Perioperative apalutamide in high-risk localized or locally advanced prostate cancer: A Phase 3 RCT (PROTEUS)[1]

Indication[2]

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration–resistant prostate cancer (nmCRPC)

Please see select safety information on page 4.

Important disclosures*

ERLEADA® is not FDA-approved for the treatment of patients with high-risk localized or locally advanced prostate cancer (LPC/LAPC) and the safety and efficacy of ERLEADA® in patients with high-risk LPC/LAPC has not been established

Investigational use of ERLEADA® in these patients is ongoing.

Background

Radical prostatectomy (RP) is a curative intent surgery for patients with high-risk LPC/LAPC; however, up to 50% relapse within 5 years[3,4]

The PROTEUS trial investigated whether 12 cycles of perioperative apalutamide + androgen deprivation therapy (ADT) vs placebo + ADT improved pathologic response and long-term outcomes in patients with high-risk LPC/LAPC undergoing RP[1]

PROTEUS: A Phase 3, double-blind, placebo-controlled study[1]

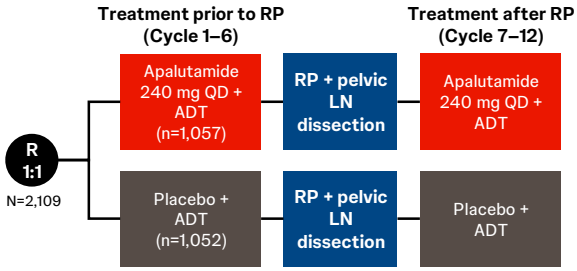
Study design

Key inclusion criteria:

- High-risk LPC/LAPC†
- Candidate for RP
- No evidence of metastatic disease‡
- ECOG PS of 0 or 1

Stratification factors:

- Loco-regional LN (N0 or N1)
- Gleason score (7 or 8–10)
- Region (North America, Europe, and rest of the world)



Patients paused treatment with apalutamide/placebo 2 weeks prior to scheduled RP and resumed 4 weeks after RP. ADT was continuous throughout the treatment phase.

Postoperative radiotherapy (adjuvant or salvage) and metastasis-directed therapy could be administered at investigator's discretion according to local standard practice.

Cardiovascular risk was assessed during screening and prior to surgery. Thromboprophylaxis was administered based on risk factors and local guidelines.

NCT03767244; published May 2026

Study endpoints included:

- **Dual 1°:**
  - Pathologic complete response (pCR)/ minimal residual disease (MRD)§
  - Metastasis-free survival (MFS), based on conventional or PSMA-PET imaging§
- **2°:** Event-free survival (EFS); time to first subsequent treatment (TTST1); time to distant metastasis (TTDM)¶; no evidence of disease at 4 years; MFS based on conventional imaging; PSA-free survival with testosterone recovery; safety
- **Select exploratory:** MRD by residual cancer burden (≤ypT2, ≤0.25 cm^3)§; overall survival (OS); time to testosterone recovery

The comparison of apalutamide + ADT + RP vs RP alone will be assessed in a complementary PROTEUS substudy

Select endpoint definitions

- **Pathologic complete response (pCR/MRD):** No residual tumor identified (ypT0) or MRD ≤5 mm in prostate-confined disease (ypT2)§
- **Metastasis-free survival (MFS):** Time from randomization to first occurrence of distant metastasis based on conventional imaging (ie, computed tomography/magnetic resonance imaging and bone scan) or PSMA-PET imaging, pathologic finding of distant metastasis, or death from any cause
- **Event-free survival (EFS):** Time from randomization to any of the following: Biochemical failure, local or regional recurrence, distant metastasis, or death
- **No evidence of disease:** Alive, undetectable PSA (<0.02 ng/mL), no distant metastasis, no local or regional recurrence, no subsequent therapy for prostate cancer, testosterone recovery (≥200 ng/dL)

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†Newly diagnosed high-risk LPC/LAPC, defined by a total Gleason score (GS) ≥4+3 (=GG 3-5) and ≥1 more of the following: any combination of GS 4+3 (GG3) and GS 8 (GG4) from ≥6 systematic cores, or any combination GS 4+3 (GG3) and GS 8 (GG4) from ≥3 systematic cores and PSA ≥20 ng/mL, or GS ≥9 (GG5) in ≥1 systematic or targeted core, or ≥2 systematic or targeted cores with continuous GS ≥8, each with ≥80% involvement.[5] ‡Based on conventional imaging, confirmed by BICR; clinical stage N1 (pelvis) was allowed. §Assessed by BICR. ¶Based on conventional or PSMA-PET imaging.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, Food and Drug Administration; GG, grade group; LN, lymph nodes; PSA, prostate-specific antigen; PSMA-PET, prostate-specific membrane antigen positron-emission tomography; QD, once daily; R, randomized; RCT, randomized controlled trial.

1. Taplin M-E, et al. *N Engl J Med.* Published online May 31, 2026. doi:10.1056/NEJMoa2603878. 2. ERLEADA® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 3. Eastham JA, et al. *J Urol.* Published online April 22.2026. doi: 10.1097/JU.0000000000005060. 4. Eiber M, et al. *J Clin Oncol.* 2024;42:5024.5. Taplin M-E, et al. *N Engl J Med.* Published online May 31, 2026. doi:10.1056/NEJMoa2603878 (Supplement).

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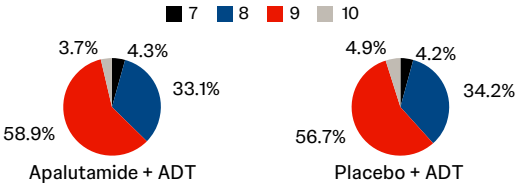
Patient characteristics

- At clinical cutoff (February 2, 2026), **median follow-up** was **61.7 months**
- **85.1% of apalutamide + ADT** and **87.6% of placebo + ADT** patients remain on study

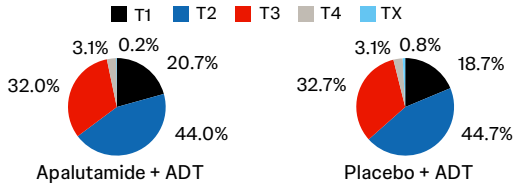
Median age across both groups
66 years

Gleason score at diagnosis



Median PSA across both groups
14.8 ng/mL (IQR: 8.1–31.5 ng/mL)

Tumor stage at diagnosis



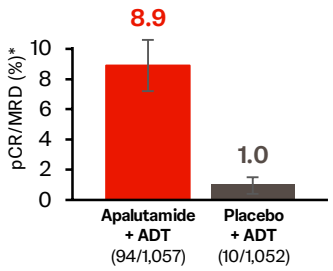
Demographic and baseline disease characteristics were well balanced between the two groups

Results

Dual primary endpoints

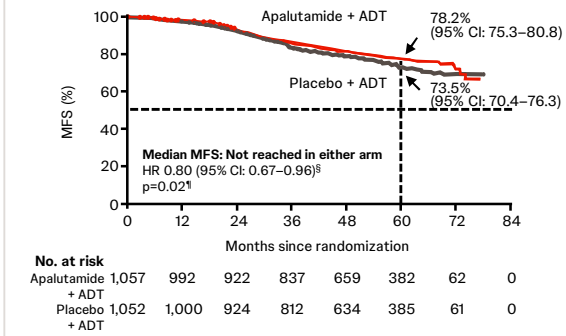
pCR/MRD

OR 10.17 (95% CI: 5.27–19.64)†; p<0.001‡



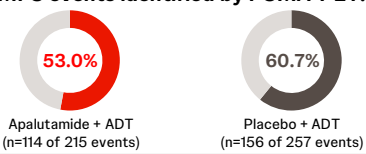
- pCR/MRD rate was 9-fold higher with apalutamide + ADT vs placebo + ADT (p<0.001)
- ypT0 disease: 5.1% in apalutamide + ADT and 0.4% in placebo + ADT group
- Positive surgical margins at surgery: 20.9% of apalutamide + ADT group and 42.7% of placebo + ADT group

MFS



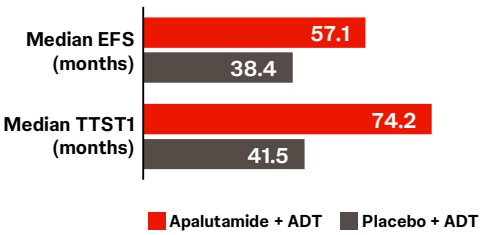
- MFS by conventional imaging or PSMA-PET was significantly longer, with a 20% reduction in risk of distant metastasis or death with apalutamide + ADT vs placebo + ADT (p=0.02)
- MFS by conventional imaging alone (secondary endpoint) was not statistically significant

MFS events identified by PSMA-PET:



Most distant metastases were identified by PSMA-PET

Secondary and exploratory endpoints



HR 0.71
(95% CI: 0.63–0.80)§
p<0.001¶

HR 0.65
(95% CI: 0.57–0.73)§
p<0.001¶

Median TTDM (months):
Not reached in either arm
HR 0.68 (95% CI: 0.55–0.83)§; p<0.001¶

Patients with no evidence of disease at 4 years:
21.9% vs **18.3%**
OR 1.25 (95% CI: 1.01–1.55)†; p=0.04‡,#

Median time to testosterone recovery (≥200 ng/dL) from end of 12-month perioperative treatment (months):
8.1 months vs 6.6 months
HR 0.92 (95% CI: 0.84–1.01)§

EFS, TTST1, and TTDM significantly favored apalutamide + ADT (all p<0.001), as did the proportion of patients with no evidence of disease at 4 years (p=0.04)

Figure from *N Engl J Med.* Taplin M-E, et al. Perioperative apalutamide in high-risk localized prostate cancer. Published online May 31, 2026. doi:10.1056/NEJMoa2603878.

See Safety Results on next page

*No pCR/MRD category includes patients who have residual disease, those not tested for pCR/MRD (n=4), or those who have not undergone RP (n=112). †OR was calculated as a logistic-regression analysis stratified according to region (Europe, North America, or the rest of the world), nodal status (N0 or N1), and Gleason score (7, ≥8). OR >1 favors apalutamide over placebo. ‡P value was calculated on the basis of a Cochran-Mantel-Haenszel test stratified according to region, nodal status, and Gleason score. §HR is from proportional hazards model stratified according to region, nodal status, and Gleason score; HR <1 favors apalutamide over placebo. ¶P value is from a log-rank test stratified according to region, nodal status, and Gleason score. #For no evidence of disease, the rates reported are based on the intent-to-treat population; however, approximately 10% of the patients could not be evaluated for this end point by the clinical cutoff date and were therefore classified as having evidence of disease.

ADT, androgen deprivation therapy; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IQR, interquartile range; MFS, metastasis-free survival; MRD, minimal residual disease; OR, odds ratio; pCR, pathologic complete response; PSA, prostate-specific antigen; PSMA-PET, prostate-specific membrane antigen positron-emission tomography; RP, radical prostatectomy; TTDM, time to distant metastasis; TTST1, time to first subsequent treatment.

1. Taplin M-E, et al. *N Engl J Med.* Published online May 31, 2026. doi:10.1056/NEJMoa2603878.

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Results, cont'd

Safety

Summary of TEAEs*, n (%)		
AE, n (%)	**Apalutamide + ADT (n=1,050)**	**Placebo + ADT (n=1,050)**
Any TEAE	1,037 (98.8)	1,027 (97.8)
Grade 3/4 TEAE	416 (39.6)	325 (31.0)
Any serious TEAE	203 (19.3)	172 (16.4)
Any TEAE leading to discontinuation	78 (7.4)	28 (2.7)
TEAEs leading to dose interruption	154 (14.7)	81 (7.7)
TEAEs leading to death	14 (1.3)	5 (0.5)

Median **treatment duration** was similar between arms:

- Apalutamide + ADT, **11.0 months**
- Placebo + ADT, **11.1 months**

Proportion of patients with **venous thromboembolism:**

- Apalutamide + ADT, **2.0%** of patients
- Placebo + ADT, **3.4%** of patients

Proportion of patients **with treatment-emergent cardiac disorders:**

- Apalutamide + ADT, **6.8%** of patients
- Placebo + ADT, **5.9%** of patients

Most common TEAE with a frequency of ≥10%*,†, n (%)				
AE, n (%)	**Apalutamide + ADT (n=1,050)**		**Placebo + ADT (n=1,050)**	
	Grade 3/4	**All grade**	**Grade 3/4**	**All grade**
≥1 TEAE	416 (39.6)	1,037 (98.8)	325 (31.0)	1,027 (97.8)
Hot flush	7 (0.7)	666 (63.4)	0	593 (56.5)
Urinary incontinence	16 (1.5)	527 (50.2)	17 (1.6)	534 (50.9)
Erectile dysfunction	35 (3.3)	437 (41.6)	27 (2.6)	435 (41.4)
Fatigue	4 (0.4)	291 (27.7)	1 (0.1)	281 (26.8)
Arthralgia	4 (0.4)	237 (22.6)	2 (0.2)	204 (19.4)
Rash	31 (3.0)	223 (21.2)	2 (0.2)	105 (10.0)
Constipation	0	200 (19.0)	0	166 (15.8)
Hypertension	80 (7.6)	169 (16.1)	91 (8.7)	184 (17.5)
Pruritus	7 (0.7)	165 (15.7)	0	90 (8.6)
Procedural pain	6 (0.6)	119 (11.3)	3 (0.3)	143 (13.6)
Urinary tract infection	18 (1.7)	116 (11.0)	11 (1.0)	124 (11.8)
COVID-19	7 (0.7)	102 (9.7)	3 (0.3)	105 (10.0)

Authors' conclusions and limitations[1]

In patients with high-risk LPC/LAPC, 1-year **perioperative apalutamide + ADT improved oncologic outcomes** vs placebo + ADT

Safety of apalutamide + ADT did not reveal any new safety signals in patients with high-risk LPC/LAPC

Limitations of the PROTEUS study include:

- A lack of comparison with RP only. PROTEUS substudy will compare apalutamide + ADT + RP vs RP
- Relative to US incidence, Black patients were under-represented (3.7%) and Asian patients were over-represented (19.3%) in the PROTEUS study

Tables from *N Engl J Med.* Taplin M-E, et al. Perioperative apalutamide in high-risk localized prostate cancer. Published online May 31, 2026. doi:10.1056/NEJMoa2603878. Copyright © 2026 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

*Data are shown for the safety population. AEs that occurred during the treatment period were specified as those events that occurred on or after the date of the first dose of apalutamide or placebo and before the start of subsequent therapy or no more than 30 days after the last dose of apalutamide or placebo, whichever occurred first, or as AEs that were considered to be related to treatment, regardless of the start date of the event. AEs were defined according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 28.0, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. For each system organ class and preferred term, patients are counted only once, even if they had multiple events that would be categorized according to the same system organ class or preferred term. In such cases, the highest-grade event is reported. If grades were unknown for all events for a given patient, the patient is counted only in the total column. COVID-19 denotes coronavirus 2019. †The most common AEs were reported in at least 10% of the patients in either group. Grade 5 events are excluded.

ADT, androgen deprivation therapy; AE, adverse event; LAPC, locally advanced prostate cancer; LPC, localized prostate cancer; RP, radical prostatectomy; TEAE, treatment-emergent adverse event.

1. Taplin M-E, et al. *N Engl J Med.* Published online May 31, 2026. doi:10.1056/NEJMoa2603878.

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Safety information summary

Please read the full Prescribing Information for ERLEADA® (apalutamide)

Indications

ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:

- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration–resistant prostate cancer (nmCRPC)

Warnings and precautions

Cerebrovascular and Ischemic Cardiovascular Events

Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. 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 3.7% of patients treated with ERLEADA® and 2% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4.4% of patients treated with ERLEADA® and 1.5% of patients treated with placebo. Across the SPARTAN and TITAN studies, 4 patients (0.3%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

In the SPARTAN study, cerebrovascular events occurred in 2.5% of patients treated with ERLEADA® and 1% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA® and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

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 nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo.

Falls

Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

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

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 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 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 or, 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.

Severe Cutaneous Adverse Reactions

Fatal and life-threatening cases of severe cutaneous adverse reactions (SCARs), including Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) occurred in patients receiving ERLEADA®.

Monitor patients for the development of SCARs. Advise patients of the signs and symptoms of SCARs (eg, a prodrome of fever, flu-like symptoms, mucosal lesions, progressive skin rash, or lymphadenopathy). If a SCAR is suspected, interrupt ERLEADA® until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, or for other Grade 4 skin reactions, permanently discontinue ERLEADA®.

Interstitial Lung Disease (ILD)/Pneumonitis

Fatal and life-threatening interstitial lung disease (ILD) or pneumonitis can occur in patients treated with ERLEADA®.

Post-marketing cases of ILD/pneumonitis, including fatal cases, occurred in patients treated with ERLEADA®. Across clinical trials (TITAN and SPARTAN, n=1327), 0.8% of patients treated with ERLEADA® experienced ILD/pneumonitis, including 0.2% who experienced Grade 3 events.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever). Immediately withhold ERLEADA® if ILD/pneumonitis is suspected.

Permanently discontinue ERLEADA® in patients with severe ILD/pneumonitis or if no other potential causes of ILD/pneumonitis are identified.

Embryo-Fetal Toxicity

The safety and efficacy of ERLEADA® have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA®.

Adverse reactions

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.

Laboratory Abnormalities — All Grades (Grade 3–4)

- Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (1.8%), placebo 21% (1.6%)
- Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (2.5%), placebo 12% (2.3%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (1.0%); hypertriglyceridemia ERLEADA® 67% (1.6%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (1.9%), placebo 22% (0.5%)

Rash

In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines and 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 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 1.5% 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, when clinically indicated, should be initiated or dose adjusted.

Drug interactions

Effect of Other Drugs on ERLEADA®

ERLEADA® Strong CYP2C8 or CYP3A4 inhibitors

Reduce the ERLEADA® dose as recommended for adverse reactions. Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide).

Effect of ERLEADA® on Other Drugs

Substrates of CYP3A4, CYP2C9, CYP2C19, p-gp, BCRP, or OATP1B1

Refer to the Prescribing Information for these substrates. Consider alternative agents when possible or evaluate for loss of activity of the substrate if concomitant use cannot be avoided.

Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9, and an inducer of P-gp, BCRP, and OATPB1. Apalutamide decreases exposure of substrates of CYP3A4, CYP2C19, CYP2C9, P-gp, BCRP, or OATP1B, which may decrease the effectiveness of these substrates.

Use in specific populations

The recommended ERLEADA® dosage in patients with (Child-Pugh C) is lower than the recommended dosage in patients with normal hepatic function. No dosage modification is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment

BCRP, breast cancer resistance protein; BSA, body surface area; CYP, cytochrome P450; OATP1B1, organic anion transporting polypeptide 1B1; P-gp, P-glycoprotein; TSH, thyroid-stimulating hormone.

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