA under the Company's license agreement with UCLA. The primary exceptions to the equal cost sharing are that each party is responsible for its own commercial FTE costs and that development costs supporting marketing approvals in both the United States and either Europe or Japan are borne one-third by the Company and two-thirds by Astellas. The Company recognizes collaboration revenue related to U.S. XTANDI sales in the period in

[40] UNITED STATES SECURITIES AND EXCHANGE COMMISSION, Form 10-K, For the Fiscal Year Ended December 31, 2014,
http://www.sec.gov/Archives/edgar/data/1011835/000119312515062576/d850483d10k.htm

which such sales occur. Collaboration revenue related to U.S. XTANDI sales consists of the Company's share of pre-tax profits and losses from U.S. sales, plus reimbursement of the Company's share of reimbursable U.S. development and commercialization costs. The Company's collaboration revenue related to U.S. XTANDI sales in any given period is equal to 50% of U.S. XTANDI net sales as reported by Astellas for the applicable period.

[...]

Collaboration Revenue Related to Ex-U.S. XTANDI Sales

Under the Astellas Collaboration Agreement, Astellas records all ex-U.S. XTANDI sales. Astellas is responsible for all development and commercialization costs for XTANDI outside the United States, including cost of goods sold and the royalty on net sales payable to UCLA under the Company's license agreement with UCLA, and pays the Company a tiered royalty ranging from the low teens to the low twenties on net ex-U.S. XTANDI sales. The Company recognizes collaboration revenue related to ex-U.S. XTANDI sales in the period in which such sales occur. Collaboration revenue related to ex-U.S. XTANDI sales consists of royalties from Astellas on those sales.

[...]

Medivation came to acquire rights to Xtandi from UCLA through an agreement initiated by Dr. Charles L. Sawyers and Dr. Michael E. Jung, researchers at UCLA working on prostate cancer screening techniques and treatments. Dr. Sawyers is an oncologist who currently runs a lab at Memorial Sloan Kettering Cancer Center and serves on the Board of Directors for Novartis.[41] He was a key participant in the development of Gleevec and Sprycel, and is a recipient of the Lasker Award. Dr. Michael E. Jung is a Distinguished Professor of Chemistry at UCLA, where he runs a lab that conducts research on chemicals related to the treatment of cancer.

Dr. Sawyers approached Medivation through its founder, Dr. David Hung, a former colleague at the University of California, San Francisco. They settled on an agreement that required Dr. Sawyers and Dr. Jung to disclose all molecules related to their prostate cancer research that benefitted from Medivation funding. Dr. Sawyers served on Medivation's Scientific Advisory Board, as did Dr. Jung, receiving $20,000 and $400,000 worth of stocks, respectively.

In addition, Dr. Sawyers and Dr. Jung used the fruits of their research to found their own pharmaceutical firm, Aragon Pharmaceuticals, which they used as a vehicle to develop a drug with a very similar chemical structure to Xtandi. Medivation sued the doctors, Aragon, and UCLA, over the development of that drug.[42] According to SEC filings, Medivation and UCLA are now engaged in separate litigation over licensing payments on Xtandi.[43]

[41] More on Dr. Sawyers is available here: http://www.bloomberg.com/research/stocks/private/person.asp?personId=12631592&privcapId=25460204.
[42] For an amended complaint, filed February 9, 2012, see here: https://goo.gl/p3Ipnm.
[43] Medivation 2015 10-K SEC filing, available here: http://files.shareholder.com/downloads/MDV/1291225255x0xS1193125-15-62576/1011835/filing.pdf.

8. Orange Book patent claims for Xtandi

As noted above, Astellas has listed three patents in the FDA Orange book for Xtandi sales. These include US patent number 7709517, for both a drug substance and drug product claim, and two additional patents, US patent numbers 8183274 and 9126941.

Table 8.1: Xtandi Patents

Patent Number	**7,709,517**	**8,183,274**	**9,126,941**
Title:	Diarylhydantoin compounds	Treatment of hyperproliferative disorders with diarylhydantoin	Treatment of hyperproliferative disorders with diarylhydantoin compounds
Publication date	May 4, 2010	May 22, 2012	Sep 8, 2015
Filing date	May 15, 2006	Feb 18, 2010	Apr 17, 2012
Priority Date	May 13, 2005	May 13, 2005	May 13, 2005
Inventors	Charles L. Sawyers, Michael E. Jung, Charlie D. Chen, Samedy Ouk, Derek Welsbie, Chris Tran, John Wongvipat, Dongwon Yoo	Charles L. Sawyers, Michael E. Jung, Charlie D. Chen, Samedy Ouk, Chris Tran, John Wongvipat	Charles L. Sawyers, Michael E. Jung, Charlie D. Chen, Samedy Ouk, Chris Tran, John Wongvipat
Original Assignee	The Regents Of The University Of California	The Regents Of The University Of California	The Regents Of The University Of California
Expiration date	Aug 13, 2027	May 15, 2026	May 15, 2026
FDA substance claim	Yes		
FDA product claim	Yes		
FDA use claim code		U - 1281; The treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have previously	U - 1588, The treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

		received docetaxel. U - 1588, The treatment of patients with metastatic castration-resistant prostate cancer (CRPC).	
Disclosure of US rights in the patent	This invention was made with United States Government support under National Institutes of Health SPORE grant number 5 P50 CA092131 and Department of Defense (Army) grant number W81XWH-04-1-0129. The Government has certain rights in the invention.	This invention was made with United States Government support under National Institutes of Health SPORE grant number 5 P50 CA092131 and Department of Defense (Army) grant number W81XWH-04-1-0129. The Government has certain rights in the invention.	This invention was made with Government support under Grant No. W81XWH-04-1-0129 awarded by the United States Army, Medical Research and Materiel Command; Grant No. CA092131 awarded by the National Institutes of Health. The Government has certain rights in this invention.

9. Non-patent exclusivity.

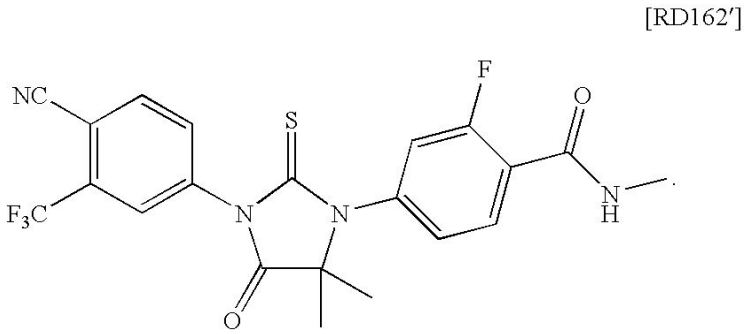
The FDA Orange Book lists two grants of non-patent exclusivity to Astellas for enzalutamide, both expiring in 2017. One was granted for enzalutamide as a new chemical entity, expiring August 31, 2017; the second was granted under code I-693 for “treatment of patients with metastatic castration-resistant prostate cancer (CRPC)”, expiring September 10, 2017. These dates are sufficiently close that they should not be used to excuse non-action on this request, particularly since it may take several months for a generic supplier to prepare data for an Abbreviated New Drug Application (ANDA).

10. Generic supply

Enzalutamide is a small molecule drug that does not have a complex structure.

Enzalutamide is a synthetic, non-steroidal pure antiandrogen, originally named MDV3100, which has the formula $C_{21}H_{16}F_4N_4O_2S$, a molar mass of 464.44 g/mol and a chemical name of 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide. The chemical structure, illustrated in Figure 1, includes a thiohydantoin and two benzene groups.

Figure 10.1: Structure of MDV3100 (CAS number: 915087-33-1)



Petitioners have excellent relations with several generic drug manufacturers, and do not anticipate difficulties obtaining the necessary FDA approvals for generic versions of enzalutamide, once the federal government provides access to the patents, either by using the royalty-free right in the patents or granting this march-in request.

Note that the 2015 U.S. AWP for Xtandi of $88.48 per 40 mg capsule is equivalent to $2,212 per gram of active pharmaceutical ingredient.

Generic products with similar complexity for manufacturing can be obtained for under $10 per gram of API, retail,[44] and considerably less in bulk.

11. Xtandi R&D investments through the 2012 approval for the lead indication

Xtandi was approved as a treatment for prostate cancer in August 31, 2012, as a priority drug under the FDA Priority Review program. The application was by Astellas, and was approved by the FDA as NDA 203415.

The application for the NDA was supported by evidence from four clinical trials, including one Phase 1 trial with 140 patients enrolled, one Phase 1/2 trial with 27 patients enrolled, one Phase 2 trial with 60 patients enrolled, and one Phase 3 trial with 1,199 patients enrolled. Total enrollment for the 4 trials was 1,426 patients.

[44] For example, generic versions of the cancer drug imatinib.

Table 11.1: Trials Reported in FDA Medical Review for 2012 Approval for Xtandi

Study Number	NCT Number	Phase	Start- End Date	Enrolled (FDA Review)	Study Sponsor	Federal Funding
S-3100-1-01	NCT00510718	1	7/2007- 1/2010	140	Medivation	NCI, DoD[45]
CRPC-MDA-1	NCT01091103	2	2/2010- 7/2011	60	Medivation	NCI, DoD[46]
CRPC2	NCT00974311	3	9/2009- 9/2011	1199	Medivation	n/a
9785-CL-0111	NCT01284920	1/2	11/2010- 7/2012	27	Astellas Pharma	n/a

The two earliest trials (NCT00510718, NCT01091103) received subsidies from the National Cancer Institute and Department of Defense, in addition to funding from the Prostate Cancer Foundation and other non-profit institutions. After receiving favorable results from the trials subsidized by NCI and DoD, Medivation and Astellas funded two additional trails.

The size of the trials for Xtandi were typical of other cancer drugs approved from 2010 to 2014 for the lead indication as a New Molecular Entity, and much smaller than trials used to approve non-cancer drugs.

Table 11.2: Trial enrollment cited in in FDA medical reviews for lead indication of new drugs, 2010 to 2014

Average for all cancer drugs	1,316
Average for non-Cancer Drugs	4,733
Xtandi	1,426

Medivation reported their direct expenditures and cost-sharing payments from Astellas for collaboration on the development of Xtandi between 2005 and 2012, when the FDA granted Xtandi marketing approval. They defined direct costs as “clinical and preclinical study costs, cost of supplying drug substance and drug product for use in clinical and preclinical studies, contract research organization fees, and other contracted services pertaining to specific clinical and preclinical studies.”[47] The number reported excludes indirect costs, which include “administrative and support costs.”[48]

Astellas contributed to half of all direct costs for R&D conducted for U.S. drug approval, two-thirds of costs for R&D directed towards trials aimed at both U.S. and non-U.S. use of

[45] Scher, Howard I., et al. "Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study." *The Lancet* 375.9724 (2010): 1437-1446.
[46] Efstathiou, Eleni, et al. "Molecular characterization of enzalutamide-treated bone metastatic castration-resistant prostate cancer." *European urology* 67.1 (2015): 53-60.
[47] Medivation 2009 10-K SEC filing, available here: http://files.shareholder.com/downloads/MDV/1291225255x0xS1193125-10-57020/1011835/filing.pdf.
[48] Ibid. Indirect costs for all drugs combined are available in Medivation SEC filings.

Xtandi, and full development costs for commercialization outside the United States. Based upon the Medivation SEC filings, R&D outlays on Xtandi were $303 million through the end of the calendar year 2012.

Table 11.3: R&D expenditures on Xtandi, 2005-2012 (in thousands of USD)

SEC 10-K Year	2005	2006	2007	2008	2009	2010	2011	2012
Medivation Direct Costs	$261	$3,021	$2,619	$8,845	$27,046	$23,454	$42,3350	$67,086
Development cost-sharing payments from Astellas					$2,784	$34,125	$44,285	$47,473
Total	$261	$3,021	$2,619	$8,845	$29,830	$57,579	$86,620	$114,559
Cumulative Total								$303,334

Medivation reported outlays of an additional $285 million in calendar years 2013 and 2014, much of that money aimed at justifying broader use of Xtandi for prostate cancer, but also on testing the drug to treat other types of cancer.

Table 11.4: R&D expenditures on Xtandi, 2013 and 2014 (in thousands of USD)

SEC 10-K Year	2013	2014
Medivation Direct Costs	$73,076	$102,669
Development cost-sharing payments from Astella	$46,594	$63,479
Total	$119,670	$166,148
Cumulative Total		$285,818

The company outlays on R&D investments were significant, although it is worth noting that the early and most risky trials were small and subsidized by the United States government.

Note that through the end of 2014, representing a little more than two years of reimbursements, Medicare spent $704 million on Xtandi. Astellas expects a sharp increase in U.S. sales in 2015 and 2016, and the company revenues also include sales from non-Medicare patients in the United States and patients outside of the United States.

12. Clinical trials on enzalutamide, including trials subsequent to 2012 NDA.

Like many cancer drugs, the initial approval of the drug for the lead indication has lead to continued research to determine the best uses of the drugs, both for prostate cancer patients and to test the benefits of using enzalutamide to treat other types of cancer.

As of January 6, 2015, there were 129 trials listed in the ClinicialTrials.Gov database.

The funding of the trials is reported under the categories Industry, U.S. Fed., NIH, and Other, as well as combinations of those categories.

- 54 of the 129 trials were reported as funded by Industry alone.
- Another 31 trials were reported as funded by Industry and some other funder.
- The NIH or other U.S. Federal agencies were reported as funders in whole or in part of 18 trials.
- The category “Other” is quite important, accounting for 29 trials funded exclusively by Other, and another 42 where “Other” is among the funders.

Many of the trials funded by “Other” refer to universities and other non-profit research organizations that receive NIH or other federal agency research grants. “Other” also refers to funding from foreign governments and charities.

Table 12.1: Number of trials funded by Industry, NIH, other “U.S. Fed” and “Other,” as reported in ClinicalTrials.Gov, January 6, 2016.

Funder	Number of Trials
“Industry” only	54
Mixed including “Industry”	31
“Other” only	29
Mixed including “Other”	42
NIH only	3
Mixed including NIH or other “U.S. Fed”	16

Table 12.2: Number of trials funded by Astellas and/or Medivation, as reported in ClinicalTrials.Gov, January 6, 2016.

Funder	Number of Trials
Astellas and/or Medivation as sponsor of industry only funded trials	39
Astellas and/or Medivation as sponsor of mixed funded trials	18

Among the trials funded in whole or in part by “Industry”, the majority, 57, were funded by Astellas and/or Medivation, and of those only for 39 (30 percent of the 129) were they the sole funder of the trials.

Other companies, such as Lilly, Gilead, Roche, Bayer, Sanofi, and smaller companies, were involved in funding 28 trials.

13. Licensing terms, including reasonable royalty.

We are requesting the federal government grant an open license to any generic drug manufacturer.

The federal government has no obligation to pay royalties on the patents when and if it exercises its royalty free rights in the patents.

If the government orders the licensing of the patents under the federal march-in statutes, the terms of the license, including the royalty, have to be "reasonable under the circumstances."[49]

The issue of the appropriate royalty rate can be briefed and argued when and if the federal government is inclined to exercise march-in rights on the patent.

"Under the circumstances" would include many factors, such as that the facts motivating the granting of the march-in request are related to abuses of the patent rights, including in particular charging an excessive price and discriminating against U.S. consumers.

Rights in test data

Patents are granted for inventions, but as noted above, patents are not the only intellectual property rights associated with drug development.

The FDA provides additional intellectual property rights for investments in clinical trials, including five years of exclusive rights to rely upon data supporting the registration of a new chemical entity, and three years of rights in the data to support new indications on a drug.

The five years of test data exclusivity for Xtandi as a treatment for patients with metastatic castration-resistant prostate cancer (CRPC) will expire on September 10, 2017 in the United States, and later in many other countries. For example, the term of protection for test data is up to 8 years in Japan and Canada, and 11 years in the European Union.[50] The rights in test data are designed to protect and reward investments in clinical trials, and they operate separately from patent protection. The existence of the test data rights eliminates the need to consider investments in clinical trials when considering the royalty to the patent holder, because those investments are protected by this separate intellectual property right. As regards the

[49] 35 USC 203(a).
[50] Comparison of the Non-patent Drug Exclusivities Available in the United States, Canada, Europe and Japan. The International Economic Forum of the Americas. Serge Lapointe, Ph.D. June 14, 2012 http://forum-americas.org/sites/default/files/documents/20120614-lapointe-pres.pdf

investments in the U.S. market, it is likely that Astellas will have earned more than $5 billion from the U.S. market alone, through September 10, 2017, the date of the most relevant test data exclusivity in the United States ends. Astellas will have also earned billions more from sales outside of the United States, where most patients reside.

Average industry royalty rates

According to the IRS, in 2012, the average rate of aggregate royalties (for all patents, know-how, trademarks, etc.[51]), reported on corporate income tax returns for the pharmaceutical and medicine manufacturing sector (MINOR CODE 325410) was 6.95 percent.

14. Funding of research to further develop enzalutamide.

One possible argument against any policy that lowers drug prices or shortens the term of a monopoly is that society benefits from the incentive to invest in R&D to find new uses for a drug.

It is possible to address the objective of providing sustainable sources of R&D funding without having high prices or longer monopolies.

On at least two occasions in the past involving NIH funded cancer drugs, and more recently in connection with proposals to create or extend monopolies in various drafts of the 21st Century Cures Act, there have been proposals to have mandates for funding R&D.

In one case, involving a dispute over the term of the monopoly on the cancer drug cisplatin in the early 1980s, there was a proposal that generic firms be obligated to contribute to the costs of ongoing research to determine new uses for the drug, following generic entry. This proposal, made by a generic drug company seeking to end the cisplatin monopoly, led to a compromise whereby Bristol-Myers was allowed to extend the monopoly for five more years, but only after they lowered the price of cisplatin and contributed tens of millions of dollars to independent research through non-profit institutions, at the direction of the NIH. Later, BMS proposed something similar, in an unsuccessful effort to extend data exclusivity on the cancer drug Taxol. In early drafts of the the 21st Century Cures legislation, there were proposals to associate extensions of drug monopolies with obligations to provide money to the NIH, and to make other investments in R&D.

In this case involving Xtandi, the NIH could simultaneously end the Xtandi monopoly and require any generic drug company to make contributions toward follow-on research to explore new and/or better uses of enzalutamide. Such obligations could be a condition of any use of the federal government's royalty free right in the drug, or as a condition of obtaining a march-in license.

[51] The IRS does not provide a definition of royalties. See: https://www.irs.gov/pub/irs-tege/eotopicd89.pdf.

Note that there are benefits in having different parties participate in the testing of drugs, including those that do not have conflicts of interest as regards reporting possible negative impact of products, or allowing greater competition in designing better delivery mechanisms or new combination products. Also, in the case of Xtandi, more than half of the trials involving enzalutamide are already funded by entities other than Astellas.

15. Standard for determining that Xtandi prices are unreasonable.

In determining if the prices for Xtandi violate the statutory obligation to make products available to the public on reasonable terms and conditions, the NIH has broad discretion to consider a variety of factors, including the high price of the drug and the fact that the high price leads to restrictions on access and financial hardships on patients. However, in this case, we recommend the NIH address a narrower question, that can be answered clearly, given the robust evidence.

Do the Astellas prices for Xtandi discriminate against consumers in the United States? And, if so, the NIH should approve the March-In request, or use its royalty free rights in the patents, to prevent U.S. residents from paying more for a drug invented on federal grants than residents of other high income countries.

We have obtained prices for Xtandi in the United States and in 13 other high income countries, and this data allows the NIH to determine whether U.S. consumers are being asked to pay more for a drug invented on federal grants than Astellas charges in other high income countries.

One possible comparison to determine if the price is unreasonable is to consider the prices in other industrialized countries outside of the United States that have (1) per capita incomes of at least half that of the United States, (2) have the large economies as measured by the GDP, and (3) are members of the OECD, and to consider the U.S. price to be unreasonable, if the average wholesale price (AWP) in the U.S. is higher than the median price in the reference countries.

We propose using an odd number of countries. The 13 countries that have incomes at least 50 percent of the United States and which have the largest economies include Japan, Germany, France, the UK, Italy, Canada, Australia, Spain, the Netherlands, Switzerland, Sweden, Belgium and Norway.

We have prices for all 13 of the reference countries. None of the prices are higher than $36.93, and the April 2015 U.S. AWP was $88.48. It is not a close call: the U.S. prices are discriminatory and are unfair to U.S. residents. Note that the *highest* price of the 13 high income reference countries was less than half (42 percent) of the average wholesale price (AWP) in the United States, the median of the 13 prices reference prices we have obtained is just 36 percent of the US AWP, and the prices in Japan and Canada are 30 percent and 23 percent respectively of US AWP. As a percentage in 2014 per capita income, the U.S. prices are also

far higher than for any of the 13 high income countries. In eight countries, the annual cost of Xtandi is between 47 percent and 97 percent of annual per capita income. In four countries, the annual cost of Xtandi is between 111 percent and 161 percent of per capita income. In the United States, the annual cost of Xtandi is 234 percent of 2014 per capita income.

Table 15.1: US Average Wholesale Price, relative to prices in 13 reference countries

	2014 GDP	2014 annual Per Capita Income	price per 40 mg unit	Annual price (x 4x 365.25) as percent of 2014 per capita income
United States, Average Wholesale price April 2015	$17,419,000,000,000	$55,200	$88.48	234%
Japan	$4,601,461,206,885	$42,000	$26.37	92%
Germany	$3,868,291,231,824	$47,640	$36.93	113%
France	$2,829,192,039,172	$42,960	$26.73	91%
United Kingdom	$2,988,893,283,565	$43,430	$35.65	120%
Italy	$2,141,161,325,367	$34,270	$26.01	111%
Canada	$1,785,386,649,602	$51,630	$20.12	57%
Australia	$1,454,675,479,666	$64,540	$23.46	53%
Spain	$1,381,342,101,736	$29,440	$32.38	161%
Netherlands	$879,319,321,495	$51,890	$31.48	89%
Switzerland	$701,037,135,966	$88,120*	$35.46	59%
Sweden	$571,090,480,171	$61,610	$26.96	64%
Belgium	$531,546,586,179	$47,260	$31.48	97%
Norway	$499,817,138,323	$103,630	$33.09	47%
Median, reference countries			$31.48	91%
Unweighted average, reference countries			$29.70	89%

* For Switzerland, only 2013 per capita income was available.

One defense for the high U.S. price for Xtandi would be that the product could not have been developed at a lower price. But given the significant market for this drug, the federal subsidies in both the preclinical and clinical stages, and the fact that prostate cancer is the among the three most common types of cancer,[52] that defense can be rejected entirely, and certainly going forward, given the billions of dollars in revenue already earned by Astellas.

16. Conclusion

We are requesting the federal government take steps to address the discriminatory and unfair pricing of Xtandi/enzalutamide by Astellas. U.S. residents should not have to pay two to four

[52] American Cancer Society: Cancer Facts and Figures 2015. Atlanta, Ga: American Cancer Society, 2015.

times as much for a cancer drug than residents of other high income countries, particularly when the drug was invented with the support of federal grants and benefited from other federal research subsidies. The average wholesale price for Xtandi was $129,269 per year in 2015, and this was more than twice as high as the price in any other high income country in our 13 country survey, and four times as high as the price in Canada. U.S. taxpayers are generous when it comes to financing research programs at the NIH, the U.S. Department of Defense, and in other federal agencies. However, we should not allow the companies that commercialize this research to discriminate and use unfair prices that impose financial hardships on U.S. residents, create access barriers for cancer patients, and make our workforce less competitive in global markets.

There are many areas where current U.S. laws are inadequate to address excessive or unfair prices. This is not one of them. The Bayh-Dole Act was passed with the promise that the federal March-In rights or the federal government royalty-free rights in patents would be available to protect the public from the unreasonable use of patented inventions. This is such a case.

Please contact Andrew S. Goldman, counsel for Policy and Legal Affairs at KEI, about this request. He can be reached at andrew.goldman@keionline.org, or by telephone at +1.202.332.2670.

Sincerely,

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Senators Boxer, Brown, Grassley, King Leahy, McCain McCaskill Nelson Sanders, Schumer Sessions, and Wyden

Representatives Doggett, Schakowsky, Tom Price, Markwayne Mullin, the Congressional Prostate Cancer Task Force