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March 15, 2019

Kristina Gregory, RN, MSN, OCN  
3025 Chemical Road  
Plymouth Meeting, PA 19462  
USA

Dear Ms. Gregory,

Please consider the following information.

**Response(s):**

- ZYTIGA - NCCN Compendium Communication - MARCH 2019

I look forward to working with you as you consider the enclosed information. The information provided is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information, including the following sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.

If you require further information, please feel free to contact me via the Janssen Medical Information Center at 1-800-JANSSEN (1-800-526-7736).

Sincerely,

*Lisa Meadows*  
Lisa Meadows, RPh  
Therapeutic Manager  
Medical Information

Inquiry #:01352175

Enclosure(s)/Electronic Link(s):

- ZYTIGA® (abiraterone acetate) Prescribing Information at [https://imedicalknowledge.veevavault.com/ui/approved\\_viewer?token=7994-ecaf8e16-61b7-48c6-a6ad-2594b810a4af](https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-ecaf8e16-61b7-48c6-a6ad-2594b810a4af)
- Low-fat abiraterone food effect is of little consequence
- Fast and flawed or scientifically sound: the argument for administering oral oncology drugs during fasting

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**ZYTIGA® (abiraterone acetate)**  
**NCCN Compendium Communication – MARCH 2019**

Name: Lisa Meadows Ambrose, RPh, BCOP  
Company/Organization: Janssen Biotech, Inc.  
Address: 850 Ridgeview Drive Horsham, PA 19044  
Phone: 804.539.7417  
E-mail: LMeadows@its.jnj.com  
Date of request: March 12, 2019  
NCCN Guidelines® Panel: Prostate Cancer

Dear NCCN,

On behalf of Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® Prostate Cancer Panel review the enclosed data regarding the recent addition of an alternate dosing study of abiraterone acetate to the Guidelines. Further, we request removal of the recommendation based on Szmulewitz et al. 2018 as the study utilized dosing of abiraterone acetate that is not FDA approved. Given the normal variation in the content and composition of meals, taking abiraterone acetate with meals has the potential to result in increased and highly variable exposures. Therefore, abiraterone acetate must be taken on an empty stomach as described in the ZYTIGA® (abiraterone acetate) Prescribing Information.<sup>1</sup> Additionally, inclusion of a recommendation based on this single small phase 2 study is inconsistent with the level of evidence required for other NCCN recommendations within these Guidelines; and this study is referenced in the Guidelines without the study limitations and without the noted increase in adverse events observed in the investigational dosing arm, such as increased reports of pain.

**Specific Changes:** We request removal of the following from the Prostate Cancer Guidelines V.1.2019, PROS-F:

- Principles of Androgen Deprivation Therapy (PROS-F) Abiraterone with prednisone can be administered at a dose of 250 mg/day following a low-fat breakfast, as an alternative to the dose of 1000 mg/day after an overnight fast. *The cost savings from this dosing may reduce financial toxicity and improve compliance.* Szmulewitz et al – Prospective international randomized phase II study of low-dose abiraterone with food vs standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol* 2018;36:1389-1395.

**FDA Clearance:** The FDA has approved ZYTIGA® (abiraterone acetate) in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) and metastatic high-risk castration-sensitive prostate cancer (CSPC).<sup>1</sup> The FDA approved dosing included in the ZYTIGA Prescribing Information is:

Metastatic castration-resistant prostate cancer:

- ZYTIGA 1,000 mg orally once daily with prednisone 5 mg orally **twice** daily.

Metastatic castration-sensitive prostate cancer:

- ZYTIGA 1,000 mg orally once daily with prednisone 5 mg orally **once** daily.

Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. ZYTIGA must be taken on an empty stomach with water at least 1 hour before or 2 hours after a meal. Do not crush or chew tablets.<sup>1</sup> Please see the ZYTIGA full Prescribing Information for Dose Modification Guidelines.

Section 12.3 CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption of the ZYTIGA Prescribing Information<sup>1</sup> also states:

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. In healthy subjects abiraterone C<sub>max</sub> and AUC<sub>0-∞</sub> were approximately 7- and 5-fold higher, respectively, when a single dose of abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting. Abiraterone AUC<sub>0-∞</sub> was approximately 7-fold or 1.6-fold higher, respectively, when a single dose of abiraterone acetate was administered 2 hours after or 1 hour before a medium fat meal (25% fat, 491 calories) compared to overnight fasting. Systemic exposures of abiraterone in patients with metastatic CRPC, after repeated dosing of abiraterone acetate were similar when abiraterone acetate was taken with low-fat meals for 7 days and increased approximately 2-fold when taken with high-fat meals for 7 days compared to when taken at least 2 hours after a meal and at least 1 hour before a meal for 7 days. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, ZYTIGA must be taken on an empty stomach, either one hour before or two hours after a meal.<sup>1</sup>

In addition, Section 17 PATIENT COUNSELING INFORMATION and PATIENT INFORMATION in the ZYTIGA Prescribing Information<sup>1</sup> state:

- Instruct patients to take ZYTIGA on an empty stomach, either one hour before or two hours after a meal. ZYTIGA taken with food causes increased exposure and may result in adverse reactions.
- Take ZYTIGA on an empty stomach, either one hour before or two hours after a meal. Do not take ZYTIGA with food. Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.

#### **Rationale:**

The small phase 2 non-inferiority study (N=72) cited as rationale for the NCCN recommended dose of abiraterone acetate 250 mg/day plus 5 mg prednisone BID with a low fat meal, a dose that is not FDA-approved nor studied in a phase 3 randomized trial and may have inter- and inpatient variation and suboptimal efficacy exposure from fluctuations in the nature and timing of food intake,<sup>2</sup> has several limitations including: the efficacy endpoint (change in PSA including log-change PSA at 12 weeks) is not a clinically validated surrogate end point<sup>3</sup> compared to overall survival, the endpoint evaluated in the 3 large phase 3, randomized, placebo-controlled, international clinical studies (COU-AA-301, N=1,195; COU-AA-302, N=1,088 and LATITUDE, N=1,199)<sup>4-9</sup> that established the efficacy and safety of ZYTIGA 1,000 mg daily plus prednisone 5 mg BID (or 5 mg daily in LATITUDE); the noninferiority margin of 15% for the PSA response rate is relatively liberal as noted by Szmulewitz et al.; PSA testing was not measured centrally as recommended by PCWG3; and PK trough levels were not comparable to prior clinical studies, in addition to other study limitations.<sup>3</sup>

The following two publications are submitted with the ZYTIGA® (abiraterone acetate) Prescribing Information:

Kolesar JM, Liu GX. Low-fat abiraterone food effect is of little consequence. *J Clin Oncol*. 2018;36:1385-1386.

Todd M, Myers ML, Charnas R, et al. Fast and flawed or scientifically sound: the argument for administering oral oncology drugs during fasting. *J Clin Oncol*. 2012;30(8):888-889.

Sincerely,

Lisa Meadows Ambrose RPh, PharmD-c, BCOP  
Therapeutic Manager, Oncology Medical Information  
Janssen Scientific Affairs, LLC

#### **REFERENCES**

<sup>1</sup>ZYTIGA (abiraterone acetate) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; [https://imedicalknowledge.veevavault.com/ui/approved\\_viewer?token=7994-ecaf8e16-61b7-48c6-a6ad-2594b810a4af](https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-ecaf8e16-61b7-48c6-a6ad-2594b810a4af)

<sup>2</sup>Todd M, Myers ML, Charnas R, et al. Fast and flawed or scientifically sound: the argument for administering oral oncology drugs during fasting. *J Clin Oncol*. 2012;30(8):888-889.

<sup>3</sup>Kolesar JM, Liu GX. Low-fat abiraterone food effect is of little consequence. *J Clin Oncol*. 2018;36:1385-1386.

<sup>4</sup>de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364:1995-2005.

<sup>5</sup>Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983-992.

<sup>6</sup>Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160.

<sup>7</sup>Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *New Engl J Med*. 2013;368:138-148.

<sup>8</sup>Fizazi K, Tran NP, Fein L, et al. Abiraterone plus prednisone in metastatic castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.

<sup>9</sup>Fizazi K, Tran N, Fein L, et al. Final analysis of phase 3 LATITUDE study in patients (pts) with newly diagnosed high-risk metastatic castration naïve prostate cancer (NDx-HR mCNPC) treated with abiraterone acetate + prednisone (AA+P) added to androgen deprivation therapy (ADT). Poster presented at: American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium; February 14-16; San Francisco, CA. 2019.

Additional pharmacokinetic study data have been published:

Chi KN, Spratlin J, Kollmannsberger C, et al. Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. *J Clin Pharmacol*. 2015;55(12):1406-1414.

Stuyckens K, Saad F, Xu XS, et al. Population pharmacokinetic analysis of abiraterone in chemotherapy-naive and docetaxel-treated patients with metastatic castration-resistant prostate cancer. *Clin Pharmacokinet*. 2014;53(12):1149-1160.

Bryce A, Ryan CJ. Development and clinical utility of abiraterone acetate as an androgen synthesis inhibitor. *Clin Pharmacol Ther*. 2012;91(1):101-108.

Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J Clin Oncol*. 2010;28(9):1481-1488.

Attard G, Reid AH, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol*. 2008;26(28):4563-4571.

Acharya M, Bernard A, Griffin T, et al. A Phase 1 study to determine the effect of food on the pharmacokinetics of abiraterone acetate (AA) in healthy male subjects. Poster presented at: The American Association of Pharmaceutical Scientists (AAPS) 2011 Annual Meeting; October 23-27, 2011; Washington, D.C.