CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203415Orig1s000

Trade Name: Xtandi® Capsules, 40 mg.

Generic Name: enzalutamide

Sponsor: Medivation, Inc.

Approval Date: August 31, 2012

Indications: Provides for the use of Xtandi® (enzalutamide) Capsules for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203415

NDA APPROVAL

Medivation, Inc.
525 Market Street, 36th Floor
San Francisco, CA 94105

Attention: Lynn Seely, M.D.
Chief Medical Officer

Dear Dr. Seely:

Please refer to your New Drug Application (NDA) dated May 21, 2012, received May 22, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xtandi® (enzalutamide) Capsules, 40 mg.

We acknowledge receipt of your amendments dated June 7, 15, 20, 21, 27, 28, 29, July 12, 13, 16, 17, 19, 23, 25, 27, and August 3, 7, 9, 15, 20, 21, 24, and 30, 2012.

This new drug application provides for the use of Xtandi® (enzalutamide) Capsules for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203415**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Xtandi® (enzalutamide) Capsules 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.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable as this indication does not occur in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of drug-drug interactions between the active metabolite N-desmethyl enzalutamide and CYP450 inducers or inhibitors.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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.

The timetable you submitted on August 9, 2012, states that you will conduct this study according to the following schedule:

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

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of seizure and signals of serious risks of impaired metabolism of enzalutamide in patients with severe hepatic impairment and of drug-drug interactions with enzalutamide.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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.

The timetable you submitted on August 9, 2012, states that you will conduct this trial according to the following schedule:

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

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.

The timetable you submitted on August 9, 2012, states that you will conduct this trial according to the following schedule:

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.

The timetable you submitted on August 9, 2012, states that you will conduct this trial according to the following schedule:

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.

The timetable you submitted on August 9, 2012, states that you will conduct this trial according to the following schedule:

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.

The timetable you submitted on August 9, 2012, states that you will conduct this trial according to the following schedule:

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

Submit the protocols to your IND 074563, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
08/31/2012