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June 11, 2019

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

Dear Ms. Gregory,

Please consider the following information in this submission for the NCCN Prostate Cancer Panel annual meeting.

Response(s):

- ZYTIGA - NCCN Compendium Communication - Product Update - June 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 #:01418574

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
- The addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomized, double-blind, placebo-controlled, phase 3 trial.
- Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE):final overall survival analysis of a randomized, double-blind, phase 3 trial.
- ZYTIGA Prescribing Information

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ZYTIGA® (abiraterone acetate)
NCCN Compendium Communication – Product Update - June 2019

Name: Lisa Meadows Ambrose, RPh, BCOP
Company/Organization: Janssen Biotech, Inc.
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Phone: 804.539.7417
E-mail: LMeadows@its.jnj.com
Date of request: June 6, 2019
NCCN Guidelines® Panel: Prostate Cancer

Dear NCCN,

On behalf of Janssen Biotech, Inc., I respectfully request review of a summary of key changes in the updated ZYTIGA® (abiraterone acetate) Prescribing Information June 2019, the LATITUDE study final survival analysis, and additional published information related to requested specific changes.

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).[1] 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.[1] Please see the ZYTIGA full Prescribing Information for Dose Modification Guidelines.

Specific Recommended Changes:

Please align all related content currently in the Guidelines® Version 2.2019, NCCN Compendium®, NCCN Templates™ and any other NCCN® publications or platforms with the current version of the ZYTIGA Prescribing Information and:

1. Please remove the language regarding abiraterone acetate use plus prednisone use in combination with Ra223 on page MS-27 and MS-28.
2. Please include the final OS analysis from the LATITUDE study on page MS-34.
3. Please remove the statement regarding abiraterone acetate monitoring on page MS-40: "…, at least initially…"
4. Please remove the statement regarding prednisone dosing on page MS-40: "Some patients may be able to avoid steroids with abiraterone, but careful monitoring is warranted, and a mineralocorticoid receptor antagonist or steroid should be added to control side effects if necessary."

Rationale:

1. Please refer to the new **WARNINGS AND PRECAUTIONS 5.4 Increased Fractures and Mortality in Combination with Radium Ra 223 Dichloride** in the ZYTIGA Prescribing Information: Increased fractures and mortality in combination with radium Ra 223 dichloride: Use of ZYTIGA plus prednisone/prednisolone in combination with radium Ra 223 dichloride is not recommended.[1,2]
2. The LATITUDE study final survival analysis is now included in the ZYTIGA Prescribing Information **Section 14 CLINICAL STUDIES**, **Patients with metastatic high-risk CSPC**, and was conducted after a median follow-up of 51.8 months: abiraterone acetate plus

prednisone with ADT continued to show significant OS improvement vs placebos plus ADT (median OS was 53.3 months vs 36.5 months in the abiraterone acetate plus prednisone with ADT group and the placebos with ADT group, respectively [HR, 0.66; 95% CI, 0.56-0.78; *P*<0.0001]), along with significant improvements in secondary endpoints; and safety results from this final analysis were consistent with prior interim analyses.[3]

3. Please refer to the monitoring recommendation in **WARNINGS AND PRECAUTIONS 5.1 Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions due to Mineralocorticoid Excess** in the ZYTIGA Prescribing Information: Closely monitor patients with cardiovascular disease. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly.[1]
4. Please refer to the new postmarketing experience added to **WARNINGS AND PRECAUTIONS 5.1 Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions due to Mineralocorticoid Excess** and **ADVERSE REACTIONS, Section 6.2 Postmarketing Experience** in the ZYTIGA Prescribing Information. ZYTIGA dosing recommendations are based on the large phase 3, randomized, double-blind, placebo-controlled, multicenter studies[1] of abiraterone acetate 1,000 mg plus daily prednisone (5 mg BID in mCRPC and 5 mg QD in metastatic high-risk CSPC). Recent case reports also describe incidents of TdP in patients receiving abiraterone acetate who experienced hypokalemia, one of whom had a reported adherence issue with prednisone.[4,5]

The following publication is submitted with the ZYTIGA full Prescribing Information and a summary of the recent Prescribing Information updates:

Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE):final overall survival analysis of a randomized, double-blind, phase 3 trial. *Lancet Oncol*. 2019;20(5):686-700.

Smith M, Parker C, Saad F, et al. The addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019; 20(3):408-419.

Sincerely,

Lisa Meadows Ambrose RPh, PharmD-c, BCOP
Manager, Medical Information & Knowledge Integration
Janssen Scientific Affairs, LLC

REFERENCES

1. ZYTIGA (abiraterone acetate) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-ecaf8e16-61b7-48c6-a6ad-2594b810a4af
2. Smith M, Parker C, Saad F, et al. The addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019; 20(3):408-419.
3. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE):final overall survival analysis of a randomized, double-blind, phase 3 trial. *Lancet Oncol*. 2019;20(5):686-700.
4. Rodieux F, Nieto N, Sunthorn H, et al. Abiraterone acetate-induced life-threatening torsade de pointes. *Ann Pharmacother*. 2015;49(1):152-153.
5. Khan A, Kneale B. Life threatening torsades de pointes due to abiraterone-induced hypokalemia in a patient with metastatic prostate cancer. *N Z Med J*. 2016;129(1445):124-127

ZYTIGA® (abiraterone acetate)
Compendia Communication – Product Update – June 2019

SUMMARY

- The current ZYTIGA® (abiraterone acetate) Prescribing Information is dated June 2019.
- Key changes to the ZYTIGA® (abiraterone acetate) Prescribing Information include the following topics:
  - Added postmarketing experience to **WARNINGS AND PRECAUTIONS 5.1 Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions due to Mineralocorticoid Excess** and **ADVERSE REACTIONS, Section 6.2 Postmarketing Experience**
  - Added new **WARNINGS AND PRECAUTIONS 5.4 Increased Fractures and Mortality in Combination with Radium Ra 223 Dichloride**
  - Added new **WARNINGS AND PRECAUTIONS 5.5 Embryo-Fetal Toxicity** and added "None" and removed "Pregnancy" from **CONTRAINDICATIONS**
  - Added final overall survival analysis for the LATITUDE study to **Section 14 CLINICAL STUDIES, LATITUDE: Patients with metastatic high-risk CSPC**
  - Revisions to **Section 17 PATIENT COUNSELING INFORMATION** and **PATIENT INFORMATION** to reflect these and additional updates.
- Please ensure monograph alignment with the current ZYTIGA Full Prescribing Information Version June 2019.

ZYTIGA® (abiraterone acetate) PRESCRIBING INFORMATION June 2019 KEY CHANGES:

- **Revised**: 06/2019
- **HIGHLIGHTS OF PRESCRIBING INFORMATION, RECENT MAJOR CHANGES:**
  Revised: "Warnings and Precautions (5.1) 06/2019" and added:
  "Warnings and Precautions (5.4) 06/2019"
  "Warnings and Precautions (5.5) 06/2019"
  WARNINGS AND PRECAUTIONS Added:
  "Increased fractures and mortality in combination with radium Ra 223 dichloride: Use of ZYTIGA plus prednisone/prednisolone in combination with radium Ra 223 dichloride is not recommended. (5.4)"
  "Embryo-Fetal Toxicity: ZYTIGA can cause fetal harm. Advise males with female partners reproductive potential to use effective contraception. (5.5, 8.1, 8.3)"
  CONTRAINDICATIONS Added:
  "None"
  Removed: "Pregnancy. (4, 8.1)"
  USE IN SPECIFIC POPULATIONS Removed:
  "Females and Males of Reproductive Potential: Advise males with female partners of reproductive potential to use effective contraception. (8.3)"
- **Section 2 DOSAGE AND ADMINISTRATION, Sections 2.1 and 2.2**: format change to capitalize Metastatic and High-risk.
- **Section 2 DOSAGE AND ADMINISTRATION**, **Section 2.3 Important Administration Instructions**: Added: "at least" prior to one hour and two hours in empty stomach description:

"ZYTIGA must be taken on an empty stomach, at least one hour before or at least two hours after a meal."

- **Section 4 CONTRAINDICATIONS** Added:
  "None"
  The following text was removed:
  "**Pregnancy**
  ZYTIGA can cause fetal harm and potential loss of pregnancy *[see Use in Specific Populations (8.1)]."*
- Revised section title: **Section 5 WARNINGS AND PRECAUTIONS, Section 5.1 Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions due to Mineralocorticoid Excess** and added:
  "In postmarketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking ZYTIGA."
- Added (new): **Section 5 WARNINGS AND PRECAUTIONS, Section 5.4 Increased Fractures and Mortality in Combination with Radium Ra 223 Dichloride:**
  "ZYTIGA plus prednisone/prednisolone is not recommended for use in combination with radium 223 dichloride outside of clinical trials.

  The clinical efficacy and safety of concurrent initiation of ZYTIGA plus prednisone/ prednisolone and radium Ra 223 dichloride was assessed in a randomized, placebo-controlled multicenter study (ERA-223 trial) in 806 patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committee recommendation.

  At the primary analysis, increased incidences of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received ZYTIGA plus prednisone/prednisolone in combination with radium Ra 223 dichloride compared to patients who received placebo in combination with ZYTIGA plus prednisone/ prednisolone."
- Added (new): **Section 5 WARNINGS AND PRECAUTIONS, Section 5.5 Embryo-Fetal Toxicity:**
  "The safety and efficacy of ZYTIGA have not been established in females. Based on animal reproductive studies and mechanism of action, ZYTIGA can cause fetal harm and loss of pregnancy when administered to a pregnant female. In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately ≥0.03 times the human exposure (AUC) at the recommended dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ZYTIGA and for 3 weeks after the last dose of ZYTIGA *[see Use in Specific Populations (8.1, 8.3)]*. ZYTIGA should not be handled by females who are or may become pregnant *[see How Supplied/Storage and Handling (16)]."*
- **Section 6 ADVERSE REACTIONS, Section 6.2 Postmarketing Experience:** Added: "Cardiac Disorders: QT prolongation and Torsades de Pointes (observed in patients who developed hypokalemia or had underlying cardiovascular conditions)."

- **Section 14 CLINICAL STUDIES, LATITUDE: Patients with metastatic high-risk CSPC:** Added: LATITUDE final OS analysis data
    - Clarified median age: The median age was 67 years "among all randomized subjects."
    - Revised: "An updated survival analysis was conducted when 618 deaths were observed. The median follow-up time was 52 months. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 10 and Figure 4). At the updated analysis, 29% of patients on the ZYTIGA arm and 45% of patients on the placebos arm received subsequent therapies that may prolong OS in metastatic CRPC."
      Removal of: including cytotoxic chemotherapy, abiraterone acetate, enzalutamide, and systemic radiotherapy.
    - Revised: Table 10: Overall Survival of Patients Treated with Either ZYTIGA or Placebos in LATITUDE (Intent-to-Treat Analysis) and added final analysis data
    - Replaced with new Figure 4: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population in LATITUDE Updated (Final) Analysis KM Plot of OS; ITT Population in LATITUDE

- **Section 17 PATIENT COUNSELING INFORMATION:**
    - Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions Added text about QT Prolongation/TdP: Inform patients that ZYTIGA is associated with hypertension, hypokalemia, and peripheral edema "that may lead to QT prolongation and Torsades de Pointes in patients who develop hypokalemia while taking ZYTIGA. Advise patients that their blood pressure, serum potassium and signs and symptoms of fluid retention will be monitored clinically at least monthly. Advise patients to adhere to corticosteroids" and to report symptoms of hypertension, hypokalemia, or edema to their healthcare provider *[see Warnings and Precautions (5.1)]*."
    - Added: "Use in Combination with Radium Ra 223 Dichloride"
      "Advise patients that radium Ra 223 dichloride showed an increase in mortality and an increased rate of fracture when used in combination with ZYTIGA plus prednisone/prednisolone. Inform patients to speak with their healthcare provider about any other medications or treatment they are currently taking for prostate cancer *[see Warnings and Precautions (5.4)]*."
    - Revised following language used Dosage and Administration, Instruct patients to take ZYTIGA on an empty stomach, "at least" one hour before or "at least" two hours after a meal."
    - Added "Embryo-" to Fetal Toxicity header and revised:
      Inform patients that ZYTIGA may harm a developing fetus "and can cause loss of pregnancy."
      "Advise females" who are pregnant or women who may be pregnant…
- Added "Product of Belgium" and Revised: 06/2019

- **PATIENT INFORMATION**
  - **Before taking ZYTIGA, tell your healthcare provider about all of your medical conditions, including if you:** Added:
    - "are receiving any other treatment for prostate cancer"
    - "are pregnant" or plan to become pregnant. "ZYTIGA can cause harm to your unborn baby and loss of pregnancy (miscarriage). Females" who are or may become pregnant should not handle ZYTIGA [removed: 250 mg] uncoated tablets or other ZYTIGA tablets if broken, crushed, or damaged without protection, such as gloves.
    - "have a partner who is pregnant or may become pregnant.
      - Males who have female partners who are able to become pregnant should use effective birth control (contraception) during treatment with ZYTIGA and for 3 weeks after the last dose of ZYTIGA." [note: this was moved from the How should I take ZYTIGA? Section]
  - **How should I take ZYTIGA?** Revised:
    - Do not "change or" stop taking….
    - Take ZYTIGA on an empty stomach, "at least" one hour before or "at least" two hours after a meal.
  - **What are the possible side effects of ZYTIGA?**
    Revised: serious side effects, heartbeats from fast to "fast or irregular" heartbeats
    Added: Increased risk of bone fracture and death when ZYTIGA and prednisone or prednisolone, is used in combination with a type of radiation called radium Ra 223 dichloride. Tell your healthcare provider about any other treatments you are taking for prostate cancer.
    Added: "ZYTIGA may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility."
    Removed: Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
    Added: "You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for health professionals."
    Added: "Product of Belgium"