Janssen Scientific Affairs, LLC

1125 Trenton-Harbourton Road
PO Box 200
Titusville, NJ 08560
800.526.7736 tel
609.730.3138 fax

February 15, 2018

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

Dear Ms. McClure,

Please consider the following information.

**Response(s):**

- ERLEADA - NCCN Compendia Communication - NM-CRPC Approval - February 2018

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 #:01081953

Enclosure(s)/Electronic Link(s):

- ERLEADA™ (apalutamide)  Prescribing Information at https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-50722e17-d630-456e-befb-8a37a3e3e99d
- SPARTAN, a phase 3 double-blind, randomized study of apalutamide vs placebo in patients with nonmetastatic castration-resistant prostate cancer
- Apalutamide treatment and metastasis-free survival in prostate cancer

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| | |
|---|---|
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**ERLEADA™ (apalutamide)**
**Compendia Communication – FEB 2018**

February 15, 2018

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: February 15, 2018
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 the SPARTAN Study, a phase 3, randomized, double-blind, placebo-controlled, multicenter study comparing apalutamide to placebo in patients with high-risk non-metastatic castration-resistant prostate cancer (NM-CRPC).[1,2]

**Specific Change:**

- Include ERLEADA™ (apalutamide) as a Category 1 evidence level rating for systemic therapy for M0 castration-resistant prostate cancer

**FDA Clearance**: The FDA has approved ERLEADA™ for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).[3]

**Rationale:** SPARTAN[1,2] was a phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the use of apalutamide vs placebo in 1207 patients with high-risk NM-CRPC (defined as PSA doubling time (PSADT] of ≤10 months). Patients were randomized 2:1 to receive apalutamide 240 mg orally once daily (n=806) or placebo (n=401). All patients received ADT throughout the study. Patients were stratified by PSADT (≤6 months vs >6 months), use of bone-sparing agents (yes vs no), and classification of local or regional nodal disease (N0 vs N1). The primary endpoint was metastasis-free survival (MFS), defined as time from randomization to first detection of distant metastasis on imaging, assessed by blinded independent central review, or death from any cause, whichever occurred first. After the first detection of distant metastasis, patients were eligible to receive sponsor-provided abiraterone acetate plus prednisone or other treatment at physician's discretion.

At the clinical cut-off (median follow-up of 20.3 months), 60.9% of patients in the apalutamide group and 29.9% of patients in the placebo group were still receiving treatment. At the final analysis for MFS, significant improvement in median MFS was observed with apalutamide compared with placebo (40.5 months vs 16.2 months, respectively; HR: 0.28; 95% CI: 0.23-0.35; *P*<0.001). The MFS treatment effect of apalutamide was consistently favorable across pre-specified subgroups, including patients with PSADT ≤6 months vs >6 months, use of bone-sparing agents, and local-regional disease. Pre-specified primary and secondary endpoints are summarized below.

**Pre-specified Primary and Secondary Endpoints[1]**

| Endpoint | Apalutamide (n=806) | Placebo (n=401) | Hazard Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Primary endpoint | | | | |
| Median MFS, months | 40.5 | 16.2 | 0.28 (0.23-0.35) | <0.001 |
| Secondary endpoints† | | | | |
| Median time to metastasis, months | 40.5 | 16.6 | 0.27 (0.22–0.34) | <0.001 |
| Median PFS, months | 40.5 | 14.7 | 0.29 (0.24–0.36) | <0.001 |
| Median time to symptomatic progression, months | NR | NR | 0.45 (0.32–0.63) | <0.001 |
| Median OS, months (interim) | NR | 39.0 | 0.70 (0.47–1.04) | 0.07 |
| Median time to initiation of cytotoxic chemotherapy, months (interim) | NR | NR | 0.44 (0.29–0.66) | – |

Abbreviations: CI, confidence interval; MFS, metastasis-free survival; NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
*The *P* value for time to symptomatic progression crossed the O'Brien-Fleming efficacy boundary of 0.00008; the *P* value for overall survival did not. The *P* value for time to initiation of cytotoxic chemotherapy was not calculated because the *P* value for overall survival did not cross the O'Brien-Fleming efficacy boundary.

For exploratory endpoints in the apalutamide vs placebo groups, median time to second progression-free survival (PFS2)[4] was not reached (NR) vs 39.0 months (HR: 0.49; 95% CI: 0.36-0.66), and median time to PSA progression was NR vs 3.7 months (HR: 0.06; 95% CI: 0.05-0.08). A total of 89.7% of patients treated with apalutamide experienced a ≥50% decline in PSA from baseline compared with 2.2% of placebo patients. Patient-reported outcomes FACT-P and European Quality of Life-5 Dimensions [EQ-5D-3L]) indicated maintenance of stable overall health-related quality of life over time in both arms.

The most common all grade adverse events (AEs) in the apalutamide vs placebo groups included fatigue (30.4% vs 21.1%), hypertension (24.8% vs 19.8%), rash (23.8% vs 5.5%), diarrhea (20.3% vs 15.1%), nausea (18.1% vs 15.8%), weight loss (16.1% vs 6.3%), arthralgia (15.9% vs 7.5%), and falls (15.6% vs 9.0%). Other AEs of interest included fracture (11.7% vs 6.5%), dizziness (9.3% vs 6.3%), hypothyroidism (8.1% vs 2.0%), mental impairment disorders (5.1% vs 3.0%), and seizure (0.2% vs 0).

The following study publications are submitted with the ERLEADA™ (apalutamide) Full Prescribing Information:

- Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. [published online ahead of print February 08, 2018]. *New Engl J Med*. doi: 10.1056/NEJMoa1715546.
- Small EJ, Saad F, Chowdhury S, et al. SPARTAN, a phase 3 double-blind, randomized study of apalutamide vs placebo in patients with nonmetastatic castration-resistant prostate cancer. Oral presentation presented at: the American Society of Clinical Oncology Genitourinary (ASCO-GU) Cancers Symposium; February 8-10, 2018; San Francisco, CA.

Additional phase 2 study data have been published:

- Smith MR, Antonarakis ES, Ryan CJ, et al. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. *Eur Urol*. 2016;70(6):963-970.

We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of these publications.

Sincerely,

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

**REFERENCES**


1. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer [published online ahead of print February 08, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1715546.

2. Small EJ, Saad F, Chowdhury S, et al. SPARTAN, a phase 3 double-blind, randomized study of apalutamide vs placebo in patients with nonmetastatic castration-resistant prostate cancer. Oral presentation presented at: the American Society of Clinical Oncology Genitourinary (ASCO-GU) Cancers Symposium; February 8-10, 2018; San Francisco, CA.

3. ERLEADA (apalutamide) [Prescribing Information]. Horsham, PA: Janssen Products, LP; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-50722e17-d630-456e-befb-8a37a3e3e99d.

4. Protocol for: Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer [published online ahead of print February 08, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1715546.