

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203415Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Management Options Review**

Date: August 7, 2012

Reviewer: Igor Cerny, Pharm.D.  
Senior Clinical Reviewer  
Division of Risk Management

Through: Cynthia LaCivita  
Division of Risk Management

Division Director: Claudia Manzo, Pharm. D.,  
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Drug Name(s): MDV3100/enzalutamide (XTANDI™)

Therapeutic Class: androgen receptor signaling inhibitor

Dosage and Route: 160 mg (four 40 mg capsules) orally once daily

Application Type/Number: NDA 203415

Submission Number: Sequence 0000

Applicant/sponsor: Medivation

OSE RCM #: 2012-1569

## 1. INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) MDV3100 (also known as enzalutamide). On May 22, 2012, the Division of Oncology Products 1 (DOP-1) received a new drug application (NDA) for MDV3100/enzalutamide with a proposed indication for treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4). This compound is being co-developed by Medivation, Inc. and Astellas Pharma Global Development, Inc.

The applicant is seeking approval on the basis of a single large, randomized, double-blind, placebo-controlled Phase 3 study (CRPC2) in 1,199 patients conducted in North America, South America, Europe, South Africa, and Australia.

The applicant did not submit a proposed REMS or risk management plan.

## 2. BACKGROUND

The CDC reports that aside from non-melanoma skin cancer, prostate cancer is the most common cancer among men in the United States. It is also one of the leading causes of cancer death among men of all races. In 2008, over 214,000 US men were diagnosed with prostate cancer, and over 28,400 US men died from prostate cancer. Patients whose prostate tumors have stopped responding to active hormone treatment strategies are considered to have advanced prostate cancer.

MDV3100 is an androgen receptor signaling inhibitor that:

- competitively inhibits the binding of androgens to androgen receptors in the cytosol; inhibits nuclear translocation of activated receptors; and
- inhibits the association of the activated androgen receptor with DNA

## 3. REGULATORY HISTORY

MDV3100 is a NME entity which is not approved or marketed in the United States or any other country. Medivation is requesting Priority Review of the MDV3100 NDA based on the following arguments:

- represents a major advancement in the treatment of a serious and life-threatening disease;
- was previously granted Fast Track Designation in November 2011;
- has a unique mechanism of action, with clinically important advantages over cabazitaxel and abiraterone acetate.

The Applicant is also (b) (4)

(b) (4)

Currently there are three FDA-approved **Androgen Receptor Antagonists** on the market: flutamide, nilutamide, and bicalutamide, all of which were approved without risk mitigation strategies:

- **flutamide** (Eulexin<sup>®</sup>, approved in 1989) is indicated for the treatment of locally confined and metastatic prostate cancer in combination with an LHRH analog. The Flutamide label contains a black box warning for hepatic injury/failure.
- **nilutamide** (Nilandron<sup>®</sup>, approved in 1995) is indicated for use in combination with surgical castration for the treatment of metastatic prostate cancer. The Nilutamide label contains a black box warning for interstitial pneumonitis.
- **bicalutamide** (Casodex<sup>®</sup>, approved in 1996) is indicated for the treatment of metastatic carcinoma of the prostate cancer in combination with an LHRH analog.

For the specific indication of the treatment of **Metastatic Castration-Resistant Prostate Cancer after Docetaxel-Based Chemotherapy**, there are two currently approved products. Neither product is an androgen receptor antagonist, and neither agent was approved with risk mitigation strategies:

- **cabazitaxel** (Jevtana<sup>®</sup>, approved in 2010) is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen. Cabazitaxel's inhibitory actions lead to the stabilization of microtubules, which results in the inhibition of mitotic and interphase cellular functions. The cabazitaxel label has a black box warning for neutropenia and severe hypersensitivity reactions. In the pivotal trial leading to approval, Cabazitaxel provided a 2.4 month overall survival benefit over mitoxantrone.
- **abiraterone** (Zytiga<sup>®</sup>, approved in 2011) is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel. CYP17 is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. In the pivotal trial leading to approval, Abiraterone provided a 3.9 month overall survival benefit over placebo.
- **abarelix** (Plenaxis, approved in 2003) is a gonadotrophin-releasing hormone receptor (GnRH) blocker initially approved for the treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia. Because of the risk of immediate onset systemic allergic reaction (IOSAR), abarelix was approved under Subpart H with a restrictive Risk Management Plan. In 2005, it was voluntarily withdrawn from the US market by the sponsor for commercial reasons.

#### 4. MATERIAL REVIEWED

- May 22, 2012 Original NDA 203415 submission. Sections reviewed include:
  - Section 1.2, Request for Priority Review

- Section 2.5, Clinical overview
- Section 2.7.3, Summary of Clinical Efficacy
- Section 2.7.4, Summary of Clinical Safety
- Section 5, Clinical Study Report CRPC2
- July 10, 2012 Slides from DOP-1 Mid-Cycle Clinical/Stat Presentation

## 5. REVIEW OF RISK MANAGEMENT OPTIONS

The sponsor did not submit a risk evaluation and mitigation strategy (REMS) or a risk management plan with the NDA.

### 5.1. OVERVIEW OF CLINICAL PROGRAM

The applicant is seeking approval on the basis of a single large, randomized, double-blind, placebo-controlled Phase 3 study (**CRPC2**). This study was performed in 1,199 patients with castration-resistant prostate cancer and progressive disease after 1 or 2 prior chemotherapy regimens, 1 of which was docetaxel-based. The proposed dosing schedule for MDV3100 is 160 mg (four 40 mg capsules) administered orally once daily.

Key inclusion criteria for study CRPC2 included:

- histologically- or cytologically-confirmed adenocarcinoma of the prostate;
- surgical and/or medical castration and castrate serum levels of testosterone;
- progressive disease in either soft tissue or bone or progressive disease as detected by rising PSA levels (metastatic disease was not required for enrollment);
- an estimated life expectancy of  $\geq 6$  months.

Key exclusion criteria included:

- History of seizure, loss of consciousness, or TIA within 12 months
- No medications which lower the seizure threshold

Patients were randomized 2:1 to receive either MDV3100 160 mg daily or placebo. The Primary Endpoint was overall survival (OS). Key Secondary Endpoints included Time to PSA progression; Radiographic Progression Free Survival; and the Time to a Skeletal-related Event (bone radiation, fracture, spinal cord compression).

A total of 1199 were randomized and were included in the Intent-to-Treat (ITT) Population used for the primary overall survival analysis. An amendment to the protocol added a formal interim analysis for overall survival at approximately 520 death events (as was also done in the abiraterone pivotal trial). This interim analysis was the only analysis and no updated analysis was provided or planned.

### RESULTS:

The following results are as per the DOP-1 clinical team's presentation at the July 10, 2012 Mid-Cycle meeting, final clinical review is pending. As of the data cutoff, 29% of patients randomized to MDV3100 remained on treatment, compared to 5% of patients randomized to placebo. The primary reason for discontinuation from study drug was

disease progression in both arms: 55% and 74% for enzalutamide and placebo, respectively. The primary reason for overall study discontinuation was death: 38% for enzalutamide and 53% for placebo. Patient demographic and baseline clinical characteristics indicated that both groups were well balanced for key prognostic characteristics. The median number of cycles of prior docetaxel received was 8.5 cycles in the MDV3100 arm and 8.0 cycles in the placebo group.

**Table 1** on the following page is taken directly from the DOP-1 Clinical Team's July 10, 2012, Mid-cycle presentation:

**Table 1: Overall Survival Results (from DOP-1's Mid-Cycle Presentation)**

	MDV3100 (n=800)	Placebo (n=399)
<b>Interim Analysis</b>		
<b>Deaths (%)</b>	308 (39%)	212 (53%)
<b>Median survival in months (95% CI)</b>	18.4 (17.3, NM)	13.6 (11.3, 15.8)
<b>p-value</b>	<b>&lt;0.0001</b>	
<b>Hazard ratio (95% CI)</b>	0.63 (0.53, 0.75)	
<b>Updated Analysis</b>		
<b>Deaths (%)</b>	344 (43%)	232 (58%)
<b>Median survival in months (95% CI)</b>	17.8 (16.7, 18.8)	13.3 (11.2, 14.1)
<b>Hazard ratio (95% CI)</b>	0.62 (0.52, 0.73)	

The data above indicates MDV3100 provided a statistically and clinically meaningful improvement in the primary endpoint of overall survival with a hazard ratio of 0.63 ( $P < 0.0001$ ). Thus, MDV3100 treatment resulted in a 37% decrease in the risk of death compared with placebo-treated patients. The overall difference in median survival with MDV3100 treatment was 4.8 months. Subgroup and sensitivity analyses showed consistent survival advantages with MDV3100. In addition, analysis of the data for the key Secondary Endpoints (Time to PSA progression; Radiographic Progression Free Survival; and the Time to a Skeletal-related Event) indicated highly significant ( $P < 0.0001$ ) benefit of MDV3100 over placebo.

The DOP-1 medical officer and statistician's slide presentation indicated that the survival benefit associated with MDV3100 treatment has been verified, is robust, and supports the proposed indication.

### 5.3 SAFETY

A total of 1027 patients received MDV3100, 909 at doses of 150-160 mg daily. Of these 909 patients, 800 were from trial CRPC2 and 109 were from the open-label studies. The bulk of the safety analyses were drawn primarily from study CRPC2.

The most frequent cause of on-study death was attributed to progression of disease. There was a slight increase in infection/septic-related deaths for MDV3100 as compared to placebo (0.9% vs. 0.3%). Overall, non-fatal serious adverse events were more common on placebo than on MDV3100 (65% vs. 34%). However, a few events were more common with MDV3100 than placebo: spinal cord compression (6.0% vs. 4.0%); pathological fracture (1.5% vs. 0.8%); cauda equina syndrome (0.8% vs. 0%); and urosepsis (0.5% vs. 0%). Overall, adverse events that were the primary reason for permanent discontinuation of MDV3100 were comparable between treatment groups with seizure as the only event with at least a 0.5% absolute increase in incidence in the MDV3100 group compared with the placebo group. In addition to seizures, other major safety concerns identified included falls and fractures.

**Seizures:** Seizures were observed in a dose dependent fashion in rat / dog toxicology studies. In the Applicant's Phase 1 trial (S-3100-1-01), 3 seizures were observed at the high doses of 360, 480, and 600 mg/day (1 at each dose).

In Study CRPC2, as described previously, key exclusion criteria included a history of seizure, loss of consciousness, or TIA within 12 months; and no medications which lower the seizure threshold. In this study, the incidence of seizures (all types reported: complex, partial, convulsive, one episode of status) was 0.8% with MDV3100 versus 0% for placebo. There were a total of 6 seizures reported with MDV3100 and one additional potential seizure (although there is some evidence of this having been a TIA). The most common adverse event leading to discontinuation of treatment was seizure. Thus, all patients who experienced seizures discontinued treatment and all seizures resolved. For 5 of the 6 cases of seizures, the DOP-1 clinical team believes that accompanying factors that may have played a role such as: co-administration of medications known to lower the seizure threshold (2 cases); brain metastases (2 cases), and alcoholism (1 case). The DOP-1 clinical team speculates that the risk of seizures *may* be increased in patients with predisposing conditions such as those listed in the previous sentence. Although the Applicant contends that dose appears to be an important predictor of the risk of seizures in humans, the DOP-1 clinical team believes that the limited number of cases makes this difficult to assess. In this NDA, there were no MDV3100 seizure-related deaths.

**Injuries:** Patients in Study CRPC2 who were on MDV3100 reported a greater incidence of injuries (12.0%) versus placebo (7.5%). These injuries were mostly composed of **falls** and **fractures**.

Falls: Treatment with MDV3100 was associated with an increase in the incidence of falls in Study CRPC2 (4.0% on MDV3100 vs. 1.3% on placebo). The majority of falls were Grade 1 or Grade 2, although 2 patients experienced Grade 3 falls (the most severe, a fall which requires medical intervention and interferes with ADLs, at a 0.3% rate vs. 0.0% for placebo). The injuries sustained in the MDV3100 group were more severe (rib, wrist, hip, facial, and patellar fractures) than those sustained by the placebo group (hematoma, cuts, bruises). Two MDV3100-treated patients discontinued treatment as a result of the

fall whereas no placebo-treated patient discontinued treatment for this event. In Study CRPC2, the incidence of falls was higher in:

- patients 75 years of age or older versus patients < 75 years (4.5% vs. 3.8%);
- patients with baseline ECOG performance status of 2 compared to patients with baseline ECOG performance status of 0 or 1 (8.6% vs. 3.6%); and
- higher in patients with less than the median weight compared to patients above the median weight (4.1% vs. 3.7%).

The etiology of this increase in falls in MDV3100-treated patients is unknown. However, it is interesting to note that if one looks at falls in terms of patient-years, the rate on placebo was actually higher than the rate on MDV3100.

Fractures: The incidence of fractures (all grades) in CRPC2 for MDV3100 was 1.4% versus 0.3% for placebo. For the most severe type of fracture, Grade 3, the incidence with MDV3100 was 0.3% versus 0.0% for placebo. A total of 9 fractures on MDV3100 were considered serious adverse events versus one fracture in a subjects taking placebo.

The majority of bone fractures that occurred during this study were considered pathological fractures and were reported in 12 (1.5%) of MDV3100-treated patients compared to 3 (0.8%) placebo-treated patients. Combining pathological fractures with non-pathological fractures, 6.8% of MDV3100-treated patients experienced these versus 4.0% for placebo. Multiple MDV3100 patients had reported falls within the two weeks preceding the fracture events whereas preceding falls were not reported in placebo patients with fractures. The specific cause of the increase in fractures in MDV3100-treated patients is not known.

In their July 10, 2012 mid-cycle presentation, the DOP-1 clinical noted the following pending safety issues that needed to be more fully explored:

- assess the impact of anti-seizure medications, bone resorption inhibitors, and corticosteroids; and
- assess QTc Prolongation (IRT consult which remains outstanding)

#### **5.4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS**

The Applicant has not submitted any proposed postmarketing studies. The DOP-1 clinical team will be asking the Applicant to conduct a safety study of patients at high risk of seizures (as defined by conditions that will be listed in the labeling such as CVA, brain metastases, alcoholism, etc.). The Applicant will be asked to examine the number of patients in terms of the incidence of seizures that will be ruled out. DOP-1 will ask the Applicant to propose various numbers of patient to study depending on the seizure incidences that will be ruled out.

On August 6<sup>th</sup>, 2012, at a Clinical Pharmacology Office Level Briefing on MDV3100, the following postmarketing studies were agreed to:

- 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 (M2, the primary metabolite);
- A drug interaction trial to evaluate the effect of rifampin (a strong CYP3A inducer and a moderate CYP2C8 inducer) on the pharmacokinetics of enzalutamide M2;
  - A drug interaction trial to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of a CYP2D6 and a CYP1A2 substrate; and
  - An in vitro screen to determine if M2 is metabolized by the major human CYP450 isozymes. Based on results from the in vitro screen, a clinical drug-drug interaction trial may be needed.

### 5.5 ODAC

This product will not be presented to the ODAC.

## 6. DISCUSSION

At the July 10, 2012 Mid-cycle meeting, the DOP-1 Clinical/Statistical team concluded that the overall data indicated that MDV3100 was favorable for use in the intended patient population since the overall survival benefit exceeds the risk. The DOP-1 clinical team also concluded that the overall safety profile of MDV3100 is similar to that of other anti-androgen agents. There appears to be no increase in cardiovascular or hepatic toxicities. Seizures, falls, fractures, and infections occur at a (~1-5%) and are somewhat increased vs. placebo.

Any assessment of risk-benefit and the need for a REMS must be made with the awareness that this is a seriously ill population with therapeutic options that are associated with serious adverse events. Currently, the serious adverse events with the other anti-androgenic agents are being managed through product labeling; two of the three marketed anti-androgenic agents have black box warnings (hepatic injury/failure for flutamide and interstitial pneumonitis for nilutamide). Likewise, product labeling is being used to manage the serious risks for the other products with the specific indication of the treatment of metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy; cabazitaxel has a black box warning for neutropenia and severe hypersensitivity reactions and abiraterone is approved with labeling alone. Aside from abiraterone, which is not currently marketed in the US, none of the other agents used to treat prostate cancer have REMS in place to manage their risks.

It is expected that the post marketing requirements will assist in further characterizing the adverse event profile. If serious adverse events can be further characterized and appear to occur at a higher frequency or are of a greater severity than has been noted heretofore, specific risk mitigation strategies can be considered. From the pivotal trial it is difficult to characterize which patient sub-populations may be at the highest risk for adverse events. Thus, based on this information, as well as a comparison of the risk/benefit profile of

MDV3100 to that of similar agents, labeling appears to be a reasonable approach to address the risks at this time.

## **7. CONCLUSION**

Labeling in conjunction with post-marketing requirements to further evaluate MDV3100's benefits and risks is a reasonable strategy and is consistent with similarly indicated agents such as cabazitaxel and abiraterone. Thus MDV3100 (enzalutamide, or XTANDI™) can be approved without a REMS.

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