CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203415Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 31, 2012
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA#	203415
Applicant Name	Medivation, Inc.
Date of Submission	May 22, 2012
PDUFA Goal Date	November 22, 2012
Proprietary Name / Established (USAN) Name	Xtandi enzalutamide
Dosage Forms / Strength	Capsule 40 mg
Proposed Indication	XTANDI is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Yangmin M. Ning (efficacy), William Pierce (safety)
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

Division Director Summary Review

1. Introduction

This new drug application for Xtandi (enzalutamide) Capsules was received on 5/22/12 and requests approval for the indication of "treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4)." Because of the survival benefit described below, this NDA is being approved well before the priority review PDUFA date of 11/22/12. This review will summarize the efficacy and safety data supporting approval and the recommendations of each review discipline.

2. Background

Enzalutamide is an androgen receptor inhibitor that competitively inhibits androgen binding to androgen receptors and androgen receptor nuclear translocation and interaction with DNA. See the CDTL and Clinical Reviews for the pertinent regulatory history. This application is primarily based on the results of a single large randomized clinical trial.

3. CMC

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

The following summary of nonclinical findings is from the Pharmacology/Toxicology NDA Review and Evaluation.

> Enzalutamide is a new molecular entity, small molecule androgen receptor inhibitor. Pharmacology studies showed that enzalutamide inhibits androgen binding to androgen receptors, inhibits androgen-dependent androgen receptor nuclear translocation, inhibits androgen-dependent androgen receptor association with DNA, and decreased proliferation and induced cell death of prostate cancer cells, *in vitro*. A major metabolite of ezalutamide (N-desmethyl enzalutamide) found in animals and humans

was shown to inhibit androgen binding to androgen receptors and inhibit androgen-dependent androgen receptor nuclear translocation *in vitro*. Enzalutamide decreased tumor volume in a mouse xenograft model of human prostate cancer. Based on primary pharmacology data submitted with this NDA and in consideration of all the pertinent information for the clinical use of enzalutamide, the Established Pharmacological Class (EPC) of "androgen receptor inhibitor" was determined to be both clinically meaningful and scientifically valid for enzalutamide.

Major target organ systems of toxicity identified in toxicity studies with enzalutamide in rats and dogs of up to 26 and 13 weeks in duration, respectively, were the central nervous system and reproductive organs. Convulsions were noted in repeat-dose studies in mice and dogs. A dose-dependent increase in convulsions was observed in mice at ≥100 mg/kg/day (0.6 times the human exposure based on AUC) and in dogs at 60 mg/kg/day (3.3 times the human exposure based on AUC). Studies submitted by Medivation suggest enzalutamide-induced convulsions may be attributed to the parent drug and its major active metabolite N-desmethyl enzalutamide, both of which have been show to cross the blood brain barrier and bind to the gamma aminobutyric acid (GABA)-gated chloride channel. Consistent with the pharmacological activity of enzalutamide, major toxicity findings were noted in male reproductive organs. In a 26-week study in rats, decreased organ weights were correlated with atrophy of the prostate and seminal vesicles which were observed at 30 mg/kg/day (similar to the human exposure based on AUC). In 4- and 13-week studies in dogs, decreased organ weights were correlated with hypospermatogenesis and atrophy of the prostate and epididymides, which were observed at ≥4 mg/kg/day (0.3 times the human exposure based on AUC). Other nonclinical findings of minimal severity and without significant adverse correlates were noted in the liver (hepatocellular hypertrophy), pituitary (hypertrophy and hyperplasia), and kidney (chronic progressive nephropathy) following repeat-dose administration of enzalutamide to rats.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma *tk* gene mutation assay or the *in vivo* mouse bone marrow micronucleus assay.

Medivation did not conduct any carcinogenicity or reproductive and developmental toxicology studies with enzalutamide. However, these studies were not considered to be essential to support approval of enzalutamide in the proposed patient population.

I concur with the conclusions reached by the pharmacology/toxicology reviewers that enzalutamide can be approved for the proposed indication from a non-clinical perspective. There are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

The Clinical Pharmacology Review provides the following summary of clinical pharmacology.

Enzalutamide is an androgen receptor inhibitor that targets steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors, inhibit activated androgen receptor nuclear translocation, and inhibit activated androgen receptor association with DNA. A major metabolite, N-desmethyl enzalutamide (M2), exhibited similar in vitro activity to enzalutamide. The proposed indication is for the treatment of patients with metastatic castration-resistant prostate cancer who have received docetaxel (b) (4).

The phase 3 trial (CRPC2) was a randomized, placebo-controlled, double blind trial in patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with docetaxel-based chemotherapy. Patients were randomized 2:1 to receive either enzalutamide (160 mg daily) (N=800) or placebo (N=399). The primary endpoint was overall survival (OS), and the final analysis showed that OS was statistically significantly prolonged on the enzalutamide arm compared to the placebo arm. Based on the results of Phase 3 trial, no exposure-response relationship for the efficacy endpoint of overall survival (OS) could be identified for enzalutamide within a single fixed dose of 160 mg/day. There were no clinically meaningful exposure-response relationships for fatigue, flushing, headache, or hypertension within the limited exposure range for 160 mg/day. The effect of enzalutamide 160 mg/day at steady state on the QTc interval was evaluated in 796 patients with castration-resistant prostate cancer. No large difference (i.e., greater than 20 ms) was observed between the mean QT interval change from baseline in patients treated with XTANDI and that in patients treated with placebo, based on the Fridericia correction method.

Following oral administration of enzalutamide at 160 mg in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations is 1 hour (range 0.5 to 3 hours). The enzalutamide mean terminal elimination half-fife ($T_{1/2}$), in patients with metastatic CRPC, following a single oral dose is 5.8 days (range 2.8 to 10.2 days). With daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide shows approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. In patients with MCRP cancer, the mean (%CV) predose C_{min} values for enzalutamide and M2 were 11.4 (25.9%) µg/mL and 13.0 (29.9%) µg/mL, respectively.

The single dose pharmacokinetics of the major active metabolite M2 was characterized in healthy volunteers following a single 160 mg oral dose of enzalutamide. The median T_{max} for M2 is 6 days (range 2 to 13 days). The mean terminal half-life for M2 is 8.6 days (%CV: 21%).

The human mass balance trial showed that enzalutamide is primarily eliminated by hepatic metabolism. The extent of enzalutamide absorption was not significantly altered by a high-fat meal. A dose reduction is not needed in patients with mild or moderate renal impairment, or mild or moderate hepatic impairment. The effect of

severe renal impairment or severe hepatic impairment on the pharmacokinetics of enzalutamide is not known.

In vitro, enzalutamide is metabolized by CYP2C8 and CYP3A4. In vivo results further suggest that CYP2C8 is primarily responsible for the formation of the active metabolite - N-desmethyl enzalutamide (M2). In vivo, the sum of enzalutamide and M2 exposure was increased by 2.2-fold and 1.3-fold when it was co-administered with gemfibrozil (strong CYP2C8 inhibitor) or itraconazole (strong CYP3A4 inhibitor), respectively. If the co-administration of enzalutamide with a strong CYP2C8 inhibitor cannot be avoided, the daily enzalutamide dose should be reduced to 80 mg. The effects of a CYP2C8 inducer or a CYP3A4 inducer on the PK of enzalutamide are not known, and co-administration of enzalutamide with CYP2C8 and/or CYP3A4 inducers (e.g. rifampin) should be avoided.

In vitro, enzalutamide, M1 and M2 caused direct inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Enzalutamide also caused time-dependent inhibition of CYP1A2. Among these enzymes, the IC50 of CYP2C8 was the lowest. However, enzalutamide at steady state did not cause a clinically relevant change in the AUC of pioglitazone (CYP2C8 substrate) in vivo. In vitro, enzalutamide caused induction of CYP3A4. In vivo, enzalutamide can be classified as a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Therefore, co-administration of enzalutamide with CYP3A4, 2C9, and 2C19 substrates with a narrow therapeutic index should be avoided. In vitro, enzalutamide, M1 and M2 are not substrates for human P-glycoprotein (P-gp). In vitro, enzalutamide and M2 are inhibitors of P-gp, while M1 is not an inhibitor of P-gp.

I concur with the conclusions reached by the clinical pharmacology reviewers that the NDA is acceptable from a clinical pharmacology perspective. I also agree with the recommended PMRs (see section 13). There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The following description of the trial design and efficacy results is taken from the Clinical Studies section of the agreed-upon package insert.

The efficacy and safety of XTANDI in patients with metastatic castration-resistant prostate cancer who had received prior docetaxel-based therapy were assessed in a randomized, placebo-controlled, multicenter phase 3 clinical trial. The primary endpoint was overall survival. A total of 1199 patients were randomized 2:1 to receive

either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo orally once daily (N = 399). All patients continued androgen deprivation therapy. Patients were allowed, but not required to continue or initiate glucocorticoids. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients with a history of seizure, taking medicines known to decrease the seizure threshold, or with other risk factors for seizure were not eligible *[see Warnings and Precautions (5.1)]*.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other. Ninety-two percent of patients had an ECOG performance status score of 0-1 and 28% had a mean Brief Pain Inventory score of ≥ 4. Ninety-one percent of patients had metastases in bone and 23% had visceral involvement in the lung and/or liver. Fifty-nine percent of patients had radiographic evidence of disease progression and 41% had PSA-only progression on study entry. All patients had received prior docetaxel-based therapy and 24% had received two cytotoxic chemotherapy regimens. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

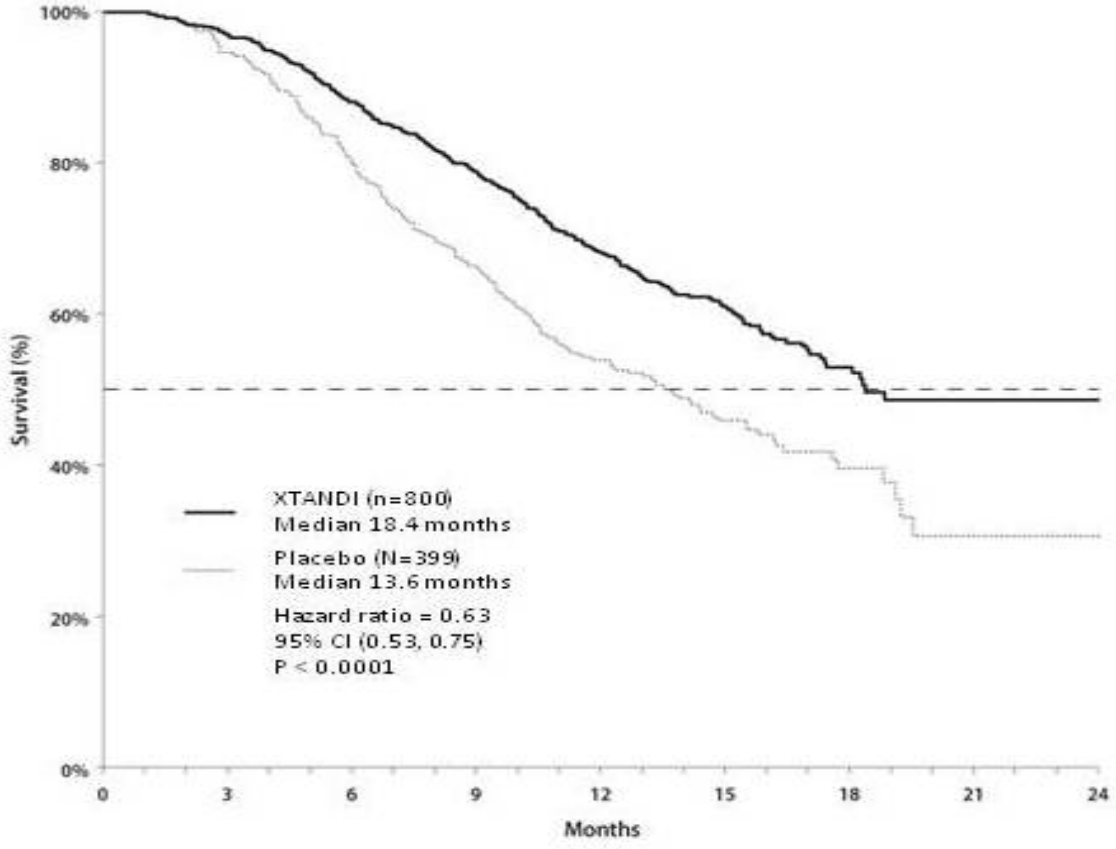
The pre-specified interim analysis at the time of 520 events showed a statistically significant improvement in overall survival in patients on the XTANDI arm compared to patients on the placebo arm (Table 2 and Figure 3).

Table 2. Overall Survival of Patients Treated with Either XTANDI or Placebo (Intent-to-Treat Analysis)

	XTANDI N = 800	**Placebo N = 399**
Number of Deaths (%)	308 (38.5%)	212 (53.1%)
Median Survival (months) (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value[a]	< 0.0001	
Hazard Ratio (95% CI)[b]	0.63 (0.53, 0.75)	

[a)] P-value is derived from a log-rank test stratified by baseline ECOG performance status score (0-1 vs. 2) and mean baseline pain score (BPI-SF score < 4 vs. ≥ 4)
[b)] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors XTANDI
NR denotes "not reached".

Figure 3. Kaplan-Meier Overall Survival Curves (Intent-to-Treat Analysis)



XTANDI	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

8. Safety

The following description of the adverse reactions reported in the randomized clinical trial is from section 6.1 of the Adverse Reactions section of the agreed-upon labeling.

> The most common adverse drug reactions (≥ 5%) reported in patients receiving XTANDI in the randomized clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients.

Table 1 shows adverse reactions reported in the randomized clinical trial that occurred at a ≥ 2% absolute increase in frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in the Randomized Trial

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[a]	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal And Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness[b]	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[c]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections And Infestations				
Upper Respiratory Tract Infection[d]	10.9	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection[e]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal And Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning And Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin And Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0

Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

a Includes asthenia and fatigue.
b Includes dizziness and vertigo.
c Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
d Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
e Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Laboratory Abnormalities

In the randomized clinical trial, Grade 1-4 neutropenia occurred in 15% of patients on XTANDI (1% Grade 3-4) and in 6% of patients on placebo (no Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was similar in both arms; 0.5% of patients on XTANDI and 1% on placebo experienced Grade 3-4 thrombocytopenia. Grade 1-4 elevations in ALT occurred in 10% of patients on XTANDI (0.3% Grade 3-4) and 18% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients on XTANDI and 2% of patients on placebo.

Infections

In the randomized clinical trial, 1.0% of patients treated with XTANDI compared to 0.3% of patients on placebo died from infections or sepsis. Infection-related serious adverse events were reported in approximately 6% of the patients on both treatment arms.

Falls and Fall-related Injuries

In the randomized clinical trial, falls or injuries related to falls occurred in 4.6% of patients treated with XTANDI compared to 1.3% of patients on placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and hematomas.

Hallucinations

In the randomized clinical trial, 1.6% of patients treated with XTANDI were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. Of the patients with hallucinations, the majority were on opioid-containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

Seizures were observed in the nonclinical toxicology studies and in the clinical trials and led to the following warning and precaution in the agreed-upon labeling.

In the randomized clinical trial, 7 of 800 (0.9%) patients treated with XTANDI 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo. Seizures occurred from 31 to 603 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy and all seizures

resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizures.

The safety of XTANDI in patients with predisposing factors for seizure is not known because these patients were excluded from the trial. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, brain arteriovenous malformation or the use of concomitant medications that may lower the seizure threshold.

Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Because patients with predisposing factors for seizure were excluded from the trial and could potentially be treated in clinical practice, there is a PMR to further evaluate the safety of enzalutamide in this patient population (see section 13).

9. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

The pediatric study requirement for this application was waived by PeRC because necessary studies are impossible or highly impracticable as this indication does not occur in children.

11. Other Relevant Regulatory Issues

Clinical inspections and financial disclosure were found to be acceptable. DDMAC recommendations were discussed during labeling meetings.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proprietary name was found to be acceptable.
- Physician labeling: Agreement has been reached on the physician labeling. The major issues that were discussed were the wording of the warning and precaution for seizure,

exclusion of the rPFS analyses from the Clinical Studies section (see Clinical Review), and the wording of the clinical pharmacology and drug interactions sections.
- Carton and immediate container labels: Agreement has been reached on the carton and container labels.
- Patient labeling/Medication guide: Agreement has been reached on patient labeling. A medication guide is not required.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The risk benefit assessment is straightforward and clearly favorable. The improvement in median OS was 4.8 months [HR=0.63 (95% CI: 0.53, 0.75), p<0.0001]. The most common adverse drug reactions (≥ 5%) in the randomized clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. However, most of these were only modestly higher in the enzalutamide arm compared to the placebo arm (see Table 1). In addition, Grade 3 and higher adverse reactions and discontinuations due to adverse events were approximately equal in the two study arms.

The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the enzalutamide-treated patients compared to none of the placebo-treated patients. Falls and fall-related injuries were higher in the enzalutamide arm than in the placebo arm (4.6% vs. 1.3%), as were grade 1 or 2 hallucinations (1.6% vs. 0.3%). All three adverse reactions may be related to CNS effects of the drug.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Routine postmarketing surveillance

- Recommendation for other Postmarketing Requirements and Commitments

There are six postmarketing requirements and no postmarketing commitments.

The first PMR is required because of an unexpected serious risk of drug-drug interactions between the active metabolite N-desmethyl enzalutamide and CYP450 inducers or inhibitors.

1918-1: 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.

Final Protocol Submission:	12/2012
Study Completion:	06/2013
Final Report Submission:	12/2013

The second PMR is required because of the known serious risk of seizure.

1918-2: Convene a panel of experts in oncology and neurology to obtain recommendations regarding which patients, if any, who were excluded from the randomized clinical trial because of increased risk of seizure should be evaluated in a postmarketing safety trial. Following the panel's recommendations, conduct a single-arm safety trial 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, e.g., patients with a history of seizure (taking/not taking anticonvulsants), 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 decrease the seizure threshold, or other risk factors for the development of seizures. The primary endpoint should be the incidence of seizure. Patients should remain on the trial until disease progression, development of a seizure or the development of an unacceptable adverse reaction. The protocol should contain clear stopping rules for an excessive incidence of seizures.

Expert Panel Recommendations:	12/2012
Final Protocol Submission:	06/2013
Trial Completion:	06/2018
Final Report Submission:	03/2019

The remaining PMRs are required because of the serious risks of impaired metabolism of enzalutamide in patients with severe hepatic impairment and of drug-drug interactions with enzalutamide.

1918-3: 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.

Final Protocol Submission:	03/2013
Trial Completion:	05/2014
Final Report Submission:	11/2014

1918-4: 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 protocol must be submitted for review prior to trial initiation.

Final Protocol Submission:	04/2013
Trial Completion:	07/2014
Final Report Submission:	04/2015

1918-5: Conduct a drug interaction trial to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP2D6 substrates. The proposed trial protocol must be submitted for review prior to initiation of the trial.

Final Protocol Submission:	07/2013
Trial Completion:	12/2014
Final Report Submission:	06/2015

1918-6: Conduct a drug interaction trial to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP1A2 substrates. The proposed trial protocol must be submitted for review prior to initiation of the trial.

Final Protocol Submission:	07/2013
Trial Completion:	12/2014
Final Report Submission:	06/2015

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L JUSTICE
08/31/2012