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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 15, 2012
From	V. Ellen Maher
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 203415
Applicant	Medivation, Inc
Date of Submission	May 22, 2012
PDUFA Goal Date	November 22, 2012
Proprietary Name / Established (USAN) names	Enzalutamide/Xtandi
Dosage forms / Strength	40 mg capsule
Proposed Indication(s)	Indicated for the treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4)
Recommended:	Approval

1. Introduction

On May 22, 2012, Medivation, Inc. submitted NDA 203-415 for the use of enzalutamide for the following indication:

- Treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4).

2. Background

Enzalutamide inhibits multiple steps in androgen receptor signaling. Normally, androgen receptor binds to androgens in the cell cytoplasm. The androgen-androgen receptor complex is then translocated to the nucleus where the activated receptor and nuclear proteins interact with hormone response elements to transactivate androgen receptor dependent gene transcription. In vitro, enzalutamide inhibits: 1) binding of androgen to androgen receptor, 2) nuclear translocation of the androgen-androgen receptor complex, and 3) interaction of the activated receptor complex with DNA elements (Science 2009 324:787). Further, while some androgen receptor inhibitors have partial agonist properties in cell lines that overexpress or contain mutations in the androgen receptor, enzalutamide has not been shown to act as a partial agonist in these cell lines (JCO 2005 23:8253; Biochem J 2004 379:731).

The Phase 3 study in support of this indication is a large randomized trial examining enzalutamide in patients with metastatic castration-resistant prostate cancer (CRPC). Three androgen receptor inhibitors (flutamide, nilutamide, and bicalutamide) are approved for use in patients with androgen sensitive metastatic prostate cancer. Small studies have examined their effects in patients with CRPC (typically patients with rising PSA and no evidence of metastases). High dose bicalutamide has resulted in a $\geq$ 50% reduction in PSA in 10/38

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patients (Urology 2010 76:1189). With nilutamide, 8/38 patients who had received prior flutamide/bicalutamide had a ≥ 50% reduction in PSA (J Urol 2003 169:1742). Finally, use of flutamide, after response to withdrawal of bicalutamide, resulted in a ≥ 50% reduction in PSA in 8/16 patients (Int J Urology 2010 17:337). It is unknown whether these 3 currently approved agents would demonstrate efficacy in a large randomized trial of patients with CRPC or whether their clinical effect is comparable to enzalutamide. Enzalutamide is currently being compared to bicalutamide in a Phase 2 study.

Four agents have been approved for use in metastatic CRPC. The table below provides information on agents and their basis of approval.

Table 1: Approved Agents in Castrate Resistant Metastatic Prostate Cancer

Approved Agent(s)	Population	Comparator	Basis of Approval
Docetaxel Prednisone	Metastatic CRPC	Mitoxantrone Prednisone	Median OS[1] 18.9 vs. 16.6 mos HR 0.65, p = 0.0094
Cabazitaxel Prednisone	Metastatic CRPC Prior Docetaxel	Mitoxantrone Prednisone	Median OS 15.1 vs. 12.7 mos HR 0.70, p < 0.0001
Abiraterone Prednisone	Metastatic CRPC Prior Docetaxel	Prednisone	Median OS 14.8 vs. 10.9 mos HR 0.65, p < 0.0001
Sipuleucel-T	Metastatic CRPC	Peripheral Blood Mononuclear Cells	Median OS 25.8 vs. 21.7 mos HR 0.78, p = 0.32 Median OS 25.9 vs. 21.4 mos HR 0.59, p = 0.01

[1]OS-overall survival, HR-hazard ratio

Regulatory History

Medivation first proposed a Phase 3 study in patients with CRPC in March 2009. In response to the questions submitted, the Agency stated that overall survival was an acceptable primary endpoint. The Agency also stated, "If you plan to include some secondary endpoints in the label, your current plan of testing those endpoints at a level of 0.05 separately is not acceptable. A statistical plan controlling overall alpha at 0.05 for those secondary endpoints needs to be pre-specified providing those secondary endpoint are agreed by the Agency."

In December 2009, the applicant submitted a request for Special Protocol Assessment. In this version of the protocol, overall survival and progression-free survival (PFS) were co-primary endpoints. An agreement was not reached and the Agency stated that "PFS is not yet acceptable as a primary endpoint in metastatic prostate cancer." In a July 2010 meeting, the Agency further stated, "This plan (for central radiology review) is acceptable for the measurement of PFS as a secondary endpoint which will be used as confirmatory of an outcome of significant OS prolongation as a primary endpoint if that occurs." The trial was initiated in September 2009 with OS as the primary endpoint.

An April 2011 meeting discussed the following changes to the primary analysis of OS: 1) a plan to reduce the target hazard ratio from 0.80 to 0.76, 2) a corresponding decrease in the number of events from 786 to 65, and 3) a formal interim analysis at 520 (80%) events. These changes were agreed to by the FDA.

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Secondary endpoints were not discussed at the meeting. However, the last protocol amendment, April 2011, changed the secondary endpoints

From:

1. Progression free survival (radiographic progression, skeletal-related event, or death)
2. Time to radiographic progression

To:

1. Radiographic progression free survival (radiographic progression or death)
2. Time to first skeletal-related event
3. Global FACT-P score
4. Time to PSA progression
5. Pain palliation at Week 13

In the final statistical analysis plan, October 2011, the applicant provided a plan for alpha spending for three secondary endpoints in this order: 1) PSA progression, 2) radiographic progression free survival (radiographic progression or death), and 3) time to first skeletal related event.

The results of the interim analysis of OS were released November 2, 2011. The NDA was submitted on May 22, 2012.

3. CMC/Device

Enzalutamide is synthesized in (b) steps from 3 commercially available materials and is a white crystalline solid. (b) (4) The solution also contains the antioxidants butylated hydroxyanisole and butylated hydroxytoluene. Six impurities in the drug substance have been identified and qualified. This includes 2 potentially genotoxic impurities and 1 reagent that is potentially genotoxic. The specifications for these 3 compounds are (b) (4) capsule and are consistent with ICH guidance. An additional impurity, a metabolite of enzalutamide, is found in the drug product and has been qualified. The applicant has provided data to support 24 months of stability for the packaged product at 20- 25^0 C with excursions to 15-30^0 C. Establishment inspections were acceptable.

4. Nonclinical Pharmacology/Toxicology

Enzalutamide and its 2 major human metabolites, M1 and M2, were not mutagenic in the Ames assay. Enzalutamide was not clastogenic in the in vitro cytogenetic assay or the in vivo mouse micronucleus assay. No carcinogenicity studies were performed.

Three and 6 month repeat dose toxicity studies were conducted in male dogs and rats. Atrophy was seen in the prostate, epididymis, and seminal vesicles. Hypertrophy/hyperplasia was seen in the pituitary gland and hypospermia was noted in dogs. Mild hepatocellular hypertrophy and chronic progressive nephropathy were seen in the rat. Seizures, apparently dose-dependent, have been seen in humans and this has been further studied in animal models. Enzalutamide is thought to induce seizures by competing for binding to the GABA-gated chloride channel in the brain. Both enzalutamide and its metabolite M2 are able to cross the

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blood-brain-barrier. Enzalutamide and M2 are weak inhibitors of hERG with an IC_{50} of 15.7 μM for enzalutamide and 18.6 μM for M2.

5. Clinical Pharmacology/Biopharmaceutics

Enzalutamide is taken orally and absorption is not altered by a high fat meal. The median time to maximal absorption is 1 hour (range; 0.5-3 hours). Enzalutamide and its metabolites M1 (inactive) and M2 (active) are highly bound to plasma proteins. The mean half-life of enzalutamide is 5.8 days (range; 2.8-10.2 days) and it takes ~ 1 month to achieve steady state.

Enzalutamide is primarily metabolized in the liver by CYP2C8 and CYP3A4. Elimination is primarily renal with 71% recovered in the urine and 14% in the feces. Enzalutamide metabolism/elimination and drug-drug interactions are complex and are bulleted below.

- Dose reduction is not needed in patients with mild-moderate renal or hepatic impairment. It has not been studied in patients with severe renal or hepatic impairment.
- Enzalutamide and M2 are increased when co-administered with strong CYP2C8 or CYP3A4 inhibitors. The dose should be reduced if administered with CYP2C8 or CYP3A4 inhibitors. The effect of a CYP2C8 or CYP3A4 inducer is unknown.
- Enzalutamide inhibits CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 and CYP1A2. Enzalutamide did not cause a clinically relevant change in the AUC of a CYP2C8 substrate (CYP2C8 is the most easily inhibited of the enzymes mentioned).
- Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer for CYP2C9 and CYP2C19. Co-administration of drugs metabolized through these pathways should be avoided.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Studies submitted in support of this indication include:

1. CRPC2: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy

2. CRPC-MDA-1: A Study of Continuous Oral Dosing of a Novel Antiandrogen MDV3100, in Castration-Resistant Bone Metastatic Prostate Cancer Patients Evaluating the Tumor Micro-Environment

3. S-3100-1-01: A Phase 1, Open-Label, Dose-Escalation Safety and Pharmacokinetic Study of MDV3100 in Patients with Castration-Resistant Prostate Cancer

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Phase 3 Trial Design

Eligibility Criteria

1. CRPC; testosterone < 50 ng/mL with any of the following:
    a. Minimum of 3 rising PSAs ≥ 1 week apart; PSA at screening ≥ 2 ng/mL
    b. Soft tissue disease progression per RECIST
    c. ≥ 2 new lesions on bone scan
2. Prior therapy
    a. ≤ 2 prior chemotherapy regimens, 1 of which contained docetaxel
    b. No sipuleucel T
    c. No progression on ketoconazole; prior androgen receptor inhibitors permitted
    d. Not > 10 mg/d prednisone (or equivalent); No herbal products that affect PSA
3. No history of seizure, events that may pre-dispose to seizure, medications that lower the seizure threshold

Randomization

Randomized 2:1 and stratified by

- ECOG performance status (0-1, 2)
- Worst pain in the last 24 h on a 0 (none)-10 (worst imaginable) scale (< 4, ≥ 4)

Treatment

1. Enzalutamide 160 mg po qd
2. Placebo

- Patients with confirmed radiographic progression or a skeletal-related event were encouraged to continue treatment until initiation of another systemic therapy.
- Investigators were encouraged not to consider PSA progression as a criterion for discontinuation.
- Grade 3-4 toxicity: hold until grade 0-2, then resume study drug at a lower dose

Monitoring

- Routine Laboratories: Baseline, Weeks 1, 2, 5, 8, 13, 17, 21, 25, and then every 12 weeks; 30 d after last dose
- EKG: Triplicate EKGs d 1, 8, 29, and 57; EKGs Weeks 13, 17, 21, 25, and then every 12 weeks; 30 d after last dose
- PSA: Baseline, Weeks 1, 13, 17, 21, 25, and then every 12 weeks; 30 d after last dose
- Bone Scan: Baseline, Weeks 13, 24, and then every 12 weeks; progression at Week 13 requires a confirmatory scan ≥ 6 weeks later
- Abd-Pelvic CT/MRI: Baseline, Weeks 13, 24, and then every 12 weeks
    - Evaluation windows for Week 13 onward for bone scan or CT are ± 2 weeks
- Brief Pain Inventory: Baseline and Week 13
- Pain Diary: Completed 6 d prior to d 1 and d 85 visits; patients report their worst pain score each day along with their use of pain meds
    - A single long-acting narcotic, rescue narcotic, and single NSAID are to be selected for each patient until the Week 13 visit

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Statistical Plan

Primary Analysis: The primary analysis of OS used a stratified (strata at randomization) logrank test and was conducted in the intent to treat population. Kaplan-Meier curves were used to estimate median OS. With 650 events, this study had 90% power to detect a hazard ratio of 0.76 using a two-sided alpha of 0.05. This corresponds to an estimated median OS of 12 mos in the placebo group compared to 15.7 mos with enzalutamide. One interim analysis was to be performed at 80% of events. The two-sided alpha assigned to the interim analysis was 0.0244 while the alpha assigned to the final analysis was 0.0429.

Secondary Endpoints: Secondary endpoints were only be analyzed if the primary analysis was statistically significant. Per the statistical analysis plan, secondary endpoints were prioritized in the order shown so that testing was continued only as long as each endpoint was found to be statistically significant using a two-sided alpha of 0.05.

- Time to PSA progression: Time from randomization to PSA progression where progression is defined as the first date at which a $\geq$ 25% increase from nadir (absolute increase of $\geq$ 2 ng/mL) occurred. The patient's nadir may be their baseline. The rise in PSA must be confirmed by a 2nd value $\geq$ 3 weeks later. The analysis censors patients who are lost to follow up, have missing values, or have an unconfirmed rise in PSA at the data cutoff. The analysis used a stratified (randomization strata) logrank test.

- Radiographic Progression Free Survival (rPFS): Time from randomization to the earliest objective evidence of radiographic progression or death.

    1. Soft tissue: Progression is defined by RECIST v1.1. However, progression at the Week 13 scan must be confirmed by a 2nd scan $\geq$ 6 weeks later.
    2. Bone disease: Progression is defined as the appearance of $\geq$ 2 new lesions on bone scan. Progression at Week 13 requires a confirmatory scan at least 6 weeks later with 2 additional new lesions. Progression after Week 13 is defined as $\geq$ 2 new lesions on bone scan when compared to Week 13. Bone scan progression was considered missing until it was confirmed.

  Each disease assessment contained 2 components, a bone scan and a CT/MRI. In addition, bone scan progression and CT/MRI progression at Week 13 must be confirmed. The date of progression is the date of the scan at which progression was first observed, not the date of confirmation.

  If 1 component of the disease assessment was missing and 1 showed SD or better, the assessment was missing. If 1 component was missing and 1 showed PD, the assessment was PD. If both components showed PD, the earlier date was used in the analysis. If neither component showed PD, the later date was used as the censored date in the analysis. In the analysis, patients with 2 missing assessments were censored at the 1st missed assessment. Patients who were lost to follow up or who did not have baseline scans were censored at randomization. The statistical plan required that patients with PD between 2 scheduled assessment have the date of the next scheduled assessment or

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death as the date of PD. The analysis used a stratified (randomization strata) logrank test.

- Time to first skeletal related event (SRE): Time from randomization to the first SRE where SREs included radiation to the bone, surgery to the bone, pathological bone fracture, spinal cord compression, or a change in anti-neoplastic therapy required to treat bone pain. The analysis used a stratified (randomization strata) logrank test.

Protocol Amendments: Please see discussion under Regulatory History.

Disposition

This study accrued patients at 156 sites from September 2009 until November 2010 with 24% of patients recruited from the US. The cutoff date for efficacy data was September 2011. The cutoff date for safety data was January 2012.

Patient disposition is shown in the table below. Note that some patients had more than 1 type (radiographic, clinical, or skeletal-related event) of progression-event recorded at discontinuation. There is an imbalance in the number of patients who discontinued due to clinical progression (29% vs. 40%). When the number of patients who discontinuation was based solely on clinical progression is considered, 18% of patients in the enzalutamide and 24% in the placebo arm discontinued due to clinical progression. These patients will be examined in a sensitivity analysis of the primary endpoint. Finally, note that when the total number of patients with progressive disease (441 and 296) was derived, each patient was counted once.

Table 2: Patient Disposition

	Enzalutamide	Placebo
Randomized and Treated	800	399
Ongoing	232 (29%)	19 (5%)
Discontinued	569 (71%)	380 (95%)
Progressive Disease	441 (55%)	296 (74%)
Radiographic	246	180
Clinical	231 (29%)	159 (40%)
Skeletal-Related Event	81	39
Adverse Event	61 (8%)	39 (10%)
Other[1]	26 (3%)	15 (4%)
Withdrawal	23 (3%)	23 (6%)
Death	17 (2%)	6 (2%)
Protocol Violation	1 (0.1%)	1 (0.3%)

[1]The majority of these patients discontinued due to PSA progression. Data Cutoff: 9-25-11

Demographics and Baseline Characteristics

The study arms were well balanced for age (median 69 years, 70% ≥ age 65), race (93% White), and performance status (92% PS 0-1). As expected, patients were well-balanced by the stratification factor, worst pain in the last 24 hours. Here, 28% of patients rated their pain as ≥ 4 on a scale of 0-10.

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The table below provides information on baseline disease characteristics. Note that at the time of study entry, median PSA was slightly higher in the placebo arm while a similar proportion of patients in each arm had visceral disease.

Table 3: Baseline Disease Characteristics		
	Enzalutamide N = 800	Placebo N = 399
Time from Diagnosis to Entry (range)	5.9 years (0.4-23.7)	5.9 years (0.9-22.3)
Gleason Score at Diagnosis[1]		
≤ 6	14%	13%
7	31%	31%
8-10	46%	48%
Median PSA at Entry (range)	107.7 ng/mL (0.2-11,794)	128.3 ng/mL (0-19,000)
Type of Disease Progression Prior to Entry		
PSA	41%	41%
Radiographic	59%	59%
Disease Sites at Entry[2]		
Bone	92%	92%
Bone Only	28%	31%
Lymph Nodes and Soft Tissue	62%	61%
Visceral	25%	21%
Measurable Disease at Entry	56%	52%

[1]Missing: 74 enzalutamide, 31 placebo [2]1 patient had no disease at entry Data Cutoff 9-25-11

The following table provides information on prior therapy for prostate cancer. The majority of patients had received 1 chemotherapeutic regimen prior to entry and the median number of cycles of docetaxel was balanced between arms. Approximately 90% of patients had received an androgen receptor inhibitor prior to entry. This will be the subject of a subset analysis of the primary endpoint (below).

Table 4: Prior Prostate Cancer Therapies		
	Enzalutamide N = 800	Placebo N = 399
Number of Prior Chemotherapeutic Regimens		
1	72%	74%
2	25%	24%
≥ 3	3%	2%
Type of Chemotherapy		
Other	28%	27%
Docetaxel	100%	100%
Median # Cycles of Docetaxel[1]	8.5	8.0
Median Time from Last Docetaxel (range)	6.1 mos (1-80.8)	5.8 mos (0.9-94.3)
Prior Hormonal Therapy		
LHRH agonist or antagonist	93%	93%
Prior Androgen Receptor Blocker	89%	91%
Ketoconazole	3%	4%

[1]Missing: 98 enzalutamide, 66 placebo Data Cutoff 9-25-11

Primary Analysis

At the pre-planned interim analysis with 80% of events, enzalutamide demonstrated a marked improvement in OS, compared to placebo. It is interesting to the note approximately half the

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patients in the placebo arm of the enzalutamide study received prednisone. A follow up analysis of OS with 89% of events found a HR of 0.62.

These results can be compared to the findings in similar patient populations. With abiraterone plus prednisone, median OS (vs. prednisone) was 14.8 vs. 10.9 months, HR 0.65. With cabazitaxel plus prednisone, median OS (vs. mitoxantrone and prednisone) was 15.1 vs. 12.7 months, HR 0.70.

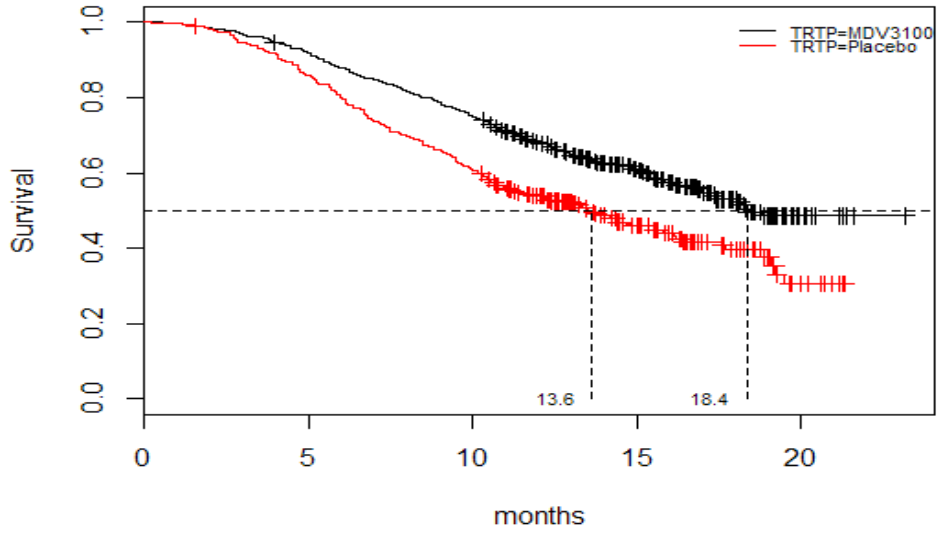
Table 5: Pre-Planned Interim Analysis of Overall Survival

	Enzalutamide N = 800	Placebo N = 399
Events		
Deaths	308 (39%)	212 (53%)
Censored	486 (61%)	182 (46%)
Missing	6	5
Median Overall Survival	18.4 mos	13.6 mos
Hazard Ratio (95% CI)[1]	0.63 (0.53, 0.75)	
p-value (logrank)	< 0.0001	

[1]Stratified proportional hazards model using the stratification factors at randomization. Data Cutoff 9-25-11

The figure below shows the Kaplan-Meier curves for OS at the time of the interim analysis.

Figure 1: Kaplan-Meier Analysis of Overall Survival



Information was collected on the use of anti-cancer agents after discontinuation of study drug. The table below provides information on both the use of any systemic anti-cancer therapy, including steroids, and the most commonly used anti-cancer therapies. Note that there was an imbalance in the use of any subsequent anti-cancer therapy between arms. Despite this imbalance, there was a clear improvement in OS with enzalutamide.

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Table 6: Anti-Cancer Therapies After Discontinuation of Study Drug		
	Enzalutamide N = 800	Placebo N = 399
Any Anti-Cancer Treatment	338 (42%)	248 (62%)

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Sensitivity and Subgroup Analyses
Multiple sensitivity analyses of OS were conducted (see primary review) and the results of all these analyses were consistent with the primary endpoint. A sensitivity analyses which removed all patients whose discontinuation was due to clinical progression (only) found a HR of 0.59. This suggests that the imbalance between arms in the number of patients who discontinued due to clinical progression had only a small effect on the hazard ratio.

The hazard ratios for various subgroup analyses were also consistent with the primary analysis. The HR for patients in the US was 0.58. Patient age did not appear to affect the efficacy of enzalutamide, while the HR for patients with visceral disease was 0.78. The hazard ratio for patients who took bicalutamide prior to entry was 0.65. The number of patients who received prior nilutamide or flutamide was too small to make this comparison. Finally, the HR for patients who used glucocorticoids during the treatment period was 0.70. Interestingly, the HR for patients who had not used glucocorticoids was 0.49. Differences in tumor burden between those on/not on glucocorticoids have not been examined.

Secondary Endpoints
Time to PSA Progression: The median time to PSA progression was 8.3 months in the enzalutamide arm and 3.6 months in the placebo arm, HR 0.29, $p < 0.0001$ (stratified logrank test). Note that this analysis does include patients whose confirmatory PSA occurred after study treatment discontinuation. However, it does not include patients whose confirmatory PSA occurred after both study treatment discontinuation and the initiation of new treatment.

Radiographic Progression-Free Survival: There were several difficulties in the use of these datasets and this endpoint will be included as an addendum to the primary review.

Time to Skeletal-Related Event: The median time to first skeletal-related event was 4.3 months in the enzalutamide arm compared to 2.5 months in the placebo arm, HR 0.47, $p < 0.0001$ (stratified logrank test). This analysis does not include patients with a SRE that occurred after treatment discontinuation or after treatment discontinuation followed by the initiation of a new treatment. The primary reviewer's rationale was that patients who discontinued, but did not start another anti-cancer treatment may be on bisphosphonates/denosumab and that these agents could affect the time to SRE. Therefore, the exclusion of these patients would help to isolate the treatment effect of enzalutamide. Note that 48% of patients in the enzalutamide arm and 46% of patients in the placebo arm used bisphosphonates or denosumab.

S-3100-1-01
This supportive trial administered 30-600 mg/d of enzalutamide to 140 patients with CRPC. Seventy-one percent (71%) of patients had received a prior androgen receptor inhibitor. Median PSA was 49 ng/mL. Dose expansion cohorts of 24 patients, 12 patients who had received prior chemotherapy and 12 chemotherapy-naïve patients, were to be accrued at 60,

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150, 240, and 360 mg/d. The 480 and 600 mg/d cohorts were to accrue 24 patients who had received prior chemotherapy. However, once the maximum tolerated dose was determined to be 240 mg/d, the 480 mg (N = 22) and 600 mg (N = 3) cohorts discontinued accrual and all patients were given 240 mg/d. Seizure, the primary dose limiting toxicity, was seen in 1 patient each at 360, 480 and 600 mg/d. At 600 mg, grade 3 confusion and grade 3 rash were also seen. The study was initiated with hard gelatin capsules contained 30 mg of enzalutamide and patients were later switched to the to-be-marketed product, soft gelatin capsules containing 40 mg enzalutamide.

Table 6: PSA Response by Dose

	Enzalutamide Dose in Chemotherapy-Naïve Patients						
Day 84	30 mg N = 3	60 mg N = 13	150-160 mg N = 13	240 mg N = 12	360 mg N = 12	480 mg N = 0	600 mg N = 0
≥ 50% Decrease in PSA	1 (33%)	8 (62%)	12 (92%)	8 (67%)	8 (67%)		
	Enzalutamide Dose in Patients Who Received Prior Chemotherapy						
Day 84	30 mg N = 3	60 mg N = 11	150-160 mg N = 11	240 mg N = 8	360 mg N = 9	480 mg N = 11	600 mg N = 3
≥ 50% Decrease in PSA	0	4 (36%)	4 (36%)	7 (88%)	7 (78%)	5 (46%)	0

Nine (9) patients with radiographic disease progression were treated at a higher dose of enzalutamide (240-480 mg depending on when they began retreatment). These patients remained on the higher dose of enzalutamide for 27 to 191 days, median 91 days.

CRPC-MDA-1

This supportive trial administered 160 mg/d of enzalutamide to 60 patients with metastatic castration resistant prostate cancer. Fifty-eight patients had a baseline and at least 1 post baseline PSA. A ≥ 50% decline in PSA at any point was seen in 27/58 (47%) of patients during the study period. This included 7/16 patients who had not received prior docetaxel and 20/42 who had received prior docetaxel.

In the Phase 1-2 study, PSA response was seen at 150-160 mg/d and it was unclear whether higher doses resulted in an additional decrease in PSA. The Phase 1 study also identified a dose-dependent risk of seizure with no seizures seen below 240 mg/d, but with 1 seizure each in the 360, 480, and 600 mg cohorts. Based on these findings, the applicant identified 160 mg/d as the dose for the Phase 3 study.

8. Safety

Exposure

In completed and ongoing trials, 2,108 patients have received 150-160 mg enzalutamide. The safety database analyzed in this review includes 925 patients who have received 150-160 mg of enzalutamide in the randomized Phase 3 trial (CRPC2), the Phase 1-2 trial (S-3100-1-01), and the Phase 2 trial (CPRC-MDA-1) described above. It also includes patients from a study (9875-CL-0111) conducted in Japan by Astellas Pharmaceuticals. It does not include healthy volunteers, patients from ongoing trials, and 21 placebo patients from CRPC2 who crossed over to enzalutamide.

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Since 800 of the 925 patients in the safety database are from the randomized Phase 3 trial, most findings from the safety database closely follow those found in the randomized Phase 3 trial.

In the randomized Phase 3 trial, the median duration of exposure was 8.4 months (range; 0.03-23.2) in the enzalutamide and 3.0 months (0.1-20.7) in the placebo arm. Dose interruption was required in 12% of patients on enzalutamide and in 15% on placebo. Dose reduction occurred in 2% of patients on the enzalutamide and 3% of patients on the placebo arm. Given the prolonged half-life of enzalutamide (5.8 d), the median duration of dose interruption was explored. Surprisingly, this was found to be similar between arms with a median duration (by event rather than by patient) of 6 days with enzalutamide and 4 days with placebo.

Safety Summary

The follow table summarizes the incidence of various adverse events between arms. Note that more serious adverse events grade 3-4 adverse events were seen in the placebo arm than in the enzalutamide arm. While the table below provides the incidence of grade 1-4 adverse events in all patients in the Phase 3 trial, the incidence of grade 1-4 adverse events was comparable in US patients.

Table 7: Incidence of Adverse Events

	Enzalutamide N = 800	Placebo N = 399
Deaths Due to an Adverse Event ≤ 30 Days[1]	2.5%	2.5%
Permanent Discontinuation	17%	19%
Serious Adverse Events	35%	37%
Grade 3-4 Adverse Events	47%	53%
Grade 1-4 Adverse Events	98%	98%

[1]Differs from all deaths due to an adverse event

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The table below provides information on the causes of death, discontinuation, serious adverse events, grade 3-4 adverse events and grade 1-4 adverse events in the enzalutamide arm.

Table 8: Enzalutamide Safety Summary

Deaths Due to AE ≤ 30 days of Study Drug	General physical health deterioration, sepsis, acute leukemia, pneumonia, MI, CVA, cardiac failure, cerebral hemorrhage/pancytopenia, death (NOS), pulmonary edema, and subdural hematoma
Permanent Discontinuation in > 2 Patients	Spinal cord compression, asthenia/fatigue, general physical health deterioration, nausea, vomiting, back pain, bone pain, CVA, renal failure, seizure, depression, diarrhea, dysphagia, and dyspnea
Serious Adverse Events in > 1% of Patients	Cord compression, hematuria, bone pain, pathologic fracture, metastatic pain, general physical health deterioration, and pneumonia
Grade 3-4 Adverse Events in > 2% of Patients	Spinal cord compression and cauda equine syndrome, back pain, arthralgia, hypertension, and lower respiratory infection
Grade 1-4 Adverse Events in ≥ 5% of Patients	Asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, URI, dizziness, spinal cord compression and cauda equine syndrome, muscular weakness, insomnia, lower respiratory infection, hematuria, paresthesias, anxiety, and hypertension

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Deaths

The table below includes deaths due to an adverse event that occurred during the treatment period or within 30 days of the patient's last dose of study drug. The table does not include patients who died due to progressive disease or underwent euthanasia. The most common cause of death due to an adverse event was general physical health deterioration. Investigators did not clearly indicate whether these deaths were due to progressive disease. Sepsis occurred in 5 patients in the enzalutamide arm and in no patients in the placebo arm. Four of these 5 patients had urosepsis and 1 cholangitis. An additional 2 patients on enzalutamide developed pneumonia compared to 1 on placebo.

Acute leukemia occurred in 2 patients in the enzalutamide arm. This is a rare event and 2 deaths due to leukemia are of concern. One death due to AML occurred on day 29. This patient had received prior radiation therapy and docetaxel. Baseline laboratories included a hematocrit of 33% up from 25% (with 1 nucleated red cell) 12 d prior and a platelet count of 210. The other death due to AML occurred on day 116 of study drug. This patient received prior docetaxel. Baseline laboratories included a hematocrit of 34% and platelet count of 277. While 1 of these patients had received prior radiation and chemotherapy and developed AML with limited exposure to study drug (day 29), the other patient received several months of enzalutamide and did not have markedly abnormal hematology values at entry. There is no clear mechanistic reason for the development of leukemia with enzalutamide, but additional reports of acute leukemia and myelodysplasia will be followed closely.

Table 7: Deaths Due to an Adverse Event Within 30 Days of Study Drug

	Enzalutamide N = 800	Placebo N = 399
All	20 (2.5%)	10 (2.5%)
General Physical Health Deterioration	4	4
Sepsis	5	0
Acute Leukemia	2	0
Pneumonia	2	1
Myocardial Infarction	1	1
Cerebrovascular Accident	1	1
Cardiac failure	1	0
Cerebral Hemorrhage/Pancytopenia	1	0
Death	1	0
Pulmonary Edema	1	0
Subdural hematoma/Pneumonia[1]	1	0
Cardiogenic Shock	0	1
Hepatic Encephalopathy	0	1
Pulmonary Embolism	0	1

[1]Normal platelet count, minimally elevated INR

Data Cutoff 1-31-12

Adverse Events of Concern

Seizures: In the Phase 3 trial, 7 (0.9%) patients on enzalutamide and no patients on placebo experienced a seizure. Patients who had a seizure permanently discontinued study drug. In Phase 1 and 2 studies of enzalutamide an additional 3 patients experienced a seizure for an overall incidence of 10/925 (1.1%) patients in the safety database. The median date of onset was study day 51 with 6/10 seizures occurring in the first 60 days of therapy. Among the 4

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patients with seizures that occurred after Day 60, 1 was attributed to lidocaine and 1 had a brain metastasis.

Enzalutamide is able to cross the blood-brain barrier and is thought to increase the risk of seizure by inhibiting the GABA gated chloride channel. The risk of seizure was identified in the Phase 1 study and the Phase 3 trial excluded patients with the following pre-disposing factors for the development of seizures: a history of seizure, loss of consciousness, transient ischemic attack within 12 months of entry, prior cerebrovascular accident, brain arteriovenous malformation, head trauma with loss of consciousness, and brain metastases. The Phase 3 trial also excluded patients who were on concomitant medications that may lower the seizure threshold. Finally, in the enzalutamide arm, 13% of patients were on medications that include indications to treat seizures (this was balanced in the placebo arm). Examples include the use of benzodiazepines for anxiety or the use of gabapentin for neuropathic pain.

9. Advisory Committee Meeting

Since there were no controversial issues in the approval of this new molecular entity, an advisory committee meeting was not held.

10. Pediatrics

Since prostate cancer rarely occurs in children, a pediatric waiver was granted for the use of enzalutamide in prostate cancer.

11. Other Relevant Regulatory Issues

Audits of 4 clinical sites by the Office of Scientific Investigation were acceptable. No investigators reported a proprietary interest in enzalutamide or significant equity in Medivation, Inc. No investigators had received significant payments for other services.

12. Labeling

Please see final printed labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
- Risk Benefit Assessment
  - Risk:
    - A dose dependent increase in the risk of seizure was seen with enzalutamide. The incidence of seizure was 0.9% when enzalutamide was administered as 160 mg po qd.
    - Grade 3-4 adverse events (47% vs. 53%) and serious adverse events (35% vs. 37%) were increased in the placebo arm.
    - Grade 1-4 adverse events in $\geq$ 5% of patients included asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral

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edema, musculoskeletal pain, headache, URI, dizziness, spinal cord compression and cauda equine syndrome, muscular weakness, insomnia, lower respiratory infection, hematuria, paresthesias, anxiety, and hypertension.

- Benefit
  - Median overall survival with enzalutamide was 18.4 months in the enzalutamide and 13.6 months in the placebo arm, hazard ratio 0.63, $p < 0.0001$.

The risk-benefit profile of enzalutamide is acceptable and approval is recommended.

- Recommendation for Postmarketing Risk Management Activities: Five postmarketing requirements have been agreed to by the applicant. These are:

  - Because patients at increased risk of developing a seizure were excluded from the randomized clinical trial, convene a panel of experts in oncology and neurology to obtain recommendations regarding which patients at increased risk for seizures are appropriate to participate in a postmarketing safety trial, e.g., patients with a history of seizure (taking/not taking anti-convulsants), loss of consciousness, transient ischemic attack or cerebrovascular accident, arteriovenous malformation in the brain, head trauma with loss of consciousness, treated brain metastases, use of medications which may increase the seizure threshold, or other risk factors known for the development of seizures. Following the panel's recommendations, conduct a single-arm safety study to assess the risk of seizure with enzalutamide 160 mg/day in at least 350 patients with metastatic castrate-resistant prostate cancer who are at increased risk for seizure. The primary endpoint should be the incidence of seizure. With 350 patients, the trial has 85% power to detect an increase in seizures from ~1% as seen in the randomized clinical trial to 3%. Patients should remain on the study until disease progression, development of a seizure or of an unacceptable adverse reaction. The protocol should contain clear stopping plans for an excessive incidence of seizures.

  - Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide. The proposed protocol must be submitted for review prior to trial initiation.

  - Conduct a drug interaction trial to evaluate the effect of rifampin (a strong CYP3A inducer and a moderate CYP2C8 inducer) on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide. The proposed trial protocol must be submitted for review prior to trial initiation.

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- Conduct drug interaction trials to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP2D6 and CYP1A2 substrates. The proposed trial protocols must be submitted for review prior to initiation of the trials.

- Perform an in vitro screen to determine if N-desmethyl enzalutamide is metabolized by the major human CYP450 isozymes. Based on results from the in vitro screen, clinical drug-drug interaction trials may be needed.

- Recommendation for other Postmarketing Study Commitments: None

- Recommended Comments to Applicant: Please see the final letter to the applicant.

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/s/

VIRGINIA E MAHER
08/19/2012