PDL DRUG REVIEW

Proprietary Name: Erleada®
Common Name: apalutamide
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Xtandi	Recommended with Conditions

Summary

Pharmacology/Usage: Apalutamide, the active ingredient of Erleada®, is an androgen receptor inhibitor that binds directly to the ligand-binding domain of the androgen receptor. Apalutamide inhibits androgen receptor nuclear translocation, inhibits DNA binding, and impedes androgen receptor-mediated transcription. In animal models of prostate cancer, apalutamide caused decreased tumor cell proliferation and increased apoptosis, leading to decreased tumor volume.

Indication: For the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).

There is no pregnancy category for this medication; however, the risk summary indicates that use is contraindicated in pregnant women as the drug can cause fetal harm and potential loss of pregnancy. Erleada® is not indicated for use in females. There are no human data on use in pregnant women. Based on it mechanism of action, it may cause fetal harm when administered during pregnancy. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Film-Coated Tablets: 60mg

Recommended Dosage: Take 240mg PO QD, taken with or without food. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy. If a patient experiences a ≥Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to ≤Grade 1 or original grade, then start at the same dose or a reduced dose (180mg or 120mg), if warranted.

Dose adjustments are not required with mild or moderate renal or hepatic impairment. The effect of severe renal impairment, end-stage renal disease, or severe hepatic impairment on apalutamide pharmacokinetics is not known.

Drug Interactions: Concomitant use of a strong CYP2C8 or CYP3A4 inhibitor with Erleada is predicted to increase the steady-state of Erleada®. While no initial dose adjustment is needed, reduce the Erleada® dose based on tolerability.

Erleada® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. 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 assess for loss of activity if the medication is continued. Use caution if substrates of UDP-glucuronosyl transferase (UGT) must be co-administered with Erleada® and assess for loss of activity.

Apalutamide was shown to be a weak inducer of 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, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with Erleada® and assess for loss of activity if medication is continued.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Erleada®) minus reported % incidence for placebo for all grades of adverse events. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included fatigue (11%), arthralgia (8%), rash (18%), decreased appetite (3%), peripheral edema (2%), fall (7%), fracture (5%), weight decreased (10%), hypertension (5%), hot flush (5%), diarrhea (5%), and nausea (2%). Laboratory abnormalities included anemia (6%), leukopenia (18%), lymphopenia (20%), hypercholesterolemia (30%), hyperglycemia (11%), hypertriglyceridemia (18%), and hyperkalemia (10%).

Hypothyroidism was reported in 8% treated with Erleada® vs 2% treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of the Erleada® group vs 7% with placebo. Thyroid replacement therapy was started in 7% of patients treated with Erleada®. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted as needed.

Falls and fractures were reported in patients treated with Erleada®. Assess patients for fracture and fall risk. Monitor and manage patients at risk for fractures per established treatment guidelines and consider use of bone targeted agents.

Seizure were also reported in patients treated with Erleada®. Permanently discontinue Erleada® in patients who develop a seizure during treatment. It is not known if anti-epileptic medications will prevent seizures with Erleada®. Advise patients of the risk of developing a seizure while receiving Erleada® and of engaging in activities where sudden loss of consciousness could cause harm to themselves or others.

Contraindications: Pregnancy, as it can cause fetal harm and potential loss of pregnancy

Manufacturer: Janssen Products

Analysis: A multicenter, randomized, double-blind, placebo-controlled study assessed the safety and efficacy of Erleada® in patients (N=1207) with NM-CRPC (the SPARTAN trial). All patients included received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median age was 74 years and 26% were ≥80 years of age. Most had a Gleason score of ≥7 (78%). In addition, 73% received prior treatment with an anti-androgen, 69% received bicalutamide and 10% received flutamide. All had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry.

The main efficacy outcome was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review (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. A statistically significant improvement in MFS was seen in patients in the Erleada® group as compared to the placebo group. The main efficacy outcome was supported by statistically significant improvements in time to metastasis (TTM), progression-free survival (PFS), and time to symptomatic progression. Overall survival data were not mature at the time of the MFS analysis. Results can be seen in the table below, which was adapted from the prescribing information.

Endpoint	Number of events (%)		Median (months)		Hazard Ratio
	Erleada® (N=806)	Placebo (N=401)	Erleada®	Placebo	
Metastasis Free Survival	184 (23%)	194 (48%)	40.51	16.20	0.28; p<0.0001
Time to Metastasis	175 (22%)	191 (48%)	40.51	16.59	0.27; p<0.0001
Progression-Free Survival	200 (25%)	204 (51%)	40.51	14.72	0.29; p<0.0001

Place in Therapy: Erleada® is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer. Patients should also receive a gonadotropin-releasing hormone analog concurrently with Erleada® or should have had a bilateral orchiectomy. Compared to placebo, Erleada® significantly prolonged metastasis-free survival, time to metastasis, and progression-free survival.

It is recommended that Erleada® be placed on the Recommended Drug List as recommended and require prior authorization to confirm the appropriate diagnosis and clinical parameters for its use.

PDL Placement:

☐ **Preferred**

☒ **Recommended with Conditions**

References

[1] Erleada [package insert]. Horsham, PA: Janssen Products; 2018.