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June 08, 2017

Joan McClure
275 Commerce Drive #300
Fort Washington, PA 19034
USA

Dear Ms. McClure,

Please consider the following information on ZYTIGA® (abiraterone acetate).

Response(s):

- ZYTIGA - Compendia Communication - NCCN LATITUDE and STAMPEDE June 2017

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, BCOP
Therapeutic Manager

Medical Information

Inquiry #:00889528

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
  - Abiraterone for prostate cancer not previously treated with hormone therapy
  - Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer

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Need Help? If you have any additional questions, please contact us via:

1-800-JANSSEN Monday - Friday, 9 am - 8 pm EST	**24x7 Access to Medical Information** www.janssenmd.com
Email Medical Information	**Locate Medical Science Liaison** www.janssenmsl.com

To report a possible adverse event or product quality complaint, please call the Medical Information Center immediately, at 1-800-JANSSEN (1-800-526-7736).

ZYTIGA® (abiraterone acetate)
Compendia Communication - LATITUDE and STAMPEDE Studies

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Date of request: June 8, 2017

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 efficacy and safety outcomes from two randomized studies of abiraterone acetate plus daily prednisone with androgen deprivation therapy (ADT) compared to ADT alone in newly diagnosed, high-risk, metastatic castration-sensitive prostate cancer.

Specific Changes:

Update Guidelines to include ZYTIGA® (abiraterone acetate) plus prednisone with androgen deprivation therapy (ADT) as a systemic therapy for locally advanced and metastatic castration-sensitive prostate cancer.

FDA Clearance: The FDA has approved ZYTIGA in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.[1]

Rationale:

LATITUDE[2] is a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of abiraterone acetate plus daily prednisone with androgen deprivation therapy (ADT) compared to placebo with ADT in 1,199 patients with newly diagnosed, high-risk, metastatic castration-sensitive prostate cancer. Patients were randomized 1:1 to receive either abiraterone acetate 1,000 mg plus prednisone 5 mg orally daily with ADT or placebo with ADT; and stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade (0-1 vs 2) and by presence or absence of visceral disease. Co-primary endpoints were overall survival (OS) and radiographic progression-free survival (rPFS). Secondary and exploratory endpoints included median time to: pain progression, PSA progression, next skeletal event, initiation of chemotherapy, and subsequent prostate cancer therapy; and the percent of patients who achieved ≥50% decline in PSA from baseline.

Key inclusion criteria were newly diagnosed, pathologically confirmed prostate cancer (≤3 months prior to randomization) with castration-sensitive metastatic disease confirmed by bone scan, CT or MRI; 2 of 3 high-risk factors (Gleason score ≥8, ≥3 bone lesions, and/or presence of measurable visceral disease); and ECOG PS ≤2. Prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer were exclusion criteria, except for ≤3 months of ADT and one course of palliative therapy for symptomatic metastases. Baseline pain scores were 0-1, 2-3, and ≥4 in 50%, 22%, and 29% of patients, respectively; 98% of patients had ≥3 bone lesions and 20% had visceral disease (viscera, lung or liver disease) in the abiraterone acetate plus daily prednisone with ADT group. Please refer to the full publication, including Supplementary Appendix, for additional details regarding baseline characteristics.

- Median follow-up in the study was 30.4 months. The first interim analysis was performed at 406 survival events: 169 (28%) deaths in the abiraterone acetate plus prednisone with ADT group and 237 (39%) in the placebo with ADT group; overall survival at 3 years was 66% and 49%, respectively. Docetaxel was the most common treatment post-progression for both groups.
- OS was significantly improved in the abiraterone acetate plus prednisone with ADT group with a 38% reduction in risk of death compared to the placebo with ADT group (median not reached vs 34.7 months, respectively; HR=0.62; 95% CI: 0.51-0.76; *P*<0.001).
- rPFS was also significantly improved in the abiraterone acetate plus prednisone with ADT group with a 53% reduction in the risk of rPFS or death compared to the placebo with ADT group (median 33.0 months vs 14.8 months (HR=0.47; 95% CI: 0.39-0.55; *P*<0.001).
- A statistically significant improvement was also demonstrated in all secondary and exploratory endpoints.
- These findings led to the unanimous Independent Data and Safety Monitoring Committee (IDMC) recommendation that the trial be unblinded and crossover allowed for patients in the placebo with ADT group to be offered treatment with abiraterone acetate.

The median time on treatment was 24 months in the abiraterone acetate plus prednisone with ADT and 14 months in the placebo with ADT group. The number of SAEs and the frequency of AEs leading to treatment discontinuation was similar between groups. Grade 3/4 events reported in >5% patients were hypertension (20%/0% vs 10%/<1%) and hypokalemia (10%/<1% vs 1%/<1%) in the abiraterone acetate plus prednisone with ADT vs placebo with ADT groups, respectively. Please refer to the study publication for additional safety data.

STAMPEDE[3] is an ongoing randomized, multi-stage, multi-arm, multicenter study evaluating systemic therapy in advancing or metastatic prostate cancer. In this analysis, 1,917 patients were randomized 1:1 to receive abiraterone acetate 1,000 mg daily plus prednisolone 5 mg daily and ADT (combination group; n=960) or ADT alone (n=957). Local radiotherapy was mandatory for patients with node-negative, nonmetastatic disease and optional for those patients with node-positive nonmetastatic disease. For patients with nonmetastatic disease with no radiotherapy planned and for patients with metastatic disease, treatment continued until prostate specific antigen (PSA), radiologic, or clinical progression or until another treatment was started. For patients with nonmetastatic disease with radiotherapy planned, treatment was to continue for 2 years or until any type of progression, whichever came first. The primary endpoint was overall survival and the intermediate primary outcome included failure-free survival, defined as the time to the first of the following forms of treatment failure: biochemical (prostate-specific antigen [PSA]) failure; progression of local, lymph-node, or distant metastases; or death from prostate cancer. Secondary endpoints included adverse events, symptomatic skeletal events, progression-free survival (i.e., failure-free survival excluding biochemical failure), prostate cancer-specific survival, and quality of life.

The study included patients with prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk locally advanced (defined as having ≥2 of the following disease characteristics: tumor stage T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥40 ng/mL) OR disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (defined as a PSA level >4 ng/mL with a doubling time of <6 months, a PSA level >20 ng/mL, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment). Key exclusion criteria included clinically significant cardiovascular disease (severe angina, recent myocardial infarction, or a history of cardiac failure). At randomization, 52% of patients in both treatment groups had metastatic disease. Patients also had newly diagnosed, node-negative, nonmetastatic disease (26% vs 27%); newly diagnosed, node-positive, nonmetastatic disease (19% vs 20%); and previously treated nonmetastatic disease (3% vs 1%), in the combination group vs ADT-alone group, respectively. WHO performance status was 0 (78%) and 1-2 (22%), for both treatment groups.

At a median follow-up of 40 months, there were 184 deaths in the combination group compared with 262 in the ADT-alone group. The reported rate of use of radiotherapy was 39% in the combination group and 40% in the ADT-alone group. Docetaxel was the most common "life-prolonging treatment" post-progression for both groups.

- The 3-year survival rate was 83% in the combination group vs 76% in the ADT-alone group (HR for death: 0.63; 95% CI: 0.52-0.76; *P*<0.001).
- There were 248 treatment-failure events in the combination group vs 535 in the ADT-alone group. The 3-year failure-free survival was 75% in the combination group vs 45% in the ADT-alone group (HR for treatment failure:0.29; 95% CI: 0.25- 0.34; *P*<0.001).
- Based on central review, 140 of the 184 deaths in the combination group (76%) and 216 of the 262 deaths in the ADT alone group (82%) were attributed to prostate cancer. The competing-risks sub-hazard ratio for death from prostate cancer was 0.58 (95% CI: 0.47-0.72).
- The 3-year rate without symptomatic skeletal events was 88% in the combination group vs 78% in the ADT-alone group (HR:0.46; 95%CI:0.37-0.58; *P*<0.001).
- Exploratory analyses of progression-free and prostate cancer-specific survival within subgroups of age at randomization suggested a favorable treatment effect regardless of age, with proportionally fewer events noted in patients ≥70 years of age compared to patients <70 years of age.

The median duration of treatment with abiraterone acetate was 23.7 months in the patients whose therapy was capped at 2 years and 33.2 months in the patients who could continue through progression. 51% of patients discontinued treatment due to progression and 20% discontinued for toxicity. Grade 3 to 5 AEs occurred in 47% of the patients in the combination group, including 9 nine grade 5 AEs and in 33% of the patients in the ADT-alone group, including 3 grade 5 AEs. Grade 3-5 events reported in >5% patients were endocrine disorders (14% in both treatment arms), cardiovascular disorders (10% vs 4%), musculoskeletal disorders (7% vs 5%), and increased ALT (6% vs <1%) in the combination group vs ADT alone groups, respectively. Please refer to the study publication for additional safety data.

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

Fizazi K, Tran NP, Fein L, et al. Abiraterone plus prednisone in metastatic castration-sensitive prostate cancer. [published online ahead of print June 4, 2017]. *New Engl J Med*. doi:10.1056/NEJMoa1704174.

James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. [published online ahead of print June 3, 2017]. *New Engl J Med*. doi:10.1056/NEJMoa1702900

Sincerely,

Lisa Meadows Ambrose RPh, PharmD-c, BCOP
Therapeutic Manager, Oncology Medical Information
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]Fizazi K, Tran NP, Fein L, et al. Abiraterone plus prednisone in metastatic castration-sensitive prostate cancer. [published online ahead of print June 4, 2017]. *New Engl J Med*. doi:10.1056/NEJMoa1704174.

[3]James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. [published online ahead of print June 3, 2017]. *New Engl J Med*. doi:10.1056/NEJMoa1702900.