ERLEADA® (apalutamide) tablets

- Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk and treat patients with bone-targeted agents according to established guidelines. (5.2)
- Falls occurred in patients receiving ERLEADA with increased incidence in the elderly. Evaluate patients for fall risk. (5.3)
- Seizure occurred in 0.4% of patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. (5.4)
- Embryo-Fetal Toxicity: ERLEADA can cause fetal harm. Advise males with female partners of reproductive potential to use effective contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) are fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-526-7736 (1-800-JNJ-SEREN) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant use with medications that are sensitive substrates of CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP, or OATP1B1 may result in loss of activity of these medications. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ERLEADA® (apalutamide) tablets are indicated for the treatment of:
- Non-metastatic castration-resistant prostate cancer (nmCRPC)
- Metastatic castration-sensitive prostate cancer (mCSPC)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ERLEADA is 240 mg (four 60 mg tablets) administered orally once daily.

2.2 Dose Modification

If a patient experiences a greater than or equal to Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to less than or equal to Grade 1 or original grade, then resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted.

2.3 Alternate Method of Administration

For patients who have difficulty swallowing tablets whole, the recommended dose of ERLEADA tablets may be mixed in applesauce.

1. Mix whole ERLEADA tablets in 4 ounces (120 mL) of applesauce by stirring.
2. Wait 15 minutes, stir the mixture.
3. Wait another 15 minutes, stir the mixture until tablets are dispersed (well mixed with no chunks remaining).
4. Using a spoon, swallow the mixture right away.
5. Rinse the container with 2 ounces (60 mL) of water and immediately drink the contents. Repeat the rinse with 2 ounces (60 mL) of water a second time to ensure the whole dose is taken.

Consume the mixture within one hour of preparation. Do not store ERLEADA that is mixed with applesauce [see Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

Tablets (60 mg): slightly yellowish to greyish green oblong film-coated tablets, debossed with “AR 60” on one side.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use

16 HOW SUPPLIED/STORAGE AND HANDLING

ERLEADA® (apalutamide) tablets, for oral use
ERLEADA® (apalutamide) tablets

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ischemic Cardiovascular Events

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within six months of randomization were excluded from the SPARTAN and TITAN studies.

5.2 Fractures

Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 952 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

5.3 Falls

Falls occurred in patients receiving ERLEADA with increased frequency in the elderly [see Use in Specific Populations (8.5)]. Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

5.4 Seizure

Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 650 days after initiation of ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

5.5 Embryo-Fetal Toxicity

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Warnings and Precautions (5.3)]. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Warnings and Precautions (5.4)]. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Warnings and Precautions (5.2)].

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Ischemic Cardiovascular Events [see Warnings and Precautions (5.1)].
- Fractures [see Warnings and Precautions (5.2)].
- Falls [see Warnings and Precautions (5.3)].
- Seizure [see Warnings and Precautions (5.4)].

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse reactions (≥ 10%) that occurred more frequently in the ERLEADA-treated patients (≥ 2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

ERLEADA® (apalutamide) tablets

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 22% of patients; the most frequent (>1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue1,2</td>
<td>26</td>
<td>3</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>0.4</td>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash2</td>
<td>28</td>
<td>6</td>
<td>9</td>
<td>0.6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>&lt;1</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>23</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>8</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia
2 Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin eruption, dermatitis, and rash vesicular

3 Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

Additional adverse reactions of interest occurring in ≥2%, but less than 10% of patients treated with ERLEADA included diarrhea (9% versus 6% on placebo), muscle spasm (3% versus 2% on placebo), dysgeusia (3% versus 1% on placebo), and hypothyroidism (4% versus 1% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>N=524</th>
<th>Grade 3-4</th>
<th>N=527</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
<td>19</td>
<td>0.6</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertiglyceridemia1</td>
<td>17</td>
<td>3</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Does not reflect fasting values

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchectomy. The median duration of exposure was 18.9 months (range: 0.1 to 42 months) in patients who received ERLEADA and 11.2 months (range: 0.1 to 37 months) in patients who received placebo.

Eight patients (1%) who were treated with ERLEADA died from adverse reactions. The reasons for death were infection (n=4), myocardial infarction (n=3), and...
ERLEADA® (apalutamide) tablets

cerebral hemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse reaction of cardiopulmonary arrest (n=1). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematemia. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (≥2%) were fracture (3%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (≥5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue1,4</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia2</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash3</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite6</td>
<td>12</td>
<td>0.1</td>
</tr>
<tr>
<td>Peripheral edema6</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall4</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Fracture4</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased4</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Hot flush</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia
2 Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
4 Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
5 Includes appetite disorder, decreased appetite, early satiety, and hypophagia
6 Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8.1% versus 2% on placebo), pruritus (6.2% versus 2% on placebo), and heart failure (2.2% versus 1% on placebo).

Table 4: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia1</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperglycemia1</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>Hypertriglyceridemia1</td>
<td>67</td>
<td>2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>32</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Does not reflect fasting values

Rash
In the combined data of two randomized, placebo-controlled clinical studies, rash associated with ERLEADA was most commonly described as maculopapular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area (BSA)) were reported with ERLEADA treatment (6%) versus placebo (0.5%). The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA.

Hypothyroidism
In the combined data of two randomized, placebo-controlled clinical studies, hypothyroidism was reported for 8% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted [see Drug Interactions (7.2)].

6.2 Post-Marketing Experience
The following additional adverse reactions have been identified during post-approval use of ERLEADA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on ERLEADA
Strong CYP3A4 or CYP3A4 Inhibitors
Co-administration of a strong CYP3A4 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide) of ERLEADA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

7.2 Effect of ERLEADA on Other Drugs
CYP3A4, CYP2C9, CYP2C19 and UGT Substrates
ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UGT-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued. Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 substrates.

P-gp, BCRP or OATP1B1 Substrates
Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP,
ERLEADA® (apalutamide) tablets

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Apalutamide is an Androgen Receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription. A major metabolite, N-desmethyl apalutamide, is a less potent inhibitor of AR, and approximately one-third the activity of apalutamide in an in vitro transcriptional reporter assay. Apalutamide administration caused decreased tumor cell proliferation and increased apoptosis leading to decreased tumor volume in mouse xenograft models of prostate cancer.

12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of apalutamide 240 mg once daily on the QTc interval was assessed in an open-label, uncontrolled, multi-center, single-arm dedicated QT study in 45 patients with CRPC. The maximum mean QTcF change from baseline was 12.4 ms (2-sided 90% upper CI: 16.0 ms). An exposure-QT analysis suggested a concentration-dependent increase in QTcF for apalutamide and its active metabolite.

12.3 Pharmacokinetics
Apalutamide pharmacokinetic parameters are presented as the mean [standard deviation (SD)] unless otherwise specified. Apalutamide Cmax and area under the concentration curve (AUC) increased proportionally following repeated once-daily dosing of 30 to 480 mg (0.125 to 2 times the recommended dosage). Following administration of the recommended dosage, apalutamide steady-state was achieved after 4 weeks and the mean accumulation ratio was approximately 5-fold. Apalutamide Cmax was 6.0 mcg/mL (1.7) and AUC was 100 mcg*h/mL (22) at steady-state. Daily fluctuations in apalutamide plasma concentrations were low, with mean peak-to-trough ratio of 1.63. An increase in apparent clearance (CL/F) was observed with repeat dosing, likely due to induction of apalutamide’s own metabolism. The auto-induction effect likely reached its maximum at the recommended dosage because exposure of apalutamide across the dose range of 30 to 480 mg is dose-proportional.

The major active metabolite N-desmethyl apalutamide Cmax was 5.9 mcg/mL (1.0) and AUC was 124 mcg*h/mL (23) at steady-state after the recommended dosage. N-desmethyl apalutamide was characterized by a flat concentration-time profile at steady-state with a mean peak-to-trough ratio of 1.27. Mean AUC metabolite/parent drug ratio for N-desmethyl apalutamide following repeat-dose administration was 1.3. Based on systemic exposure, relative potency, and pharmacokinetic properties, N-desmethyl apalutamide likely contributed to the clinical activity of apalutamide.

Absorption
Mean absolute oral bioavailability was approximately 100%. Mean time to achieve peak plasma concentration (tmax) was 2 hours (range: 1 to 5 hours). Oral administration of four 60 mg apalutamide tablets dispersed in applesauce resulted in no clinically relevant changes in Cmax and AUC when compared to administration of four intact 60 mg tablets under fasting condition.

Effect of Food
Administration of apalutamide to healthy subjects under fasting conditions and with a high-fat meal (approximately 500 to 600 fat calories, 250 carbohydrate calories, and 150 protein calories) resulted in no clinically relevant changes in Cmax and AUC. Median time to reach tmax was delayed approximately 2 hours with food.

Distribution
The mean apparent volume of distribution at steady-state of apalutamide was approximately 276 L. Apalutamide was 96% and N-desmethyl apalutamide was 95% bound to plasma proteins with no concentration dependency.

Elimination
The CL/F of apalutamide was 1.3 L/h after single dosing and increased to 2.0 L/h at steady-state after once-daily dosing likely due to CYP3A4 auto-induction. The mean effective half-life for apalutamide in patients was approximately 3 days at steady-state.

Metabolism
Metabolism is the main route of elimination of apalutamide. Apalutamide is primarily metabolized by CYP2C8 and CYP3A4 to form active metabolite, N-desmethyl apalutamide. The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady-state.

Apalutamide represented 45% and N-desmethyl apalutamide represented 44% of the total AUC following a single oral administration of radiolabeled apalutamide 240 mg.
Up to 70 days following a single oral administration of radiolabeled apalutamide, 65% of the dose was recovered in urine (1.2% of dose as unchanged apalutamide and 2.7% as N-desmethyl apalutamide) and 24% was recovered in feces (1.5% of dose as unchanged apalutamide and 2% as N-desmethyl apalutamide).

Specific Populations

No clinically significant differences in the pharmacokinetics of apalutamide or N-desmethyl apalutamide were observed based on age (18-94 years), race (Black, non-Japanese Asian, Japanese), mild to moderate (eGFR 30-89 mL/min/1.73m²) estimated by the modification of diet in renal disease (MDRD) equation) renal impairment, or mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment. The effect of severe renal impairment or end stage renal disease (eGFR ≤29 mL/min/1.73m², MDRD) or severe hepatic impairment (Child-Pugh C) on apalutamide pharmacokinetics is unknown.

Drug Interactions

Effect of Other Drugs on ERLEADA

Strong CYP2C8 inhibitors

Apalutamide Cmax decreased by 21% while AUC increased by 68% following co-administration of ERLEADA as a 240 mg single dose with gemfibrozil (a strong CYP2C8 inhibitor). Gemfibrozil is predicted to increase the steady-state apalutamide Cmax by 32% and AUC by 44%. For the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide), the predicted steady-state Cmax increased by 19% and AUC by 23%.

Strong CYP3A4 inhibitors

Apalutamide Cmax decreased by 22% while AUC was similar following co-administration of ERLEADA as a 240 mg single dose with itraconazole (a strong CYP3A4 inhibitor). Itraconazole (a strong CYP3A4 inhibitor) is predicted to increase the single-dose apalutamide AUC by 24% but have no impact on Cmax. N-desmethyl apalutamide is predicted to increase the steady-state apalutamide Cmax by 38% and AUC by 51%. For the active moieties, the predicted steady-state Cmax increased by 23% and AUC by 28%.

CYP3A4/CYP2C8 inducers

Rifampin (a strong CYP3A4 and moderate CYP2C8 inducer) is predicted to decrease the steady-state apalutamide Cmax by 25% and AUC by 34%. For the active moieties, the predicted steady-state Cmax decreased by 15% and AUC by 19%.

Acid lowering agents

Apalutamide is not ionizable under relevant physiological pH condition, therefore acid lowering agents (e.g. proton pump inhibitor, H₂-receptor antagonist, antacid) are not expected to affect the solubility and bioavailability of apalutamide.

Drugs affecting transporters

In vitro, apalutamide and N-desmethyl apalutamide are substrates for P-gp but not BCRP, OATP1B1, and OATP1B3. Because apalutamide is completely absorbed after oral administration, P-gp does not limit the absorption of apalutamide and therefore, inhibition or induction of P-gp is not expected to affect the bioavailability of apalutamide.

Effect of ERLEADA on Other Drugs

CYP substrates

In vitro studies showed that apalutamide and N-desmethyl apalutamide are moderate to strong CYP3A4 and CYP2B6 inducers, are moderate inhibitors of CYP2B6 and CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4. Apalutamide and N-desmethyl apalutamide do not affect CYP1A2 and CYP2D6 at therapeutically relevant concentrations.

Co-administration of ERLEADA with single oral doses of sensitive CYP substrates resulted in a 92% decrease in the AUC of midazolam (a CYP3A4 substrate), 85% decrease in the AUC of omeprazole (a CYP2C19 substrate), and 46% decrease in the AUC of S-warfarin (a CYP2C9 substrate). ERLEADA did not cause clinically significant changes in exposure to a CYP2C9 substrate.

P-gp, BCRP and OATP1B1 substrates

Co-administration of ERLEADA with single oral doses of transporter substrates resulted in a 30% decrease in the AUC of fexofenadine (a P-gp substrate) and 41% decrease in the AUC of rosuvastatin (a BCRP/OATP1B1 substrate) but had no impact on Cmax.

UGT substrates

Apalutamide may induce UGT. Concomitant administration of ERLEADA with medications that are substrates of UGT may result in lower exposure to these medications.
Table 5: Summary of Efficacy Results – Intent-to-treat mCSPC Population (TITAN)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ERLEADA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=525</td>
<td>N=527</td>
<td></td>
</tr>
<tr>
<td>Overall Survivala</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>83 (16%)</td>
<td>117 (22%)</td>
</tr>
<tr>
<td>Median, months (95% CI)c</td>
<td>NE (NE, NE)</td>
<td>NE (NE, NE)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)b</td>
<td>0.67 (0.51, 0.89)</td>
<td>0.0053</td>
</tr>
<tr>
<td>Radiographic Progression-free Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression or death (%)</td>
<td>134 (26%)</td>
<td>231 (44%)</td>
</tr>
<tr>
<td>Median, months (95% CI)c</td>
<td>NE (NE, NE)</td>
<td>22.1 (18, 33)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)b</td>
<td>0.48 (0.39, 0.60)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

a  Interim analysis is based on 50% of the number of events planned for the final analysis. Allocated alpha = 0.01.
b  Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors ERLEADA.
c  p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
d  NE=Not Estimable

Consistent improvement in rPFS was observed across the following patient subgroups: disease volume (high vs low), prior docetaxel use (yes or no), and Gleason score at diagnosis (≤7 vs. >7).

Consistent improvement in OS was observed across the following patient subgroups: disease volume (high vs low) and Gleason score at diagnosis (≤7 vs. >7).

Treatment with ERLEADA statistically significantly delayed the initiation of cytotoxic chemotherapy (HR = 0.39, 95% CI = 0.27, 0.56; p < 0.0001).

Figure 1: Kaplan-Meier Plot of Overall Survival (OS); Intent-to-treat mCSPC Population (TITAN)

SPARTAN (NCT019462204): Non-metastatic, Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN was a multicenter, double-blind, randomized (2:1), placebo-controlled clinical trial in which 1207 patients with nmCRPC were randomized (2:1) to receive either ERLEADA orally at a dose of 240 mg once daily (N = 806) or placebo once daily (N = 401). All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchiectomy. Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT), the use of bone-sparing agents, and locoregional disease. Patients were required to have a PSADT ≤ 10 months and confirmation of non-metastatic disease by blinded independent central review (BICR). PSA results were blinded and were not used for treatment discontinuation. Patients randomized to either arm discontinued treatment for radiographic disease progression confirmed by BICR, locoregional-only progression, initiation of new treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 74 years (range 48-97) and 26% of patients were 80 years of age or older. The racial distribution was 66% Caucasian, 12% Asian, and 6% Black. Seventy-seven percent (77%) of patients in both treatment arms had prior surgery or radiotherapy of the prostate. A majority of patients had a Gleason score of 7 or higher (78%). Fifteen percent (15%) of patients had <2 cm pelvic lymph nodes at study entry. Seventy-three percent (73%) of patients received prior treatment with an anti-androgen; 69% of patients received bicalutamide and 10% of patients received flutamide. All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry. Among the patients who discontinued study treatment (N = 279 for placebo and N = 314 for ERLEADA), a greater proportion (80%) of patients treated with placebo received subsequent therapy compared to patients treated with ERLEADA (56%). Locoregional-only progression occurred in 2% of patients overall.

The major efficacy outcome measure of the study was 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 above the iliac bifurcation, or death due to any cause, whichever occurred first. Additional efficacy endpoints were time to metastasis (TTM), progression-free survival (PFS) which also includes locoregional progression, time to symptomatic progression, and overall survival (OS).

A statistically significant improvement in MFS was demonstrated in patients randomized to receive ERLEADA compared with patients randomized to receive placebo. Consistent results were observed across patient subgroups including prior surgery or radiotherapy of the prostate (≤ 6 months or > 6 months), use of a prior bone-sparing agent (yes or no), and locoregional disease (N0 or N1). The major efficacy outcome was supported by statistically significant improvements in TTM, PFS, and time to symptomatic progression. Overall survival (OS) data were not mature at the time of final MFS analysis (24% of the required number of events). The efficacy results of MFS, TTM, and PFS from SPARTAN are summarized in Figure 3 and Table 6.
Figure 3: Kaplan-Meier Metastasis-Free Survival (MFS) Curve in SPARTAN (nmCRPC)

Table 6: 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) p-value (log-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis Free Survival</td>
<td>ERLEADA (N=806)</td>
<td>184 (22%)</td>
<td>40.5 (NE, NE)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=401)</td>
<td>194 (48%)</td>
<td></td>
</tr>
<tr>
<td>Time to Metastasis</td>
<td>ERLEADA (N=806)</td>
<td>175 (22%)</td>
<td>40.5 (NE, NE)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=401)</td>
<td>191 (48%)</td>
<td></td>
</tr>
<tr>
<td>Progression-Free Survival</td>
<td>ERLEADA (N=806)</td>
<td>200 (25%)</td>
<td>40.5 (NE, NE)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=401)</td>
<td>204 (51%)</td>
<td></td>
</tr>
</tbody>
</table>

1 All analyses stratified by PSA doubling time, bone-sparing agent use, and locoregional disease status.
NE=Not Estimable

16 HOW SUPPLIED/STORAGE AND HANDLING
ERLEADA (apalutamide) 60 mg film-coated tablets are slightly yellowish to greyish green, oblong-shaped tablets debossed with “AR 60” on one side. ERLEADA 60 mg tablets are available in bottles of 120 tablets. Each bottle contains silica gel desiccant.
NDC Number 59676-600-12

Storage and Handling
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Store in the original package. Do not discard desiccant. Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION
Advising the patient to read the FDA-approved patient labeling (Patient Information).

Ischemic Cardiovascular Events
• Inform patients that ERLEADA has been associated with ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur [see Warnings and Precautions (5.1)].

Falls and Fractures
• Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see Warnings and Precautions (5.2, 5.3)].

Seizures
• Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure [see Warnings and Precautions (5.4)].

Rash
• Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash [see Adverse Reactions (6.1)].

ERLEADA® (apalutamide) tablets
Dosage and Administration
• Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.
• Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.
• Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1)].
• Instruct patients who have difficulty swallowing tablets whole to mix the recommended dose of ERLEADA tablets with applesauce. Do not crush tablets [see Dosage and Administration (2.3)].

Embryo-Fetal Toxicity
• Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman [see Warnings and Precautions (5.5)].

Infertility
• Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA [see Use in Specific Populations (8.3)].

Manufactured by: Janssen Ortho LLC
Gurabo, PR 00778
Manufactured for: Janssen Products, LP
Horsham, PA 19044
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### What is ERLEADA?
ERLEADA is a prescription medicine used for the treatment of prostate cancer:
- that has spread to other parts of the body and still responds to a medical or surgical treatment that lowers testosterone, **OR**
- that has not spread to other parts of the body and no longer responds to a medical or surgical treatment that lowers testosterone.

It is not known if ERLEADA is safe and effective in females.

It is not known if ERLEADA is safe and effective in children.

### Before taking ERLEADA, tell your healthcare provider about all your medical conditions, including if you:
- have a history of heart disease
- have high blood pressure
- have diabetes
- have abnormal amounts of fat or cholesterol in your blood (dyslipidemia)
- have a history of seizures, brain injury, stroke, or brain tumors
- are pregnant or plan to become pregnant. ERLEADA can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- 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 and for 3 months after the last dose of ERLEADA.
  - Males should use a condom during sex with a pregnant female. Talk with your healthcare provider if you have questions about birth control.
- are breastfeeding or plan to breastfeed. It is not known if ERLEADA passes into breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ERLEADA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ERLEADA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

### How should I take ERLEADA?
- Take ERLEADA exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ERLEADA without talking with your healthcare provider first.
- Take your prescribed dose of ERLEADA 1 time a day, at the same time each day.
- Take ERLEADA with or without food.
- Swallow ERLEADA tablets whole.
- If you miss a dose of ERLEADA, take your normal dose as soon as possible on the same day. Return to your normal schedule on the following day. You should not take extra tablets to make up the missed dose.
- You should start or continue a gonadotropin-releasing hormone (GnRH) analog therapy during your treatment with ERLEADA unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you take too much ERLEADA, call your healthcare provider or go to the nearest hospital emergency room.
- **If you are unable to swallow ERLEADA tablets whole, you may:**
  - Place your dose of ERLEADA in a container that contains 4 ounces (120 mL) of applesauce and stir. Do not crush the tablets.
  - Wait 15 minutes and stir the mixture.
  - Wait another 15 minutes and stir the mixture until the tablets are well mixed with no chunks remaining.
  - Swallow the mixture right away using a spoon.
  - Rinse the container with 2 ounces (60 mL) of water and drink the water mixture right away.
  - Repeat the rinse with 2 ounces (60 mL) of water one more time to make sure that you take your full dose of ERLEADA.
  - Swallow all the applesauce and medicine mixture within 1 hour of preparation. Do not store ERLEADA that is mixed with applesauce.
What are the possible side effects of ERLEADA?

ERLEADA may cause serious side effects including:

- **Heart Disease.** Blockage of the arteries in the heart that can lead to death has happened in some people during treatment with ERLEADA. Your healthcare provider will monitor you for signs and symptoms of heart problems during your treatment with ERLEADA. Call your healthcare provider or go to the nearest emergency room right away if you get chest pain or discomfort at rest or with activity, or shortness of breath during your treatment with ERLEADA.

- **Fractures and falls.** ERLEADA treatment can cause bones and muscles to weaken and may increase your risk for falls and fractures. Falls and fractures have happened in people during treatment with ERLEADA. Your healthcare provider will monitor your risks for falls and fractures during treatment with ERLEADA.

- **Seizure.** Treatment with ERLEADA may increase your risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have a loss of consciousness or seizure. Your healthcare provider will stop ERLEADA if you have a seizure during treatment.

The most common side effects of ERLEADA include:

- feeling very tired
- joint pain
- rash. Tell your healthcare provider if you get a rash.
- decreased appetite
- fall

ERLEADA 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. Do not donate sperm during treatment with ERLEADA and for 3 months after the last dose of ERLEADA.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ERLEADA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ERLEADA?

- Store ERLEADA at room temperature between 68°F to 77°F (20°C to 25°C).
- Store ERLEADA in the original package.
- The bottle of ERLEADA contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not throw away (discard) the desiccant.
- Protect ERLEADA from light and moisture.

Keep ERLEADA and all medicines out of the reach of children.

General information about the safe and effective use of ERLEADA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ERLEADA for a condition for which it was not prescribed. Do not give ERLEADA to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ERLEADA that is written for health professionals.

What are the ingredients in ERLEADA?

**Active ingredient:** apalutamide

**Inactive ingredients:** colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl methylcellulose-acetate succinate, magnesium stearate, microcrystalline cellulose, and silicified microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured by: Janssen Ortho LLC, Gurabo, PR 00778
Manufactured for: Janssen Products, LP, Horsham, PA 19044
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For more information, call Janssen Products, LP at 1-800-526-7738 (1-800-JANSSEN) or go to www.erleada.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 07/2020

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