CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203415Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	August 31, 2012
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
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	Xtandi/Enzalutamide
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

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Robert Justice
Medical Officer Review	Yangmin M. Ning (efficacy), William Pierce (safety)/ Ellen Maher (CDTL)
Statistical Review	Stella Karuri, Shenghui Tang
Pharmacology Toxicology Review	Haw-Jyh Chiu, Todd Palmby, John Leighton
CMC, Biopharmaceutics, Product Quality Microbiology Reviews	Debasis Ghosh, Gaetan Ladouceur, Sarah Pope Miksinski, Deepika Lakhani, John Metcalfe
Microbiology Review	N/A
Clinical Pharmacology Review	Jeanne Fourie Zirkelbach
DPDP	Marybeth Toscano
OSI	Jean Mulinde
CDTL Review	Ellen Maher
OSE/DMEPA	Kimberly DeFronzo
OSE/DRM	Igor Cerny
DMPP	Latonia Ford
QT-IRT	Jeffrey Florian, Kevin Krudys, Monica Fiszman

OND = Office of New Drugs
DDMAC = Division of Drug Marketing, Advertising and Communication
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
OSI = Office of Scientific Investigations
DDRE = Division of Drug Risk Evaluation
DRM = Division of Risk Management
DPDP = Division of Professional Drug Promotion
DMPP = Division of Medical Policy Programs
CDTL = Cross-Discipline Team Leader
QT-IRT = Interdisciplinary Review Team for QT Studies
N/A = not applicable

1. Introduction & Background

On May 22, 2012, Medivation, Inc. submitted NDA 203415 for enzalutamide for the treatment of patients with castration-resistant prostate cancer who have received docetaxe (b) (4).

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 patients (Urology 2010 76:1189). With nilutamide, 8/38 patients who had received prior flutamide/bicalutamide had a $\geq$ 50% reduction in PSA (J Urol 2003 169:1742). Finally, use of flutamide, after response to withdrawal of bicalutamide, resulted in a $\geq$ 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

2. CMC/Device

There are no CMC issues that preclude approval. 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.

3. Nonclinical Pharmacology/Toxicology

There are no nonclinical issues that preclude approval. 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 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.

4. 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.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

This application is primarily supported by a single randomized, placebo-controlled, multicenter trial enrolling 1199 patients with metastatic castration-resistant prostate cancer who had received prior docetaxel. Patients were randomly allocated to receive enzalutamide 160 mg orally once daily (N = 800) or placebo (N = 399). Study treatment continued until disease progression, initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients were required to continue androgen deprivation therapy and were allowed, but not required, to continue or initiate glucocorticoids during the study period. Forty-eight percent (48%) of patients on enzalutamide and 46% on placebo received glucocorticoids.

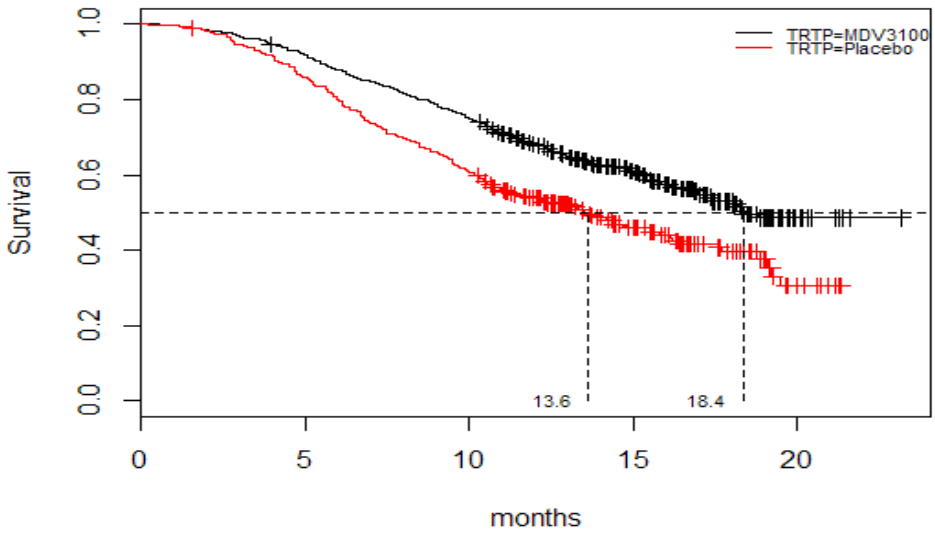
The primary efficacy endpoint was overall survival (OS). At the pre-specified interim analysis after 520 events, a statistically significant improvement in OS [HR 0.63 (95% CI: 0.53, 0.75), $p < 0.0001$, log rank test] was observed. The median OS was 18.4 and 13.6 months in the enzalutamide and placebo arms, respectively.

Table 2: 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



7. Safety

The most common (≥5%) grade 1-4 adverse reactions included asthenia or fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, spinal cord compression and cauda equina syndrome, muscular weakness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3-4 adverse reactions were reported in 47% of patients treated with enzalutamide and in 53% of those on placebo.

Seizures occurred in 0.9% of patients on enzalutamide. No patients on the placebo arm experienced seizures. In the clinical trial, patients experiencing a seizure were permanently discontinued from therapy. All seizures resolved. Patients with a history of seizure, taking medications known to decrease the seizure threshold, or with other risk factors for seizures were excluded from the clinical trial. The safety of enzalutamide in patients with predisposing factors for seizures is unknown.

8. Advisory Committee Meeting

There were no controversial issues in the application, therefore, an ODAC was not held.

9. Pediatrics

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

10. Other Relevant Regulatory Issues

Audits of 4 clinical sites by the Office of Scientific Investigation were acceptable.

11. Labeling

Please see final printed labeling.

12. 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 daily. 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 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, which was also evaluated by Drs. Justice, Maher and Ning, is acceptable. In addition, the review team recommends approval of this NDA, and I concur.

- Recommendation for Postmarketing Risk Management Activities: A REMS is not recommended.

- Recommendation for other Postmarketing Requirements and Commitments: See action letter.

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/s/

TAMY E KIM
08/31/2012

RICHARD PAZDUR
08/31/2012