CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202379Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	*electronic stamp date*
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
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 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
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Division Director	Robert Justice
CDTL Review	Ke Liu
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
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

1. Introduction

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 ZYTIGA™ (abiraterone acetate) tablets NDA 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) (b) (4) (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a

2. Clinical - Efficacy

This application is supported by the results of a randomized, placebo-controlled, multicenter trial in 1195 patients with metastatic CRPC (mCRPC) previously treated with docetaxel-containing regimens. Patients were randomly allocated (2:1) to receive either abiraterone acetate orally at a dose of 1000 mg once daily (N=797) or placebo once daily (N=398). Patients in both arms (abiraterone acetate and placebo) received prednisone 5 mg orally twice daily. Treatment continued until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), unacceptable toxicity, initiation of new treatment, or withdrawal. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded.

A pre-specified interim overall survival (OS) analysis was performed when 552 events had occurred. This analysis demonstrated a statistically significant improvement in OS in patients receiving abiraterone acetate compared to those on the placebo-containing arm (HR=0.646; 95% CI: 0.543, 0.768; $p < 0.0001$). The median OS was 14.8 versus 10.9 months in the abiraterone and placebo arm, respectively. An updated OS analysis, conducted after 775 events, demonstrated a median OS of 15.8 versus 11.2 months in the abiraterone acetate and placebo-containing arms, respectively (HR=0.740; 95% CI: 0.638, 0.859).

3. Clinical - Safety

The most common adverse reactions (> 5%) were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia and upper respiratory tract infection. The most common adverse drug reactions resulting in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase, urosepsis and cardiac failure (each in < 1% of patients taking abiraterone).

The most common electrolyte imbalances in patients receiving abiraterone were hypokalemia (28%) and hypophosphatemia (24%). Following interruption of daily corticosteroids and/or with concurrent infection or stress, adrenocortical insufficiency (<1%) has been reported in clinical trials in patients receiving abiraterone acetate at the recommended dose in combination with prednisone.

Abiraterone acetate Cmax and exposure were increased up to 17-fold and 10-fold higher, respectively, when a single dose was administered with a meal compared to a fasting state.

The recommended dose and schedule for abiraterone acetate is 1000 mg orally once daily in combination with prednisone 5 mg orally twice daily. Abiraterone acetate should be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the abiraterone acetate dose.

4. Other Discipline Reviews

There are no outstanding issues that preclude approval from other disciplines and a summary of other discipline reviews is below.

CMC
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.

Nonclinical Pharmacology/Toxicology
Pharmacology/Toxicology reviews concluded that nonclinical studies with abiraterone acetate support the safety of its use in metastatic prostate cancer. As noted in the review:

> 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.
>
> No additional nonclinical studies are required.

Clinical Pharmacology
The Clinical Pharmacology review outlined several issues that are addressed in labeling.

- Abiraterone is an inhibitor of CYP2D6. Based on *in vitro* data, abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors and inducers on the PK of abiraterone have not been evaluated *in vivo*.

- The PK of abiraterone were examined in subjects with baseline mild or moderate 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 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. As stated in labeling, no food should be consumed for at least two hours before and one hour after the dose of abiraterone acetate is taken.

Please refer to the action letter for Clinical Pharmacology postmarketing requirements.

5. Other Regulatory Issues

Advisory Committee Meeting:
The benefit risk assessment is favorable for the indicated population and there were no issues that would benefit from ODAC discussion, therefore, this NDA was not presented at ODAC.

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

DSI Audits: DSI inspected five clinical sites and the parent sponsor of the study and concluded that the study data appear reliable.

Labeling:
Proprietary name - DMEPA concurred with the proposed proprietary name.
Labeling - All major issues have been resolved.

6. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

Risk Benefit Assessment
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 (a 3.9-month improvement in median overall survival compared to placebo) with an acceptable toxicity profile. Distinct from myelosuppression-related toxicities (e.g., severe neutropenia and/or febrile neutropenia) commonly observed with cytotoxic chemotherapy in the treatment of patients with mCRPC, abiraterone acetate has unique toxicities that include mineralocorticoid excess-associated adverse reactions, adrenocortical insufficiency, and hepatotoxicity. These unique safety issues have been addressed in the product labeling.

The benefits and risks of abiraterone were discussed in the Division Director's Summary Review, the CDTL and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable. In conclusion, I concur with Dr. Justice's assessment in his summary review as well as the review team's recommendation for approval.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies*:* None

Recommendation for other Postmarketing Requirements and Commitments: Please refer to the action letter.

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/s/

TAMY E KIM
04/28/2011

RICHARD PAZDUR
04/28/2011