CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202379Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 27, 2011
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	202379
Applicant Name	Centocor Ortho Biotech, Inc.
Date of Submission	December 20, 2010
PDUFA Goal Date	June 20, 2011
Proprietary Name / **Established (USAN) Name**	ZYTIGA™ abiraterone acetate
Dosage Forms / Strength	250 mg tablets
Proposed Indication(s)	"Zytiga™ is indicated with prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4)
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Yangmin Ning, Paul Kluetz
Statistical Review	Lijun Zhang, Shenghui Tang
Pharmacology Toxicology Review	Robeena Aziz, Robert Dorsam, John Leighton
CMC Review/OBP Review	Debasis Ghosh, Tien-Mien Chen, Rik Lostritto
Microbiology Review	N/A
Clinical Pharmacology Review	Elimika Pfuma
DDMAC	Adora Ndu, Karen Rulli
DSI	Lauren Iacono-Conners
CDTL Review	Ke Liu
OSE/DMEPA	Jibril Adus-Samad
OSE/DDRE	N/A
OSE/DRISK	Steve Morin
Other	QT-IRT

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
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This new drug application for ZYTIGA™ (abiraterone acetate) Tablets was submitted on 12/20/10 for the following proposed indication: "Zytiga™ is indicated with prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4) Because of the improvement in overall survival described below, this application is being given an expedited review. This review will summarize the design and results of the randomized trial and the recommendations of each review discipline.

2. Background

Abiraterone acetate is a prodrug that is converted *in vivo* to abiraterone. Abiraterone inhibits 17 α-hydroxylase/C17,20-lyase (CYP17) which is expressed in testicular, adrenal and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyzes the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives and the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione which are androgenic precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals. The rationale for studying the drug in patients with castration-resistant prostate cancer (CRPC) is based on the fact that androgen deprivation therapies such as GnRH agonists/antagonists decrease androgen production in the testes but do not affect androgen production by the adrenal glands or in the tumor. The phase 3 trial was initiated after PSA responses were seen in Phase 2 in patients with CRPC and prior docetaxel treatment. The phase 3 trial was subject to a Special Protocol Assessment agreement.

3. CMC/Device

The CMC Review made the following recommendation and conclusion on approvability.

> From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA cannot be recommended for 'approval' from a CMC standpoint until the following three issues are addressed and completely resolved:
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> • An overall "acceptable" recommendation has not yet been issued by the Office of Compliance
> • As per the 3/30/2011 memorandum, the ONDQA Biopharmaceutics reviewer identifies one outstanding deficiency related to dissolution acceptance criteria.
> • Final labeling needs to be negotiated.

The ONDQA Division Director's Memo recommended approval from the CMC perspective and noted that the final dissolution specification was agreed upon and that EES was acceptable. 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] was recommended.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 12 months. The issues identified in the CMC review have been resolved. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology NDA Review and Evaluation stated that the non-clinical studies with abiraterone acetate support the safety of its use in metastatic prostate cancer and provided the following summary of nonclinical findings.

> The nonclinical findings have shown the target sites of toxicity with abiraterone acetate (CB7630 or JNJ-589485-AAA) to be the liver, adrenals, male and female reproductive organs, male mammary gland (26 and 39-week rat and monkey studies), pituitary (rats only), and eye (26-week rat study). Many of these toxicities are seen clinically and appear to be direct effects of the androgen depletion resulting from the pharmacology of abiraterone acetate.
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> Two different formulations of abiraterone acetate as well as abiraterone were shown not to be mutagenic or clastogenic in the *in vitro* assays. Abiraterone acetate and abiraterone was not clastogenic (induction of micronuclei) in the *in vivo* rat micronucleus assay at the highest dose tested, 2000 mg/kg (≈12,000 mg/m^2).
>
> Due to the patient population, embryo fetal development studies were not conducted and are not necessary to support the safety of abiraterone acetate for the proposed metastatic cancer indication in males. However, based on studies in rats (13- and 26-week studies) and monkeys (13- and 39-week studies), male and female reproductive organs were a target organ of toxicity therefore administration of this drug may impair reproduction.

The review stated that no additional non-clinical studies are required. The secondary and tertiary reviewers concurred.

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review stated that this NDA is considered acceptable from a clinical pharmacology perspective but identified several issues that are addressed in labeling.

- Abiraterone is an inhibitor of CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily.

- Based on *in vitro* data, abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors and inducers on the pharmacokinetics of abiraterone have not been evaluated *in vivo*.

- The pharmacokinetics of abiraterone were examined in subjects with baseline mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment and in subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1000 mg dose of abiraterone acetate increased by approximately 1.1-fold and 3.6 fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function. A dose reduction to 250 mg daily is recommended in patients with moderate hepatic function. The safety of abiraterone acetate in patients with severe hepatic impairment has not been studied.

- In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function and those with end stage renal disease on hemodialysis after a single oral 1000 mg dose of abiraterone acetate. No dosage adjustment is necessary for patients with renal impairment.

- Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone Cmax and $AUC_{0-\infty}$ were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal and approximately 17- and 10-fold higher, respectively, when administered with a high-fat meal. Therefore, no food should be consumed for at least two hours before and one hour after the dose of abiraterone acetate is taken.

The review recommended the following post-marketing requirements:

1. 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.

2. Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inducer (e.g., rifampin) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate.

3. Conduct a trial to determine the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate in individuals with severe hepatic impairment.

4. 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.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. I also concur with the recommended PMR's.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The design and efficacy results from the single Phase 3 trial are described below in the following excerpt from the Clinical Review.

> The key clinical study supporting this NDA is a randomized, double-blind, placebo-controlled, multicenter phase 3 trial that evaluated the efficacy and safety of abiraterone acetate in patients with mCRPC who had previously received docetaxel-based chemotherapy. A total of 1195 patients were stratified and randomized 2:1 to receive either abiraterone orally at a dose of 1000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo orally once daily plus prednisone 5 mg orally twice daily (N=398). Treatment continued until disease progression, unacceptable toxicity, initiation of new treatment, or withdrawal. The primary endpoint was overall survival.
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> All patients had received prior docetaxel-based chemotherapy. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens. At enrollment, 89% of patients had an ECOG performance status score of 0-1, 45% had a Brief Pain Inventory score of ≥ 4 (patient's reported worst pain over the previous 24 hours), 30% had visceral metastases, 70% had radiographic evidence of disease progression while 30% had PSA-only disease progression. These characteristics as well as other baseline characteristics examined were well balanced between the two arms.
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> Efficacy
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> The protocol pre-specified interim analysis of overall survival was conducted with 69% of the 797 deaths required for the planned final analysis. The results from this analysis demonstrated a statistically significant improvement in overall survival in patients on

the abiraterone arm compared to patients on the placebo arm (HR=0.646; 95% CI: 0.543, 0.768; p<0.0001). The median survival for patients in the abiraterone arm was 14.8 months compared to 10.9 months for patients in the placebo arm. The significance level of this interim analysis (p< 0.0001) crossed the pre-specified efficacy boundary of a two-sided alpha of 0.0141. As a result, the trial was unblinded and terminated prior to the planned final analysis. This overall survival benefit was consistently demonstrated in an updated survival analysis (with 97% of the required number of events for final analysis), sensitivity analyses and subgroup analyses.

Evaluable secondary endpoints that demonstrated the antitumor activity of abiraterone in the phase 3 trial included percentage of patients with PSA declines of ≥50% and objective tumor response evaluated by Response Evaluation Criteria in Solid Tumors (RECIST criteria). Confirmed PSA responses, as assessed with the central laboratory measurement of PSA levels, were detected in 29% of patients on the abiraterone arm compared to 6% in patients on the placebo arm, favoring abiraterone acetate treatment and corroborating the previously reported antitumor activity in the same patient population in two previous Phase 2 trials conducted by the applicant. In addition, confirmed radiographic tumor response rate, assessed by investigators according to the RECIST criteria in 48% of patients with measurable disease at baseline, was higher in the abiraterone acetate arm (14%) than in the placebo arm (3%). Although being exploratory in nature (see Section 6.1.5), these results demonstrated the anti-tumor activity of abiraterone acetate and appear to support its treatment effect on overall survival.

The Statistical Review and Evaluation confirmed the results of the overall survival analyses and provided following efficacy conclusions.

The pivotal trial COU-AA-301 met the study objective by showing a hazard ratio of 0.646 (95% CI: 0.543 – 0.768, p-value < 0.0001) for the abiraterone acetate arm versus the placebo arm in overall survival at the interim analysis with 69% information (552 deaths). The median survival time was 14.8 months in the abiraterone acetate arm compared to 10.9 months in the placebo arm. The finding was confirmed by the updated overall survival analysis with 775 deaths (97% of the planned number of deaths for final analysis), with a HR of 0.740 (95% CI: 0.638-0.859; p<0.0001) and a median survival of 15.8 months versus 11.2 months for the abiraterone acetate arm and the placebo arm, respectively. Furthermore, subgroup analyses showed consistent results in favor of abiraterone acetate. Sensitivity analyses confirmed the findings of the primary analysis. There are no major statistical issues in the efficacy analyses.

8. Safety

The safety of abiraterone acetate and the risk benefit assessment is provided in the following excerpt from the Clinical Review.

> Safety
> Adverse reactions reported in >10% patients and more frequently in the abiraterone acetate arm were joint swelling/discomfort, muscle discomfort, edema, hot flush, diarrhea, urinary tract infection and cough. The majority of these adverse reactions were Grade 1 or 2 according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 3.
>
> Adverse reactions associated with mineralocorticoid excess occurred more frequently in the abiraterone arm, including edema (27%), hypokalemia (17%) and hypertension (8.5%). However, Grade 3 or 4 of these adverse reactions occurred in < 4% of patients (1.9%, 3.8% and 1.3% respectively). None of these adverse reactions led to treatment discontinuations or deaths.
>
> Adrenocortical insufficiency (AI) was reported in 2 patients receiving abiraterone and none in the placebo arm in the Phase 3 trial. In a combined safety analysis of trials in which abiraterone acetate was administered at the recommended dose of 1000 mg once daily, a total of 5 patients were diagnosed with AI, leading to an estimated AI incidence rate of 0.5%. AI occurred both when patients were taking the recommended dose of corticosteroids and after patients discontinued prednisone. Three of the five cases with AI resolved, one was ongoing at the end of study visit and one case was ongoing at the time of death from disease progression.
>
> Hepatotoxicity associated with abiraterone acetate treatment was also reported. In the integrated safety population, alanine and/or aspartate aminotransferase (ALT) [*sic*] elevations were reported in 7.5% of patients taking abiraterone versus 3.8% of patients taking placebo. Grade 3 or 4 elevations of either ALT or AST were reported in 1.5% of patients taking AA versus 1.0% of patients taking placebo. No hepatic failure or death was observed in abiraterone clinical trials.
>
> Review of 4-month safety update to the NDA did not identify new safety signals.

9. Advisory Committee Meeting

This NDA was not presented at a meeting of the Oncologic Drugs Advisory Committee because there were no issues that needed discussion. The benefit risk assessment is straightforward and clearly favorable for the indicated population.

10. Pediatrics

A pediatric waiver was granted by PeRC because the disease does not occur in pediatric patients.

11. Other Relevant Regulatory Issues

- DSI Audits: DSI inspected five clinical sites and the parent sponsor of the study and concluded that the study data appear reliable.
- Financial Disclosure: See Clinical Review. No significant issues were identified.
- DDMAC recommendations were considered during the labeling meetings.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: DMEPA concurred with the proposed proprietary name.
- Physician labeling: The indication was revised (b) (4) "ZYTIGA™ in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel."
- Carton and immediate container labels: Agreement has been reached on the carton and container labels.
- Patient labeling/Medication guide: The applicant submitted a PPI which is being revised to incorporate DRISK recommendations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The following is the risk benefit assessment in the Clinical Review.

Risk-Benefit Analysis

The efficacy and safety findings from the clinical review of this NDA provide substantial evidence for the effectiveness of abiraterone acetate in the intended patient population, in which treatment with abiraterone acetate was associated with a 3.9-month improvement in median overall survival compared to placebo, and with an acceptable toxicity profile. Distinct from myelosuppression-related toxicities (e.g., severe neutropenia and/or febrile neutropenia) that are commonly observed with cytotoxic chemotherapy in the treatment of patients with mCRPC (see Sections 2.2 and 2.6), abiraterone acetate has unique toxicities that include mineralocorticoid excess-associated adverse reactions, adrenocortical insufficiency, and hepatotoxicity. These unique safety issues have been discussed and addressed during this NDA review and in the labeling of the product.

Given the totality of data, the clinical reviewers concluded that abiraterone acetate treatment offers a highly favorable risk-benefit profile for patients with mCRPC who have received prior chemotherapy containing docetaxel.

I concur with this assessment. There are no unresolved issues.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  I concur with the PMR's recommended by Clinical Pharmacology in section 5.

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/s/

ROBERT L JUSTICE
04/27/2011