APPLICATION NUMBER:

210951Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th><strong>Application Type</strong></th>
<th>NDA 210951</th>
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<td><strong>Application Number</strong></td>
<td>210951</td>
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<tr>
<td><strong>PDUFA Goal Date</strong></td>
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<td><strong>OSE RCM #</strong></td>
<td>2017-1945</td>
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<td><strong>Reviewer Name(s)</strong></td>
<td>Naomi Redd, Pharm.D.</td>
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<td><strong>Review Completion Date</strong></td>
<td>January 30, 2018</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>Apalutamide</td>
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<tr>
<td><strong>Trade Name</strong></td>
<td>Erleada</td>
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<tr>
<td><strong>Name of Applicant</strong></td>
<td>Janssen Biotech, Inc</td>
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<tr>
<td><strong>Therapeutic Class</strong></td>
<td>Androgen Receptor Inhibitor</td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>240 mg (four 60 mg tablets) by mouth once daily with or without food</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Erleada (apalutamide) is necessary to ensure the benefits outweigh its risks. Janssen Biotech, Inc submitted a New Drug Application (NDA 210951) for apalutamide with the proposed indication for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC). The risks associated with apalutamide include falls, fractures, and seizures. The applicant did not submit a proposed REMS or risk management plan with this application.

Due to the nature of the disease of NM-CRPC, the lack of treatment options available, and the improvement in metastasis-free survival (MFS) compared to placebo in the apalutamide clinical trial, in addition to the likely prescribers will be medical oncologists, this DRISK reviewer’s recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks for apalutamide.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME Erleada (apalutamide) is necessary to ensure the benefits outweigh its risks. Janssen Biotech, Inc submitted a NDA 210951 for apalutamide with the proposed indication for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC). The risks associated with apalutamide include falls, fractures, and seizures. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION
Apalutamide is an Androgen Receptor (AR) inhibitor that binds directly to the ligand-binding domain of androgen receptors. This inhibition prevents DNA binding and AR-mediated transcription, resulting in decreased tumor cell proliferation, increased apoptosis, and hence decreased tumor volume.⁠

The proposed indication is for the treatment of patients with NM-CRPC. Apalutamide is supplied as 60 mg tablets, dosed at 240 mg orally once daily with or without food until disease progression or unacceptable toxicity.⁠ Apalutamide is expected to be prescribed by oncologists and is likely to be dispensed to patients in an outpatient setting. There are currently no FDA approved treatments for patients with NM-CRPC. Apalutamide is an NME and has been granted Fast Track Designation under IND 104676 and granted Priority Review. Apalutamide is not currently approved in any jurisdictions at the time of this writing.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 210951 relevant to this review:

- 08/17/2017: Fast track designation granted under IND 104676

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⁠a Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

b Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.
3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition
Prostate cancer is the second most commonly diagnosed cancer in men worldwide, and accounts for over 25% of newly diagnosed cancer in men in the United States. Due to advancements and education about prostate screening, the disease has been diagnosed in earlier stages, and less than 20% of men have imaging evidence of metastasis at the time of diagnosis. Prognosis is poor if the disease progresses to metastatic castration resistant prostate cancer (mCRPC), with the bone, lymph nodes, and liver being common sites of metastasis. Once the cancer has progressed to this stage, median survival rates are approximately 3 years. The delay in the time to metastatic disease has the potential to delay cancer-related symptoms and may help prolong survival.

3.2 Description of Current Treatment Options
Delaying metastases for as long as possible is the goal of therapy in NM-CRPC. The National Comprehensive Cancer Network (NCCN) guidelines recommend monitoring of prostate specific antigens (PSA) once every 6 to 12 months with administration of an extended-release gonadotropin-releasing hormone agonist (GnRHa).

Currently, there are no approved treatments for patients with NM-CRPC. Treatment usually occurs once patients become symptomatic. First generation anti-androgens such as bicalutamide, nilutamide, and flutamide used in combination with Androgen Deprivation Therapy (ADT) have been used, due to their partial AR agonists activity. Other hormonal therapies that have been used indirectly to treat NM-CRPC include low-dose corticosteroids such as hydrocortisone, dexamethasone, and prednisone; and ketoconazole for its indirect effects to inhibit adrenal production. If approved, apalutamide will be the first therapy approved for the treatment of NM-CRPC, when used in combination with ADT.

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\(^c\) Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

\(^d\) Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*
4 Benefit Assessment

For a full review of the clinical trial for apalutamide, please see the clinical statistical review in DARRTS.

The Applicant’s registrational trial, SPARTAN, was a multicenter, double-blind, registrational clinical trial in which 1207 patients with NM-CRPC were randomized 2:1 to receive either apalutamide orally 240 mg once daily in combination with ADT (medical castration or surgical castration) (n = 806) or placebo (n=401) once daily with ADT. Patient demographics and baseline characteristics were balanced between the treatment arms, with a median age of 74 years (range 48-97 years), and 26% of patients were 80 years of age or older. Sixty-six percent were Caucasian, 12% Asian, and 6% were Black; with 77% of patients in both treatment arms having prior surgery or radiotherapy of the prostate.

Primary efficacy was based on metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes outside the pelvis, or death due to any cause; whichever occurred first. Additional efficacy endpoints were time to metastasis (TTM), progression-free survival (PFS) that also included locoregional progression, time to symptomatic progression, and overall survival (OS).

A summary of the results of the SPARTAN trial is listed below. Of note, a statistically significant improvement in MFS was demonstrated in patients randomized to receive apalutamide compared to those patients receiving placebo.

Table 1: BICR-assessed Efficacy Results (SPARTAN)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Number of Events (%)</th>
<th>Median [Months (95% CI)]</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ERLEADA+ADT (N=806)</td>
<td>Placebo+ADT (N=401)</td>
<td></td>
</tr>
<tr>
<td>Metastasis Free Survival</td>
<td>184 (23%)</td>
<td>194 (48%)</td>
<td>40.51</td>
</tr>
<tr>
<td></td>
<td>(NE, NE)</td>
<td>(16.20)</td>
<td>0.28 (0.23, 0.35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to Metastasis</td>
<td>175 (22%)</td>
<td>191 (48%)</td>
<td>40.51</td>
</tr>
<tr>
<td></td>
<td>(NE, NE)</td>
<td>(16.59)</td>
<td>0.27 (0.22, 0.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Progression-Free Survival</td>
<td>200 (25%)</td>
<td>204 (51%)</td>
<td>40.51</td>
</tr>
<tr>
<td></td>
<td>(NE, NE)</td>
<td>(14.72)</td>
<td>0.29 (0.24, 0.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Reference ID: 4214277
5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for apalutamide. This safety information is from the Applicant’s registrational trial, SPARTAN, where the median duration of exposure for patients receiving apalutamide was 16.9 months in the treatment arm (range 0.1 – 42 months) and 11.2 months (range 0.1 – 37 months) for patients receiving placebo. Adverse events highlighted in this section include the risk of falls and fractures, which will be communicated in section 5.1, and seizures, which will be communicated in section 5.2. There is currently no Boxed Warning for apalutamide.

5.1 Falls and Fractures\(^1,\text{e}\)

Falls occurred in 16% of patients treated with apalutamide compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 12% of patients treated with apalutamide and in 7% of patients; of these 3% of patients treated with apalutamide experienced Grade 3-4 fractures. One percent of patients in the placebo arm experienced a fracture of Grade 3-4. The median time to onset of fractures were 314 days (range 20 to 953 days).

Recommendations in section 5.1 of the label are to monitor and evaluate patients for the risk of falls and fractures, as well as manage these patients who may be at risk with the use of bone targeted agents.

5.2 Seizures\(^1,\text{e}\)

Two patients treated with apalutamide experienced a seizure, while there were no patients that experienced a seizure in the placebo arm. Patients with a history of seizures, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded from the clinical trial. The median time to onset for these seizures occurred from 354 to 475 days after initiation of apalutamide.

Recommendations in section 5.2 of the label are to permanently discontinue apalutamide in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures while receiving apalutamide. It is also recommended that patients be advised of the risk of developing a seizure while receiving apalutamide, and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

6 Expected Postmarket Use

Apalutamide is expected to be prescribed by oncologists and healthcare professionals in the care and management of patients with prostate cancer. Apalutamide will be dispensed in an ambulatory care setting.

\(^{\text{e}}\) Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
7  Risk Management Activities Proposed by the Applicant
The Applicant did not propose any risk management activities for apalutamide beyond routine pharmacovigilance and labeling.

8  Discussion of Need for a REMS
Delaying metastases for as long as possible is the goal of therapy, and treatment is often begun with ADT (medical castration or surgical castration), as well as in combination with first generation anti-androgens such as bicalutamide, nilutamide, and flutamide to slow progression of disease. Currently there are no FDA approved treatments for patients with NM-CRPC and therefore, there remains a need for therapeutic options to address the medical need in these patients.

The Clinical Reviewer recommends approval of apalutamide based on the efficacy and safety information currently available. A statistically significant improvement in MFS was demonstrated in patients randomized to receive apalutamide compared to those patients receiving placebo. The risk of falls and fractures was a risk identified with the use of apalutamide in the clinical trial. This risk occurred in 16% of patients. The risk of seizure was another adverse event identified with the use of apalutamide. This adverse event occurred in 2 patients in the clinical trial, with no known mechanisms of action for this risk.

The risks of falls, fractures and seizures will be communicated in the Warnings and Precautions Section of the Prescribing Information for apalutamide in sections 5.1 and 5.2 respectively. In addition, the label will include Patient Counseling Information that describes these risks and the management thereof.

Due to the nature of the disease of NM-CRPC and the likely prescribers would be medical oncologists, the lack of treatment options available, the improvement in MFS compared to placebo, and the severity of the risks, this DRISK reviewer’s recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks for apalutamide.

9  Conclusion & Recommendations
The DRISK and DOP-1 agree that the benefit-risk profile for apalutamide is favorable, therefore a REMS is not necessary for apalutamide to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated.
10 References

1 Erleada (apalutamide) US Prescribing Information (DRAFT) January 24, 2018


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/s/

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01/30/2018

CYNTHIA L LACIVITA
01/30/2018
Concur