DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202379

NDA APPROVAL

Ortho Biotech Oncology Research and Development
Unit of Cougar Biotechnology, Inc.
Agent for Centocor Ortho Biotech, Inc.
Attention: Christine Woods
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024-3913

Dear Ms. Woods:

Please refer to your New Drug Application (NDA) dated December 18, 2010, received December 20, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zytiga (abiraterone acetate) Tablets, 250 mg.

We acknowledge receipt of your amendments dated January 6 and 28; February 1, 17, 22 and 23; March 7, 14, 21, 25, 28, 30, 31; April 4, 8, 12, 13, 18, 19, 22, 25, 26 and 28 (via electronic mail), 2011.

This new drug application provides for the use of Zytiga (abiraterone acetate) Tablets in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing 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.

A shelf-life of 12 months at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) [USP Controlled Room temperature] is approved.

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 and 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.

CONTAINER LABEL

Submit a final printed container label that is identical to the container label submitted on April 22, 2011 as soon as it is available, but no more than 30 days after it is printed. Please submit this label 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 Container Label for approved NDA 202379**." Approval of this submission by FDA is not required before the label 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.

MARKET PACKAGE

Please submit one market package of the drug product when it is available.

If sending via USPS, please send to:

Amy Tilley
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2177
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS (e.g., UPS, DHL), please send to:

Amy Tilley
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2177
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Your application for Zytiga 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 because the disease does not exist 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 assess a signal of a serious risk of an *in vivo* drug interaction in which abiraterone could increase concentrations of sensitive CYP2C8 substrates..

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

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

1748-1 Perform an *in vitro* screen to determine if abiraterone is an inhibitor of human CYP2C8. Based on results from the *in vitro* screen, a clinical drug-drug interaction trial may be needed.

The timetable you submitted on April 19, 2011, states that you will conduct this study according to the following schedule:

Study Completion:	January 2012
Final Report Submission:	June 2012

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of: 1) an increase in abiraterone exposure in individuals with severe hepatic impairment; 2) a decrease in abiraterone concentrations when abiraterone acetate is co-administered with a potent CYP3A inducer, and;

3) an increase in abiraterone concentrations when abiraterone acetate is co-administered with a potent CYP3A inhibitor.

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

1748-2 Conduct a trial to determine the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate in individuals with severe hepatic impairment. The proposed protocol should contain the rationale for dose selection, and must be submitted for review prior to trial initiation. In the design of the trial, consider development of lower dosage strengths to allow for administration of a safe dose in patients with severe hepatic impairment.

The timetable you submitted on April 19, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 2011
Trial Completion:	October 2013
Final Report Submission:	April 2014

1748-3 Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A inducer (*e.g.,* rifampin) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed trial protocol must be submitted for review prior to trial initiation.

The timetable you submitted on April 19, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 2011
Trial Completion:	April 2013
Final Report Submission:	November 2013

1748-4 Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (*e.g.,* ketoconazole) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed trial protocol must be submitted for review prior to trial initiation.

The timetable you submitted on April 19, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 2011
Trial Completion:	April 2013
Final Report Submission:	November 2013

Submit the protocol to your IND 071023, with a cross-reference letter to this NDA. Submit all final report(s) 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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), 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, contact Amy Tilley, Regulatory Project Manager, at 301-796-3994.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
Container Label

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
04/28/2011