PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrERLEADA®

apalutamide tablets

tablet, 60 mg, oral

ATC Code: L02BB05

Anti-androgen

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RECENT MAJOR LABEL CHANGES

- Indications (1.0): 12/2019
- Dosage and Administration (4.0) 06/2021
- Warnings and Precautions, Cardiovascular (7.0) 06/2021
- Warnings and Precautions, Monitoring and Laboratory Tests (7.0) 12/2019
- Warnings and Precautions, Musculoskeletal (7.0) 12/2019
- Warnings and Precautions, Neurologic (7.0) 06/2021
- Warnings and Precautions, Sexual Health, (7.0) 12/2019
- Warnings and Precautions, Geriatrics (7.1.4) 12/2019

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

- ERLEADA® is indicated for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).

- ERLEADA® (apalutamide tablets) is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

  ERLEADA® has not been studied in patients with nmCRPC at low risk of developing metastases. The benefit and risk profile in these patients is unknown.

1.1 Pediatrics (< 18 years of age)

The safety and efficacy of ERLEADA® in children have not been evaluated.

1.2 Geriatrics (> 65 years of age)

No overall differences in efficacy were observed between geriatric patients and younger patients (see **DOSAGE AND ADMINISTRATION**; **WARNINGS AND PRECAUTIONS, Special Populations**).

2 CONTRAINDICATIONS

ERLEADA® is contraindicated in

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing (see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING)**.
- women who are or may become pregnant.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Not applicable.

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dose and Dosage Adjustment

ADULTS
The recommended dose of ERLEADA® is 240 mg (four 60 mg tablets) administered orally once daily. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

ERLEADA® tablets should be swallowed whole.

ERLEADA® can be taken with or without food.

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

- Mix whole ERLEADA® tablets in 4 ounces (120 mL) of applesauce by stirring. Do not crush the tablets.
- Wait 15 minutes, stir the applesauce mixture.
- Wait another 15 minutes, stir the applesauce mixture until tablets are fully dispersed (well mixed with no chunks remaining).
- Using a spoon, swallow the mixture right away.
- Rinse the mixture container with 2 ounces of water and immediately drink the contents. Repeat the rinse with 2 ounces of water one more time to ensure the whole dose is taken.
- The mixture should be consumed within one hour of preparation (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).
- Do not store ERLEADA® mixed in applesauce for later use beyond the one-hour window of preparation.

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 resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted. If the toxicity recurs at Grade 3 or higher, then the dose of apalutamide should be reduced to the next lower dose level. A maximum of 2 dose level reductions (to 120 mg) is allowed. If further dose reductions are needed, apalutamide should be discontinued. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment.

Pediatrics (< 18 years of age): Safety and efficacy of ERLEADA® in pediatric patients have not been evaluated.

Geriatrics (≥65 years of age): No dose adjustment is necessary for elderly patients. In general, patients in the oldest group (≥75 years) treated with ERLEADA® experienced higher toxicity and lower tolerance than patients in the younger age groups (≤65 years and 65-74 years), see **WARNINGS AND PRECAUTIONS, Geriatrics**. Monitor elderly patients more closely for toxicity and adjust dose when needed.

Renal insufficiency: No dosage adjustment is necessary for patients with mild to moderate renal impairment. No data are available in patients with severe renal impairment or end-stage renal disease (eGFR ≤ 29 mL/min/1.73m^2) (see **ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency**).

Hepatic insufficiency: No dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh Class C) (see **ACTION AND CLINICAL PHARMACOLOGY, Hepatic Insufficiency**).

4.2 Missed Dose

If the patient misses a dose, it should be taken 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.

5 OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA®, undertake general supportive measures until clinical toxicity has been diminished or resolved.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	tablet 60 mg	Tablet Core: colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl methylcellulose-acetate succinate (HPMC-AS), magnesium stearate, microcrystalline cellulose, and silicified microcrystalline cellulose. Tablet Coating: iron oxide black (E172), iron oxide yellow (E172), polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

ERLEADA® 60 mg tablets are slightly yellowish to greyish green, oblong-shaped, film-coated and debossed with “AR 60” on one side.

ERLEADA® tablets are supplied in bottles of 120 tablets. Each bottle contains silica gel desiccant.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Ischemic Cardiovascular Events

Ischemic events (all Grades: 5% vs. 2%), Grade 3 (1% vs. 0.8%), Grade 4 (0.3% vs. 0.1%) and Grade 5 events (0.3% vs. 0.2%) occurred in patients treated with apalutamide versus patients treated with placebo across both the clinical trials, TITAN (mCSPC population) and SPARTAN (nmCRPC population).

Reported deaths due to ischemic heart disease were 0.5% in the apalutamide arm and 0.2% in the placebo arm for the combined clinical trials.

In TITAN, cardiovascular ischemic events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Two patients in each arm died from an ischemic cardiovascular event.

In SPARTAN, higher incidences of ischemic heart disease and cardiac failure were reported in patients treated with ERLEADA® (see **ADVERSE REACTIONS**). Majority of patients in TITAN and SPARTAN had cardiac risk factors.

Patients with clinically significant cardiovascular disease in the past 6 months including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, stroke, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias were excluded from both clinical trials.

Patients with a cardiac history should be assessed for active cardiac disease before starting therapy with ERLEADA® (**see Monitoring and Laboratory tests).** Patients should be monitored for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia (see **DOSAGE AND ADMINISTRATION**).

QTc prolongation

In a dedicated QT study in men with CRPC administered apalutamide 240 mg once daily plus ADT, based on the longest QTcF change at any time for each patient at steady-state, the mean maximum QTcF change from baseline (ΔQTcF) was 20.2 msec with the upper bound limit of 90% CI of 23.7 msec (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics**). Syncope was reported in 2.1% of patients treated with ERLEADA® compared to 1.0% of patients treated with placebo in SPARTAN. Apalutamide and N-desmethyl apalutamide inhibit hERG K^+ channel with IC_{50} below the C_{max} at steady-state at the clinically recommended ERLEADA® daily dose (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**). Monitor patients with known history of QT prolongation, risk factors for torsades de pointes, or taking medications known to prolong the QT interval.

Monitoring and Laboratory Tests

Monitoring for laboratory or clinical parameters should be conducted per routine practice. In addition, the following clinical monitoring and laboratory tests are recommended for patients treated with ERLEADA®.

- Monitor TSH during the treatment for hypothyroidism (See **ADVERSE REACTIONS, Hypothyroidism)**.
- Monitoring of ECG at baseline and during the treatment of ERLEADA® should be considered for patients at risk for QTc prolongation or taking medications known to prolong QT interval.
- Patients with a cardiac history should be assessed for active cardiac disease before and during therapy with ERLEADA®.
- Patients with a history of stroke should be assessed before and during therapy with ERLEADA®.
- Patients receiving ERLEADA® should be assessed for the risk of fracture and fall and treated to prevent clinical fractures according to national guidelines, with consideration given to use of bone-targeted agents.

Patients should be monitored for disease progression radiographically in addition to serum PSA, as 87 out of 175 patients treated with ERLEADA® reported radiographic progression

(distant metastases) without PSA progression in the SPARTAN trial.

Musculoskeletal

Fall and Fractures

Falls and fractures were reported more frequently in patients receiving ERLEADA®.

In SPARTAN, falls were reported in 15.6% of patients treated with ERLEADA® vs.9.0% of patients treated with placebo, with 1.7% of patients in the apalutamide arm and 0.8% in the placebo arm experiencing a fall resulting in hospitalization. Falls were not associated with loss of consciousness or seizure. In TITAN, falls were reported by a small percentage of patients in both the treatment arms (7.4% patients treated ERLEADA® vs.7.0% patients treated with placebo), nearly all were low-grade (Grade 1 or 2) and non-serious.

In SPARTAN, fractures were reported for 11.7% of patients treated with ERLEADA® compared to 6.5% of patients treated with placebo. Serious fractures occurred in 3.4% of patients treated with ERLEADA® vs. 0.8% of patients treated with placebo. Of all serious fractures reported in the ERLEADA® arm, 74% occurred in the weight bearing bones (see **Clinical Trials Adverse Reactions**, Table 3 footnote). The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA®. Forty percent of the patients experienced a fall within 7 days before the fracture event. In TITAN, fractures were reported for 6% of patients treated with ERLEADA® vs. 5% patients treated with placebo, and nearly all were low grade. Serious fractures occurred in 1.1% of patients treated ERLEADA® with vs. 0.8% patients treated with placebo. Rib fracture was the most common fracture in both treatment arms reported equally by 2.3% of patients in each treatment arm. Nearly half of the patients experienced a fall within 7 days before the fracture event.

Patients receiving ERLEADA® should be assessed for the risk of fracture and fall and treated to prevent clinical fractures according to national guidelines, with consideration given to use of bone-targeted agents.

Neurologic

Ischemic Cerebrovascular Events

In the final analysis of SPARTAN, with a median exposure of 33 months for ERLEADA® and 12 months for placebo, ischemic cerebrovascular disorders occurred in 4% of patients treated with ERLEADA® and 1% of patients treated with placebo. In the TITAN study, with a median exposure of 20 months for ERLEADA® and 18 months for placebo, ischemic cerebrovascular disorders occurred in a similar proportion of patients in the ERLEADA® (1.5%) and placebo (1.5%) groups.

Across both SPARTAN and TITAN, Grade 3-4 events were reported for 1.2% of patients in the ERLEADA® and 0.4% in the placebo groups and 2 patients (0.2%) treated with ERLEADA® died from an ischemic cerebrovascular disorder.

Patients with a history of stroke or transient ischemic attack within 6 months of randomization were excluded from both clinical trials.

Patients with a history of stroke should be assessed before starting therapy with ERLEADA® (see **Monitoring and Laboratory tests).** Patients should be monitored for signs and symptoms of ischemic cerebrovascular disorders. Optimize management of ischemic cerebrovascular risk factors, such as hypertension, diabetes, and/or high cholesterol.

Seizures
Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. In SPARTAN and TITAN, five patients (0.4%) treated with ERLEADA® and two patients (0.2%) treated with placebo experienced a seizure. Patients with a history of seizure or predisposing factors for seizure were excluded from these clinical studies and medications known to lower seizure threshold were prohibited while receiving ERLEADA®. There is no clinical experience in re-administering ERLEADA® to patients who experienced a seizure.

Sexual Health
Reproduction
ERLEADA® can cause harm to the developing fetus and/or lead to loss of pregnancy. Patients having sex with female partners of reproductive potential should use a condom along with another highly effective contraceptive method during treatment and for 3 months after the last dose of ERLEADA®.

Fertility
Based on animal studies, ERLEADA® may impair fertility in males of reproductive potential (see **NON-CLINICAL TOXICOLOGY**). Male patients should not donate sperm during treatment and for 3 months after the last dose of ERLEADA®.

7.1 Special Populations

7.1.1 Pregnant Women

ERLEADA® is contraindicated in women who are or may become pregnant (see **CONTRAINDICATIONS**). Based on its mechanism of action, ERLEADA® can cause fetal harm when administered during pregnancy. There are no data available with the use of ERLEADA® during pregnancy.

Animal Data
Animal embryo-fetal developmental toxicology studies have not been conducted with ERLEADA®.

7.1.2 Breast-feeding

ERLEADA® is not indicated for use in women. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed infant, or the effect on milk production.

7.1.3 Pediatrics

Safety and efficacy of ERLEADA® in pediatric patients have not been evaluated. There is no relevant use of ERLEADA® in pediatric patients < 18 years of age.

7.1.4 Geriatrics

Of the 1327 patients who received ERLEADA® in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over in age. No overall differences in efficacy and safety were observed between these patients and younger patients. However, there was a trend for older patients (≥75) to experience higher

incidence of grade 3/4 adverse events when treated with ERLEADA as compared to younger patients (<65, and 65-74).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of ERLEADA® has been assessed in randomized, double-blind, placebo-controlled, multi-centre clinical study, SPARTAN, a Phase 3 trial of 1201 patients with non-metastatic castration-resistant prostate cancer (nmCRPC), (see **CLINICAL TRIALS**) and in a randomized, double-blind, placebo-controlled, multi-center study, TITAN, a Phase 3 trial of 1051 patients with metastatic castration-sensitive prostate cancer (mCSPC), (see **CLINICAL TRIALS**).

In the combined data for apalutamide treatment versus placebo, from SPARTAN and TITAN, the most common adverse reactions (all Grades, ≥10%) were: fatigue (28% vs.19%), grouped term of skin rash (27% vs. 8%), hypertension (24% vs.18%), hot flush (18% vs.13%), arthralgia (19% vs.12%), diarrhoea (18% vs.10%), nausea (15% vs. 12%), fall (16% vs. 8%), weight decreased (14% vs. 6%), pain in extremity (11% vs. 9%), and decreased appetite (10% vs. 7%), respectively.

Commonly reported serious adverse reactions for apalutamide treatment versus placebo from combined clinical trials were hypertension (13% vs.11%) and skin rash (6% vs. 0.6%) respectively.

Across both clinical trials, the incidence of adverse reactions leading to dose reduction, dose interruption and dose discontinuation was 8.8% vs. 2%, 29% vs. 15% and 13% vs. 6% respectively for apalutamide treatment versus placebo.

Skin rash was the most common adverse reaction leading to dose reduction, dose interruption and treatment discontinuation in the combined population.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)
In the TITAN clinical study, 524 patients (safety population) received ERLEADA® at a dose of 240 mg daily. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. 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. At the time of interim analysis, 66% patients remained on apalutamide and 46% on placebo.

The most common all grades adverse reactions (≥15%) that occurred more commonly (>2%) in the ERLEADA® arm than the placebo arm were arthralgia, fatigue, rash, hypertension, and hot flush (see Table 2). The frequency of Grade 3/4 adverse events were, 42% in the ERLEADA® arm and 41% in the placebo arm, respectively. Grade 3 and 4 adverse events (occurring in ≥1%) reported at a higher incidence in the ERLEADA® arm than the placebo arm were, the

grouped term of skin rash (6.3% vs. 0.6%), asthenia (1.9% vs. 0.6%) and fatigue (1.5% vs. 1.1%) respectively.

The frequency of serious adverse events was 20% in both arms of the trial. The frequently reported serious adverse events (occurring in ≥1%) that occurred at a higher incidence in the ERLEADA® arm than the placebo arm were pneumonia (1.3% vs. 0.6%) and hematuria (1.3% vs. 0.6%).

Ten patients (2%) who were treated with ERLEADA® and 16 patients (3%) treated with placebo died from adverse events. The causes of death in the ERLEADA arm were ischemic heart disease (n=2), acute kidney injury (n=2) and one event each of cardiorespiratory arrest, cardiogenic shock, sudden death, respiratory failure, cerebrovascular accident, and large intestinal ulcer perforation.

Treatment discontinuations due to adverse events were reported for 8% of patients treated with ERLEADA® and 5% patients treated with placebo. Adverse events leading to dose interruption were reported for 20% of patients treated with ERLEADA® and 12% treated with placebo. Dose reduction due to adverse events was reported for 7% of patients treated with ERLEADA® and 2% of patients treated with placebo. Rash as a grouped term was the most frequently reported adverse event which led to dose interruptions (7%), dose reductions (5%) or treatment discontinuations (2%) respectively.

Table 2 shows treatment-emergent adverse events on the ERLEADA® arm in TITAN, as compared to placebo listed by system organ class and frequency.

Table 2: Treatment-Emergent Adverse Events at an Incidence of ≥10% in Patients Randomized to ERLEADA® that occurred with a 2% absolute increase in frequency compared to placebo in TITAN (mCSPC)

	ERLEADA® N=524		**Placebo N=527**	
System/Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and administration site conditions				
Fatigue[1,3]	20	2	17	1
Musculoskeletal and connective tissue disorders				
Arthralgia[3]	17	0.4	15	0.9
Skin and subcutaneous tissue disorders				
Rash[2]	28	6	9	0.8
Pruritus	11	0.2	5	0.2
Vascular disorders				
Hot flush	23	0	16	0
Hypertension	18	8	16	9

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

Additional adverse events reported in 1% to less than 10% of TITAN patients treated with ERLEADA® versus placebo included diarrhea (9% vs. 6%), hypothyroidism (7% vs. 1%), hypercholesterolemia (5 % vs. 1%), ischemic heart disease (4% vs. 2%), hypertriglyceridemia

(3% vs. 1%), dysgeusia (3% vs. 1%), and muscle spasm (3% vs. 2%).

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)
In the SPARTAN clinical study, 803 patients received ERLEADA® at a dose of 240 mg daily in combination with androgen deprivation therapy (ADT) in the treatment arm and 398 received placebo with ADT in the control arm. At interim analysis, the median treatment duration for ERLEADA®-treated patients was 16.9 (0.1-42.0) months compared to 11.2 (0.1-37.1) months for placebo-treated patients, and 61% of patients were still on ERLEADA® and 30% of patients were still on placebo. At final analysis, the median treatment duration was 33 months in the ERLEADA® arm and 12 months in the placebo (ADT alone) arm. The safety profile remained consistent for both the interim and final analysis.

In the SPARTAN clinical trial, the most common adverse reactions (≥15%) that occurred more commonly (>2%) in the ERLEADA® arm than the placebo arm were fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, and fall.

Frequently reported serious adverse events (occurring in ≥1%) that occurred at a higher incidence in the ERLEADA® arm than the placebo arm, were fracture as a grouped term (3.4% versus 0.8%), urinary tract infection (1.2% versus 0.8%), pneumonia (1.1% versus 0.5%), and sepsis (1.0% versus 0%).

Death due to adverse event was reported in 3%patients in the ERLEADA® arm and 1% patients in the placebo arm. The causes of death in the ERLEADA® arm were infection (n = 7: sepsis or pneumonia), general disorders (n=5), cardiac disorders (n=5), and one case each of cerebral hemorrhage and cerebrovascular accident.

Treatment discontinuations due to adverse events were reported for 15% of patients treated with ERLEADA® and 7% of patients treated with placebo. Adverse events leading to dose interruption were reported for 35% of patients treated with ERLEADA® and 18% treated with placebo. Dose reduction due to adverse events was reported for 10% of patients treated with ERLEADA® and 1.8% of patients treated with placebo. The most frequently reported adverse event that led to dose modifications was skin rash as a grouped term.

Table 3 shows treatment-emergent adverse events that occurred in ≥10% in patients on the ERLEADA® arm with a 2% absolute increase in frequency compared to placebo in the SPARTAN study.

Table 3: Treatment-Emergent Adverse Events at an Incidence of ≥10% in Patients Randomized to ERLEADA® that occurred with a 2% absolute increase in frequency compared to placebo in SPARTAN

System/Organ Class Adverse reaction	ERLEADA®+ADT N=803		Placebo + ADT N=398	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal disorders				
Diarrhea	20	1	15	0.5
Nausea	18	0	16	0
General disorders and administration site conditions				
Fatigue[1,6]	39	1.4	28	0.3
Injury, poisoning and procedural complications				
Fall[6]	16	2	9	0.8
Fracture[2]	12	3	7	0.8
Investigations				
Weight decreased[6]	16	1	6	0.3
Metabolism and nutrition disorders				
Decreased appetite[3]	12	0.1	9	0
Peripheral edema[4]	11	0	9	0
Musculoskeletal and connective tissue disorders				
Arthralgia[6]	16	0	8	0
Skin and subcutaneous tissue disorders				
Rash[5]	25	5	6	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0

1 Includes fatigue and asthenia
2 Includes rib fracture, lumbar vertebral fracture, spinal compression fracture, spinal fracture, foot fracture, hip fracture, humerus fracture, thoracic vertebral fracture, upper limb fracture, fractured sacrum, hand fracture, pubis fracture, acetabulum fracture, ankle fracture, compression fracture, costal cartilage fracture, facial bones fracture, lower limb fracture, osteoporotic fracture, wrist fracture, avulsion fracture, fibula fracture, fractured coccyx, pelvic fracture, radius fracture, sternal fracture, stress fracture, traumatic fracture, cervical vertebral fracture, femoral neck fracture, tibia fracture
3 Includes appetite disorder, decreased appetite, early satiety, and hypophagia
4 Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema
5 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]
6 Grade 4 definitions do not exist for these reactions

Additional adverse events reported in 1% to less than 10% of SPARTAN patients treated with ERLEADA® versus placebo included hypothyroidism (8% vs. 2%), dysgeusia (7 % vs. 2%), pruritis (6% vs. 2%), hypercholesterolemia (6% vs. 2%), muscle spasms (4% vs. 2%), hypertriglyceridemia (4% vs. 1%), ischemic cerebrovascular events[1] (4% vs.1%), ischemic heart disease (3.7% vs. 2 %), and heart failure (2.2% vs. 1 %).

Rash

In the combined data of two randomized, placebo-controlled clinical studies, rash associated with ERLEADA® was most commonly described as macular or maculo-papular. Adverse events of rash were reported for 26% of patients treated with ERLEADA® versus 8% of patients

[1] identified in the final analysis of the SPARTAN study after a longer median exposure to ERLEADA® (~2 fold longer than the interim study)

treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) versus placebo (0.5%). In these clinical studies, the incidence of all-grade rash and Grade 3 rash was more than 2-fold higher in the Japanese population compared with the entire study population.

The onset of rash occurred at a median of 83 days of ERLEADA® treatment and resolved within a median of 78 days from onset of rash for 78% of patients. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Median time to resolution was 3 times longer for patients on the apalutamide arm (100 days) than those on placebo (29 days). Skin rash led to treatment discontinuation in 7% of all subjects who experienced rash. 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®. (see **DOSAGE AND ADMINISTRATION**).

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. There were no grade 3 or 4 adverse reactions. Hypothyroidism occurred in 30% of patients already receiving thyroid replacement therapy in the ERLEADA® arm and in 3% of patients in the placebo arm. In patients not receiving thyroid replacement therapy, hypothyroidism occurred in 7% of patients treated with ERLEADA® and in 2% of patients treated with placebo. The median onset was at the first scheduled assessment. Monitor TSH regularly during the treatment of ERLEADA®. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

Apalutamide may induce UDP-glucuronosyl transferase (UGT). Levothyroxine and thyroxine are substrates of UGT. Patients on ERLEADA® who are receiving levothyroxine should be monitored for loss of levothyroxine efficacy (see **DRUG INTERACTIONS**).

8.3 Less Common Clinical Trial Adverse Reactions

The following are selected clinically significant adverse reactions reported in less than 1% of patients receiving ERLEADA® and with higher incidences reported than the placebo arm, across both the clinical studies:

Nervous system disorders: Seizure (0.4% versus 0.2% on placebo)

8.4 Abnormal Laboratory Findings: Hematologic and Clinical Chemistry

Table 4 and Table 5 shows laboratory abnormalities from both the clinical studies.

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 population)

Laboratory Abnormality	ERLEADA® N=803		Placebo N=398	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology				
Anemia	70	0.4	64	0.5
Leukopenia	47	0.3	29	0
Lymphopenia*	41	2	21	2
Chemistry				
Hypercholesterolemia[1]	76	0.1	46	0
Hyperglycemia[1*]	70	2	59	1
Hypertriglyceridemia[1]	67	2	49	0.8
Hyperkalemia	32	2	22	0.5

[1]Does not reflect fasting values

Table 5: 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 population)

Laboratory Abnormality	ERLEADA® N=524		Placebo N=527	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology				
White blood cell decreased	27	0.4	19	0.6
Chemistry				
Hypertriglyceridemia[1]	17	3	12	2

[1]Does not reflect fasting values
Additional laboratory abnormalities which were reported in < 15% of ERLEADA®-treated patients and at a higher incidence than Placebo (between arm difference <5%) were hyperkalemia, hypercholesterolemia, and Vitamin D deficiency.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported during post-marketing experience.

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease
Skin and subcutaneous tissue disorder: Stevens-Johnson syndrome/Toxic epidermal necrolysis

9 DRUG INTERACTIONS

9.1 Overview

Medications that Inhibit CYP2C8 or CYP3A4
Co-administration of strong CYP2C8 or CYP3A4 inhibitors is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Medications that Induce CYP3A4 or CYP2C8
The effects of CYP3A4 or CYP2C8 inducers on the pharmacokinetics of apalutamide have not been evaluated *in vivo*. Co-administration of strong CYP3A4 or CYP2C8 inducers are predicted to decrease the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide).

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 that affect transporters
In vitro, apalutamide and its N-desmethyl metabolite are substrates for P-glycoprotein (P-gp) but not breast cancer resistance protein (BCRP), organic anion transporting polypeptide 1B1 (OATP1B1), or 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 Drug Metabolizing Enzymes
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.

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 efficacy if medication is continued. ERLEADA® did not cause clinically meaningful changes in exposure to the CYP2C8 substrate.

Apalutamide may induce UDP-glucuronosyl transferase (UGT). Concomitant administration of ERLEADA® with medications that are substrates of UGT can result in decreased exposure of these medications. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of efficacy.

Effect of ERLEADA® on Drug Transporters
Apalutamide was shown clinically to be a weak inducer of P-gp, BCRP, and OATP1B1. 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 evaluate for loss of efficacy

if medication is continued.

Based on *in vitro* data, inhibition of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3) and multidrug and toxin extrusions (MATEs) by apalutamide and its N-desmethyl metabolite cannot be excluded. No *in vitro* inhibition of organic anion transporter 1 (OAT1) was observed. Simulations suggest that apalutamide does not cause clinically meaningful changes in exposure to benzylpenicillin (OAT3 substrate).

Effect of ERLEADA® on GnRH Analog
In mCSPC subjects receiving leuprolide acetate (a GnRH analog) co-administered with apalutamide, PK data indicated that apalutamide had no apparent effect on the steady-state exposure of leuprolide.

9.2 Drug-Drug Interactions

The drugs listed in Table 6 below are based on either drug interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 6: Established or Potential Drug-Drug Interactions

Drug Common name	Source of Evidence	Effect	Clinical comment
Effect of strong CYP2C8 inhibitors on apalutamide such as:			
Gemfibrozil 600 mg BID	CT T* T*	↑ apalutamide Single dose 240 mg: C_{max} ↓ 21%, AUC ↑ 68% Steady State C_{max} ↑ 32%, AUC ↑ 44% Active moieties (sum of unbound apalutamide plus potency-adjusted active metabolite) the steady state C_{max} ↑ 19%, AUC ↑ 23% *represents the worst- case scenario	No initial dose adjustment is necessary. Consider reducing the ERLEADA® dose based on tolerability (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**).
Effect of Strong CYP3A4 inhibitors on apalutamide such as:			
Itraconazole, 200 mg QD	CT	↔ apalutamide Single dose 240 mg: C_{max} ↓ 22%, AUC ↔	No initial dose adjustment is necessary. Consider reducing the ERLEADA® dose based on tolerability (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**).
Ketoconazole, 400 mg QD	T* T*	↑ apalutamide Steady State C_{max} ↑ 38%, AUC ↑ 51% Active moieties (sum of unbound apalutamide plus potency-adjusted active metabolite) the steady state C_{max} ↑ 23%, AUC ↑ 28% *represents the worst- case scenario	No initial dose adjustment is necessary. Consider reducing the ERLEADA® dose based on tolerability (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**).

Drug Common name	Source of Evidence	Effect	Clinical comment
Effect of CYP3A4/CYP2C8 inducers on apalutamide such as:			
Rifampin 600 mg QD	T T	↓ apalutamide Steady State C_{max} ↓ 25%, AUC ↓ 34% Active moieties (sum of unbound apalutamide plus potency-adjusted active metabolite) the steady state C_{max} ↓ 15%, AUC ↓ 19%	No dose adjustment necessary.
Effect of apalutamide on drugs metabolized by CYP3A4 such as:			
Midazolam 2 mg	CT	Multiple oral doses of ERLEADA® resulted in midazolam AUC ↓92%, C_{max} ↓77%	Substitution is recommended when possible or evaluate for loss of efficacy if medication is continued.
Effect of apalutamide on drugs metabolized by CYP2C19 such as:			
Omeprazole 40 mg	CT	Multiple oral doses of ERLEADA® resulted in omeprazole AUC ↓85%, C_{max} ↓77%	Substitution is recommended when possible or evaluate for loss of efficacy if medication is continued.
Effect of apalutamide on drugs metabolized by CYP2C9 such as:			
Warfarin 10 mg	CT	Multiple oral doses of ERLEADA® resulted in S-warfarin AUC ↓46%, C_{max} ↓16%	Substitution is recommended when possible or evaluate for loss of efficacy if medication is continued. Monitor the international normalized ratio (INR) during ERLEADA® treatment.
Effects of apalutamide on drugs metabolized by CYP2C8 such as:			
Pioglitazone 15 mg	CT	Multiple oral doses of ERLEADA® resulted in pioglitazone AUC ↓ 18%, C_{max} ↔	No dose adjustment
Effect of apalutamide on substrates of P-gp such as:			
Fexofenadine 30 mg	CT	Multiple oral doses of ERLEADA® resulted in fexofenadine AUC ↓ 30%, C_{max} ↔	Use caution and evaluate for loss of efficacy if medication is continued.
Effect of apalutamide on substrates of BCRP or OATP1B1 such as:			
Rosuvastatin 10 mg	CT	Multiple oral doses of ERLEADA® resulted in rosuvastatin AUC ↓41%, C_{max} ↔	Use caution and evaluate for loss of efficacy if medication is continued.
Effect of apalutamide on substrates of OAT3 such as:			
Benzylpenicillin 240 mg	T	Multiple oral doses of ERLEADA® resulted in ↔ benzylpenicillin AUC ↔ C_{max} ↔	No dose adjustment

Legend: CT = Clinical Trial; T = Theoretical (based on simulations)

9.3 Drug-Food Interactions

ERLEADA® can be administered with or without food (see **ACTION AND CLINICAL PHARMACOLOGY**). In clinical studies, ERLEADA® was administered without regard to food.

9.4 Drug-Herb Interactions

Drug-Herb Interactions have not been studied (see **Drug-Drug Interactions**).

9.5 Drug-Laboratory Test Interactions

No Drug-Laboratory Test Interactions have been identified.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Apalutamide is an orally administered Androgen Receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide prevents AR nuclear translocation, inhibits DNA binding, impedes AR-mediated transcription, and lacks androgen receptor agonist activity in preclinical studies. In mouse models of prostate cancer, apalutamide administration causes decreased tumour cell proliferation and increased apoptosis leading to tumour growth inhibition and regression. A major metabolite, N-desmethyl apalutamide, exhibited one-third the *in vitro* AR transcription activity of apalutamide.

10.2 Pharmacodynamics

Effect of QT/QTc interval and Cardiac Electrophysiology

Apalutamide and N-desmethyl apalutamide inhibit hERG K^+ channel with IC_{50} below the C_{max} at steady-state at the clinically recommended 240 mg daily dose. In a dedicated QT study in men with CRPC administered apalutamide 240 mg once daily plus ADT, based on the longest QTcF change at any time for each patient at steady-state, the mean of individual maximum QTcF change from baseline (ΔQTcF) was 20.2 msec with the upper bound of 90% CI of 23.7 msec. Pharmacokinetic and pharmacodynamic analysis showed a concentration-dependent increase in QTcF with apalutamide and N-desmethyl apalutamide.

Effect on $GABA_A$-Gated Chloride Channel

$GABA_A$ inhibition is an off-target activity of both apalutamide and N-desmethyl apalutamide. This interaction is considered the mechanism for the seizures/convulsions observed in general toxicology studies at high doses in animals (see **NON-CLINICAL TOXICOLOGY**)

10.3 Pharmacokinetics

Table 7: Arithmetic Mean (SD) Pharmacokinetic Parameters of Apalutamide and N-Desmethyl Apalutamide at Steady-State Following Administration of 240 mg QD ERLEADA® in Patients with Prostate Cancer

Moiety	C_{max} (µg/mL)	AUC_{tau} (µg/mL)	t_{max} (h) [a]	Peak-to-trough ratio	Vd/F (L) [b]	CL/F (L/h) [b]	Effective $t_{1/2}$ (h)
Apalutamide	6.0 (1.7)	100 (32)	2 (1-4)	1.63 (0.25)	276	2.0	74 (28)
N-desmethyl apalutamide	5.9 (1.0)	124 (23)	1 (0-4)	1.27 (0.13)	238	1.5	Not determined

[a] Median and range for t_{max}
[b] Based on population PK analysis

Following repeat once-daily dosing, apalutamide exposure (C_{max} and area under the concentration curve [AUC]) increased in a dose-proportional manner across the dose range of

30 to 480 mg. Following administration of 240 mg once daily, apalutamide steady state was achieved after 4 weeks and the mean accumulation ratio was approximately 5-fold relative to a single dose. An increase in apparent clearance (CL/F) was observed with repeat dosing, likely due to induction of apalutamide's own metabolism.

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.

Food Effect:
Administration of apalutamide to healthy subjects under fasting conditions and with a high-fat meal resulted in no clinically relevant changes in C_{max} and AUC. Median time to reach peak plasma concentration (t_{max}) was delayed about 2 hours with food (see **DOSAGE AND ADMINISTRATION**).

Administration of apalutamide as a dispersed mixture using applesauce resulted in comparable exposures and shorter time (shorter by 1 hour) to reach peak plasma concentration (t_{max}) compared to administration of apalutamide as whole tablets.

Absorption:
After oral administration, median time to achieve t_{max} was 2 hours. Mean absolute oral bioavailability is approximately 100% in healthy subjects, indicating that apalutamide is completely absorbed after oral administration.

Following oral administration of 4x60 mg apalutamide tablets dispersed in applesauce, C_{max} and AUC were 28% and 5% higher, respectively, when compared to administration of 4 intact 60 mg tablets under fasting condition (see **DOSAGE AND ADMINISTRATION)**.

Distribution:
The mean apparent volume of distribution at steady-state of apalutamide is about 276 L, indicative of extensive extravascular distribution.

Apalutamide and N-desmethyl apalutamide are 96% and 95% bound to plasma proteins, respectively, and mainly bind to serum albumin with no concentration dependency. Apalutamide and N-desmethyl apalutamide can cross the blood brain barrier based on animal studies.

Metabolism:
Following single oral administration of ^{14}C-labeled apalutamide 240 mg, apalutamide, the active metabolite, N-desmethyl apalutamide, and an inactive carboxylic acid metabolite accounted for the majority of the ^{14}C-radioactivity in plasma, representing 44%, 44%, and 3%, respectively, of the total ^{14}C-AUC.

Metabolism is the main route of elimination of apalutamide. It is metabolized primarily by CYP2C8 and CYP3A4 to form N-desmethyl apalutamide. Apalutamide and N-desmethyl apalutamide are further metabolized to form the inactive carboxylic acid metabolite by carboxylesterase. 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.

Elimination:
Apalutamide, mainly in the form of metabolites, is eliminated primarily via urine. Following a single oral administration of radiolabeled apalutamide, 89% of the radioactivity was recovered up to 70 days post-dose: 65% 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).

The CL/F of apalutamide is 1.3 L/h after single dosing and increases to 2.0 L/h at steady-state after once-daily dosing. The mean effective half-life for apalutamide in subjects is about 3 days at steady-state.

Special Populations and Conditions
The effects of intrinsic factors such as renal impairment, hepatic impairment, age, race, and body weight on the pharmacokinetics of apalutamide are listed individually below and summarized in Figure 1 below. No clinically significant differences in the pharmacokinetics of apalutamide and N-desmethyl apalutamide were observed in subjects with mild (eGFR 60-89 mL/min/1.73m^2) or moderate renal impairment (eGFR 30-59 mL/min/1.73m^2), mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, age ranging from 18 to 94 years, different body weight, or between different races.

Pediatrics:
ERLEADA® has not been evaluated in pediatric patients.

Geriatrics:
Of the 1327 patients who received ERLEADA® in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 75 years, and 40% were 75 years and over in age. Population PK analyses showed that there was no clinically relevant difference in systemic exposure of apalutamide and N-desmethyl apalutamide between patients of ≥ 65 years and patients < 65 years.

Sex:
All data were derived from male patients.

Pregnancy and Breast-feeding:
ERLEADA® is contraindicated in women who are or may become pregnant. Based on its mechanism of action, ERLEADA® can cause fetal harm when administered during pregnancy. There are no human data available with the use of ERLEADA® during pregnancy. Animal embryo-fetal developmental studies have not been conducted with ERLEADA®. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed infant, or the effect on milk production.

Ethnic origin:
Majority of apalutamide-treated patients in clinical studies were White (Caucasian or Hispanic or Latino). Based on population PK analysis, there were no clinically relevant differences in exposure between White (Caucasian or Hispanic or Latino), Black (of African heritage or African American), Asian (non-Japanese), or Japanese patients.

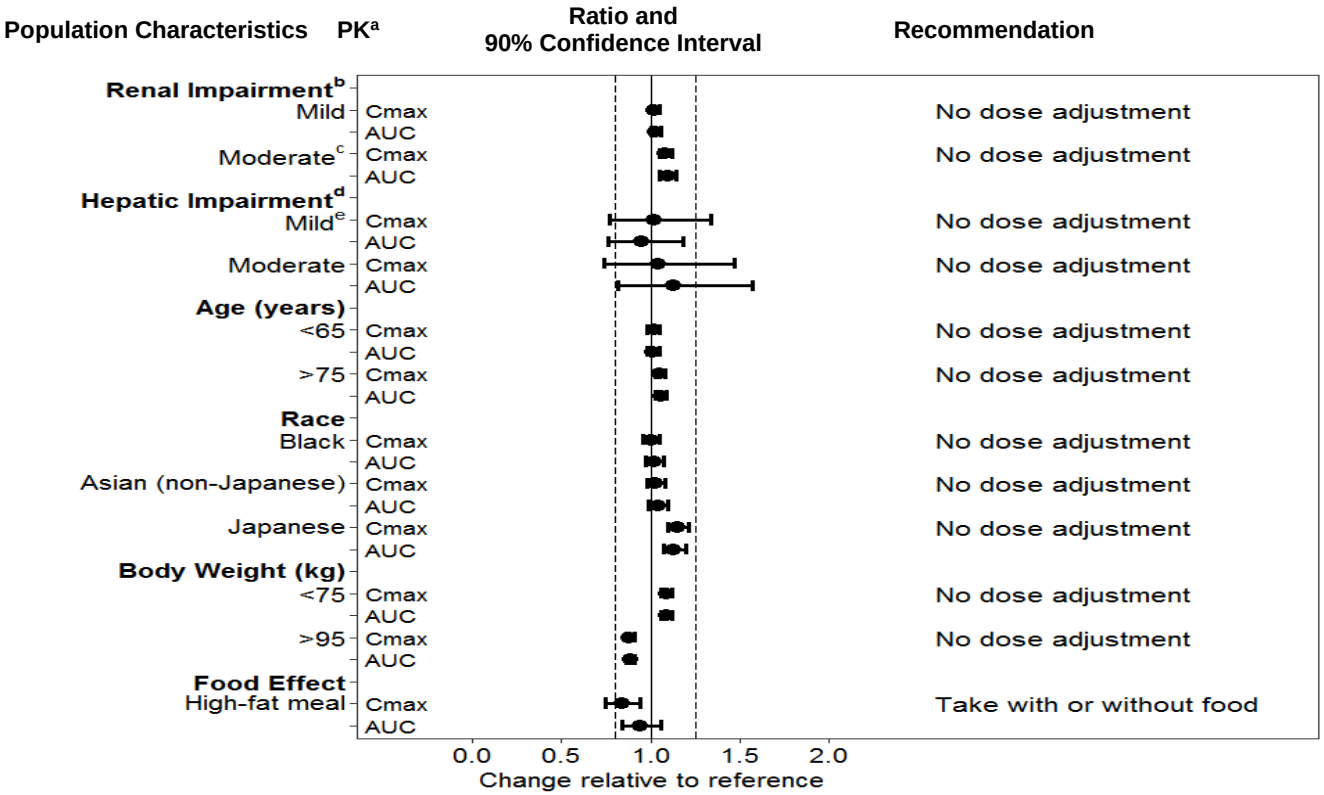
Hepatic Insufficiency:
In a dedicated Phase I hepatic impairment study systemic exposure of apalutamide and N-desmethyl apalutamide was similar in subjects with mild or moderate baseline hepatic impairment (Child-Pugh Class A or B, respectively) compared to subjects with normal hepatic

function. No dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh Class C).

Renal Insufficiency:
A dedicated renal impairment study for ERLEADA® has not been conducted. Based on the population PK analysis using data from clinical studies in patients with CRPC and healthy subjects, no significant difference in systemic exposure was observed in subjects with pre-existing mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] between 30 to 89 mL/min/1.73m^2) compared to subjects with baseline normal renal function (eGFR ≥ 90 mL/min/1.73m^2). No dosage adjustment is necessary for patients with mild to moderate renal impairment. No data are available in patients with severe renal impairment or end-stage renal disease (eGFR ≤ 29 mL/min/1.73m^2).

Body Weight:
Population PK analyses showed that body weight (range: 45-182 kg) did not have a clinically meaningful influence on the exposure to apalutamide.

Figure 1: Effects of Intrinsic and Food on ERLEADA®



[a] Pharmacokinetic (PK) parameters (C_{max} and AUC) are for apalutamide,
[b] Degree of renal impairment was determined based on eGFR using the modification of diet in renal disease (MDRD) study equation; normal (≥90 mL/min/1.73m^2), mild (60-89 mL/min/1.73m^2), moderate (30-59 mL/min/1.73m^2)
[c] Data included 2 subjects with severe renal impairment (≤29 mL/min/1.73m^2)
[d] Degree of hepatic impairment was determined based on Child-Pugh classification; mild (Child-Pugh A), moderate (Child-Pugh B)
[e] A population PK analysis demonstrated that mild hepatic impairment (based on the National Cancer Institute criteria) does not influence the exposure of apalutamide

11 STORAGE, STABILITY AND DISPOSAL

Store ERLEADA® at 15°C to 30°C, in the original package to protect from light and moisture. If ERLEADA® tablets are provided in a bottle, do not remove the silica gel desiccant from the bottle.

Healthcare professionals should recommend that their patients return all unused medications to pharmacy for proper disposal.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

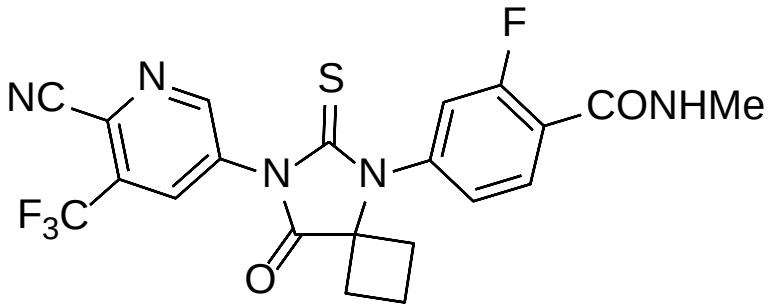
Drug Substance

Proper/Common name: apalutamide

Chemical name: 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-*N*-methylbenzamide

Molecular formula and molecular mass: $C_{21}H_{15}F_4N_5O_2S$ and molecular weight is 477.43

Structural formula:



Physicochemical properties: The drug substance is a white to slightly yellow powder. The drug substance is practically insoluble in aqueous media over a wide range of pH values. The drug substance has a dissociation constant pKa of 9.7 (acidic carboxamide moiety).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy and safety of ERLEADA® was established in two randomized placebo-controlled clinical trials. All patients in these studies received concomitant GnRH analog or had prior bilateral orchiectomy.

TITAN Study: Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN was a randomized, double-blind, placebo-controlled, multinational, multicenter clinical trial in which 1052 patients with mCSPC were randomized (1:1) to receive either ERLEADA® orally at a dose of 240 mg once daily (N = 525) or placebo once daily (N = 527). All patients received concomitant GnRH analog or had prior bilateral orchiectomy. Patients were stratified

by Gleason score at diagnosis, prior docetaxel use, and region of the world. Patients with both high- and low-volume mCSPC were eligible for the study.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 68 years (range 43-94) and 23% of patients were 75 years of age or older. The racial distribution was 68% Caucasian, 22% Asian, and 2% Black. Sixty-three percent (63%) of patients had high-volume disease and 37% had low-volume disease. Sixteen percent (16%) of patients had prior surgery, radiotherapy of the prostate or both. Majority of patients had a Gleason score of 7 or higher (92%). All patients except one in the placebo group, had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry.

The TITAN population consisted of newly diagnosed patients with metastatic disease and patients who had developed metastasis after being diagnosed with localized disease. These patients had low-volume/high-volume disease burden; and/or low-risk /high-risk disease (Table 8).

High-volume of disease was defined as metastases involving the viscera with 1 bone lesion or the presence of 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bones. Low-volume disease is defined as the presence of bone lesions not meeting the definition of High-volume disease.

High-risk disease is the presence of any 2 prognostic factors of a Gleason score of ≥8; and/or at least 3 bone lesions; or the presence of visceral metastasis. Low-risk disease is the presence of disease not meeting the definition of high-risk disease.

Sixty-eight percent (68%) of patients received prior treatment with a first-generation anti-androgen in the non-metastatic setting.

The summary of key baseline disease characteristics is provided in Table 8 below:

Table 8: Key Baseline Disease Characteristics; Intent-to-treat Population (TITAN)

	ERLEADA®	**Placebo**
ITT Population	525	527
Time from initial diagnosis to randomization (months)		
Median (range)	4.11 (0.5; 222.9)	4.04 (0.7; 341.4)
Time from metastatic diagnosis to randomization (months)		
Median (range)	2.63 (0.5;28.2)	2.69 (0.4; 27.1)
Metastasis stage at diagnosis		
M0	16.2%	11.2%
M1	78.3%	83.7%
MX	5.5%	5.1%
Gleason score at initial diagnosis		
<7	7.8%	7.4%
7	25.3%	24.7%
8	30.7%	29.2%
9	31.4%	33.0%
10	4.8%	5.7%
ECOG Performance Status Grade		
0	62.5%	66.0%
1	37.5%	33.8%

Table 8: Key Baseline Disease Characteristics; Intent-to-treat Population (TITAN)		
	ERLEADA®	**Placebo**
2	0	0.2%
Prior docetaxel use		
No	89.0%	89.6%
Yes	11.0%	10.4%
Extent of disease at study entry		
Bone	100.0%	100.0%
Bone Only	55.0%	51.0%
Lymph Node	37.9%	41.6%
Visceral	10.7%	13.7%
Lung	9.0%	12.1%
Liver	2.3%	2.5%
Soft tissue	4.2%	5.1%
Number of bone lesions at study entry		
≤10	60.6%	62.8%
>10	39.4%	37.2%
High-volume disease	62%	64%
Low-volume disease	38%	36%
High-risk disease	55%	54%
Low-risk disease	45%	46%

14.2 Study Results (TITAN Study: mCSPC)

The dual endpoints of the study were overall survival (OS) and radiographic progression-free survival (rPFS). Radiographic progression-free survival as assessed by the investigator is the duration from the date of randomization to the date of first documentation of radiographic progressive disease (progression of soft tissue lesions as per modified RECIST 1.1 criteria or ≥2 bone lesions on bone scan compared to baseline lesions), or death due to any cause, whichever comes first.

The secondary endpoints were time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use and time to skeletal related events.

At the time of analysis, 66% patients in the ERLEADA® arm and 46% of patients in the placebo arm were continuing study treatment. The median treatment duration was 20.5 months in the ERLEADA® arm and 18.3 months in the placebo arm.

A statistically significant improvement in OS and rPFS was demonstrated in patients receiving ERLEADA® compared to those patients receiving placebo. This improvement represented a 33% reduction in the risk of death, and a 52 % reduction in the risk of radiographic progression or death in patients receiving ERLEADA® compared to those patients receiving placebo (Table 9).

Table 9: Summary Results of Primary Endpoints in the ITT Population (Study TITAN)

Endpoint	Number of Events (%)		Median [Months (95% CI)]		HR (95%CI) [a] p-value (log-rank test) [b]
	ERLEADA® +ADT (N=525)	Placebo +ADT (N=527)	ERLEADA® +ADT (N=525)	Placebo +ADT (N=527)	
Overall Survival (OS)	83 (16%)	117 (22%)	NE	NE	0.67 (0.51-0.89) 0.0053
Radiographic Progression-free Survival (rPFS)	134 (26%)	231 (44%)	NE	22.1 (18.5-33.0)	0.48 (0.39-0.60) <0.0001

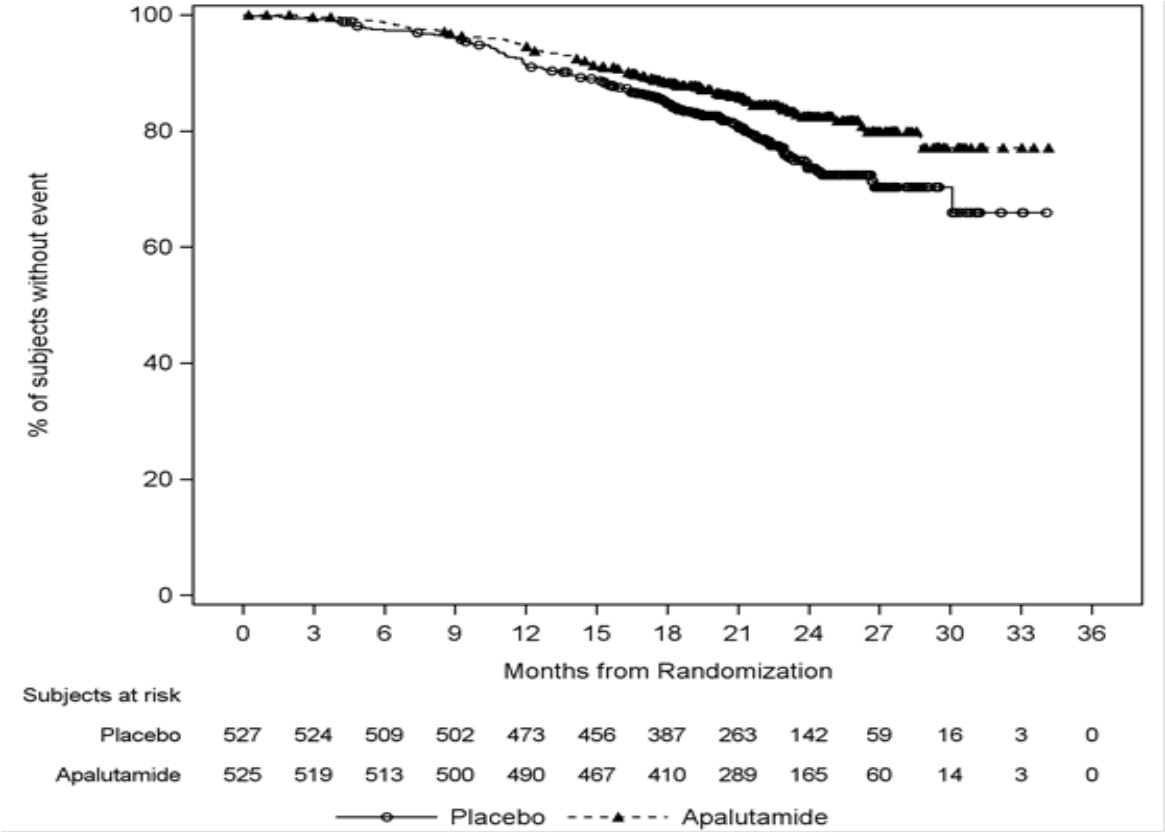
[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors active treatment.

[b] 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).

NE=Not Estimable

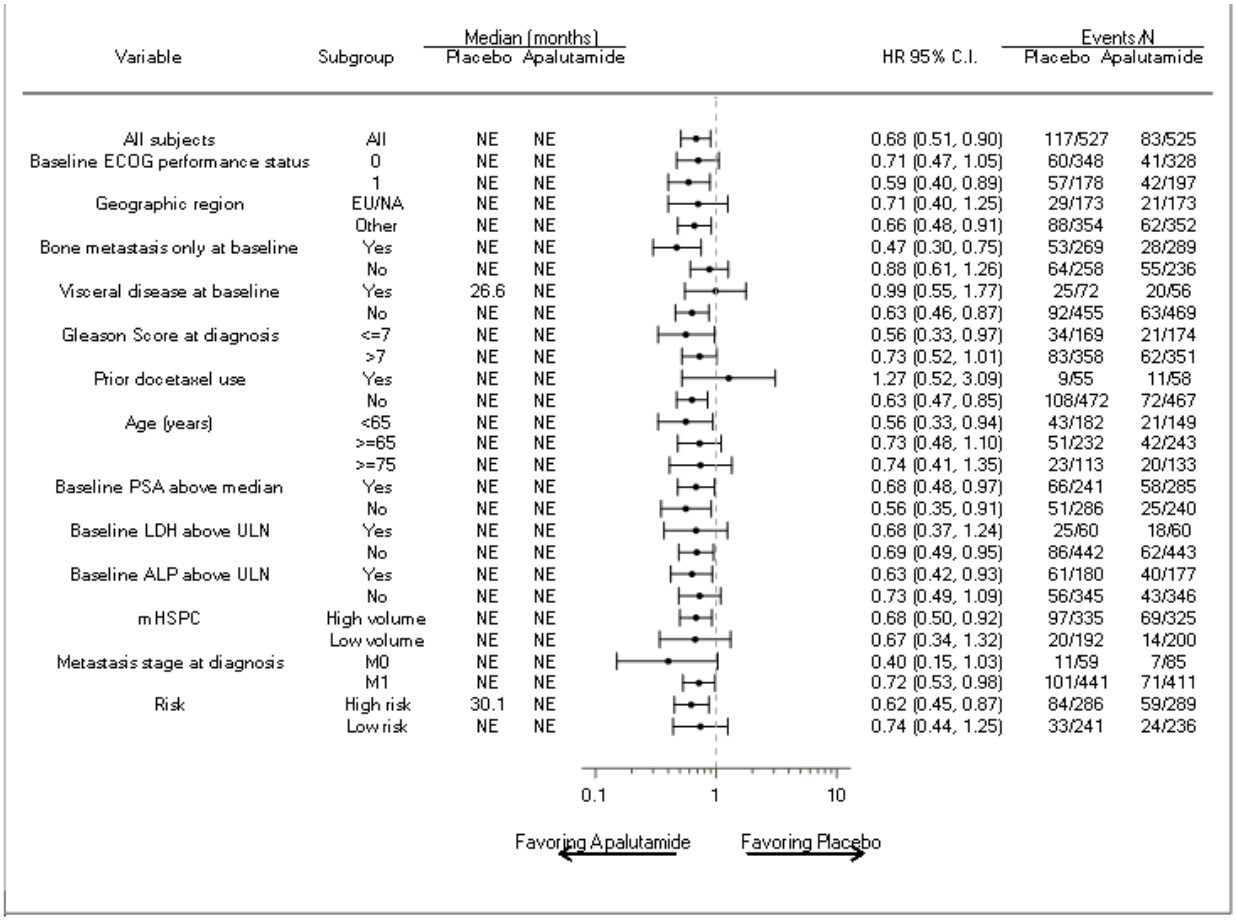
The Kaplan-Meier plot (Figure 2) demonstrates the OS benefit of the addition of apalutamide to ADT treatment compared to ADT alone.

Figure 2: Kaplan-Meier Plot of Overall Survival (OS); Intent-to-Treat mCSPC Population (TITAN)



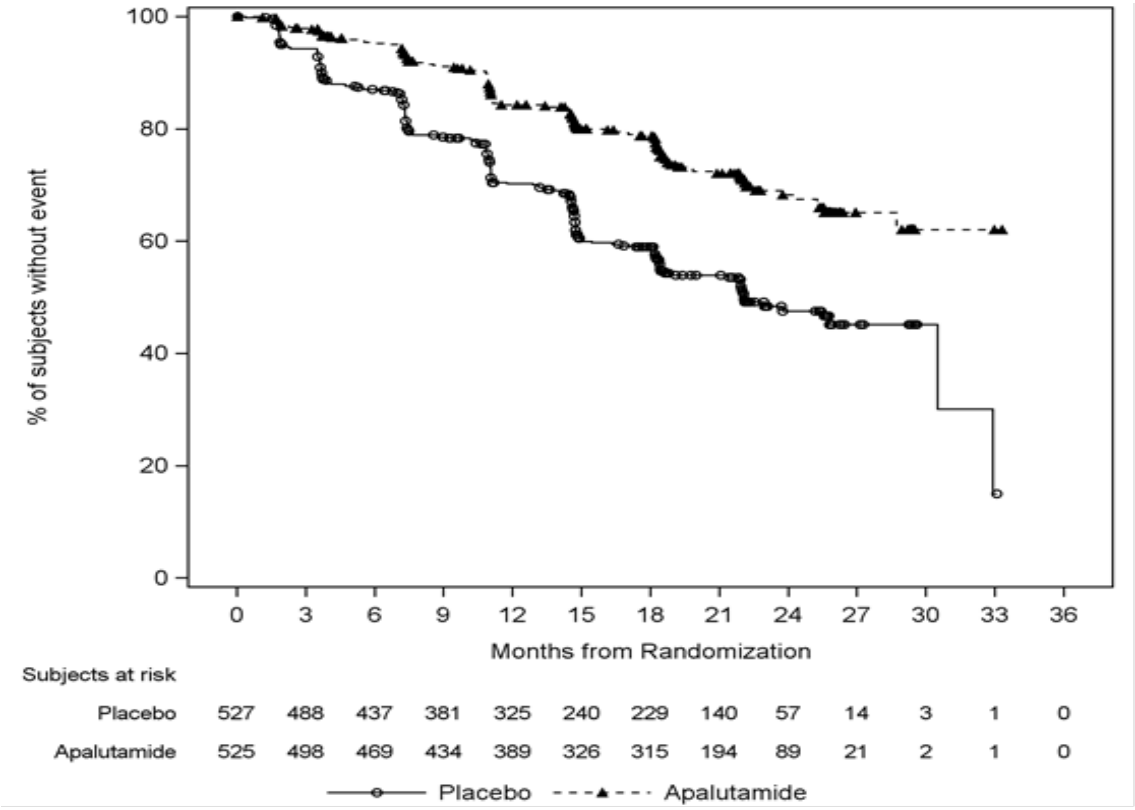
Consistent improvement in OS benefit was observed across most patient subgroups (see Forest-plot in Figure 3) including high- or low-volume disease, geographic region, Gleason score at diagnosis, and low and high risk disease.

Figure 3: Forest Plot of Overall Survival Defined by Baseline Clinical Disease Characteristics Intent-to-Treat Population (TITAN)



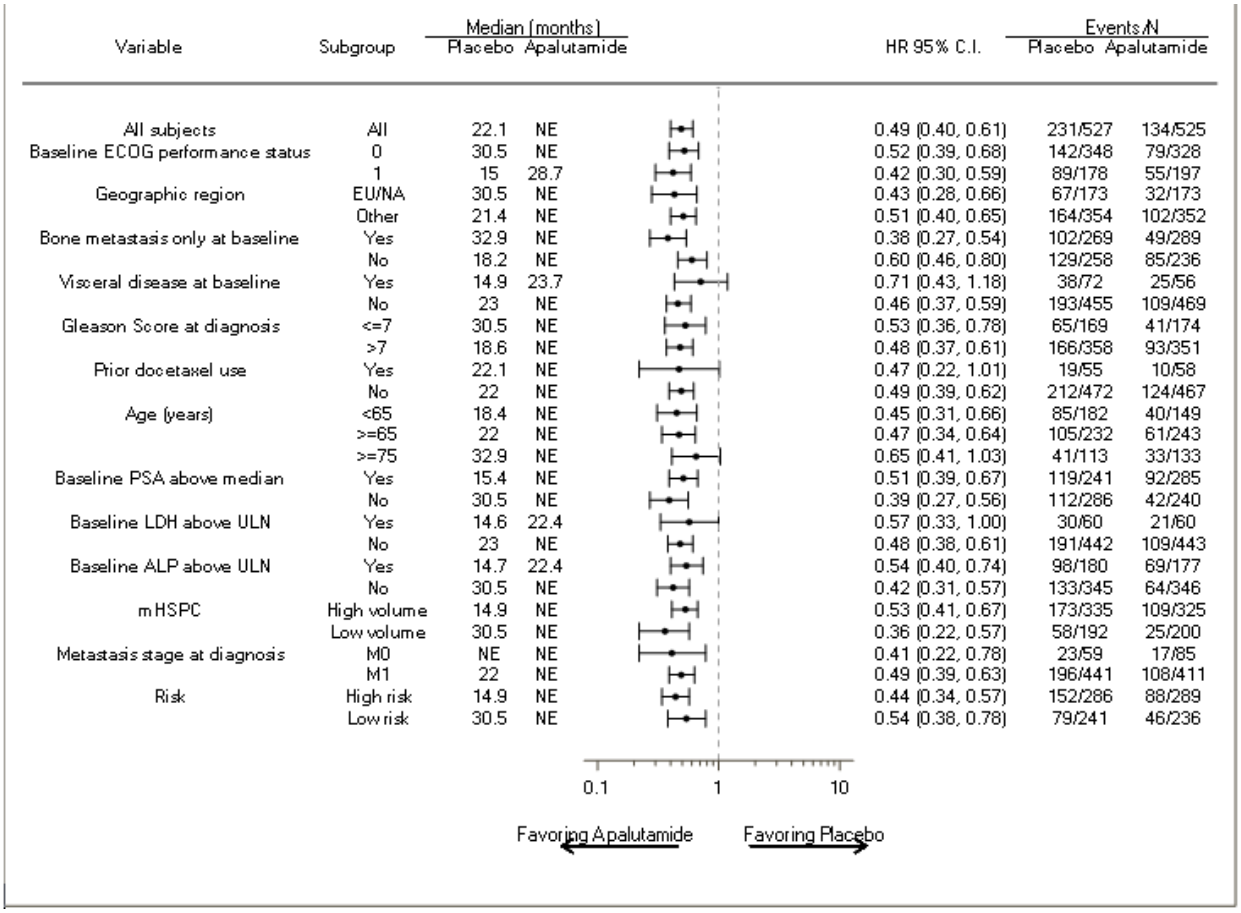
The Kaplan Meier plot (Figure 4) demonstrates the rPFS benefit of the addition of apalutamide to ADT treatment as compared to ADT alone.

Figure 4: Kaplan-Meier Plot of Radiographic Progression-Free Survival (rPFS); Intent-to-Treat mCSPC Population (TITAN)



Consistent improvement in rPFS was observed across all analyzed subgroups, including high and low volume disease, geographic regions, low-risk and high-risk disease, prior docetaxel use, and Gleason score at diagnosis (see Forest-plot in Figure 5)

Figure 5: Forest Plot of Radiographic Progression-Free Survival Defined by Baseline Clinical Disease Characteristics Intent-to-Treat Population (TITAN)



Prespecified key secondary endpoints:
Treatment with ERLEADA led to a statistically significant delay in the initiation of cytotoxic chemotherapy (HR=0.39, 95% CI: 0.27-0.56; p<0.0001).

At the time of the interim analysis, time to pain progression did not reach prespecified statistical significance. Due to the hierarchical testing scheme of the secondary endpoints, time to chronic opioid use and time to skeletal related events could not be formally analyzed.

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

14.3 Trial Design and Study Demographics

In a multicenter, double-blind, placebo-controlled clinical trial (SPARTAN) a total of 1207 patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC) were randomized 2:1 to receive either ERLEADA® orally at a dose of 240 mg once daily in combination with Androgen Deprivation Therapy (ADT, gonadotropin-releasing hormone analog or bilateral orchiectomy) or placebo with ADT.

Patients randomized to either arm were to continue treatment until disease progression assessed by blinded central imaging review (BICR), initiation of new treatment, unacceptable

toxicity or withdrawal. Prostate Specific Antigen (PSA) results were blinded and were not used for treatment discontinuation.

Eligible patients enrolled were confirmed to be non-metastatic by conventional scans (computerized tomography (CT) scan, magnetic resonance imaging (MRI) and technetium-99m bone scan) assessed by BICR. All patients enrolled had a PSA Doubling Time (PSADT) ≤ 10 months, considered to be at high risk of developing metastases.

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, 5.6% Black, 12% Asian, and 0.2% Other. Seventy-seven percent (77%) of patients in both treatment arms had prior surgery or radiotherapy of the prostate. Seventy-three percent (73%) of patients received prior treatment with a first-generation anti-androgen; 69% of patients received bicalutamide and 10% of patients received flutamide. Patients with prior treatment with abiraterone, ketoconazole or enzalutamide were excluded. Systemic corticosteroids were not allowed at study entry.

The summary of key baseline disease characteristics is provided in Table 10 below.

Table 10: Key Baseline Disease Characteristics; Intent-to-Treat Population (SPARTAN)

	ERLEADA®	Placebo
ITT Population	806	401
Time from initial diagnosis to randomization (years)		
N	806	400
Median (range)	7.95 (0.3; 30.4)	7.85 (0.8; 26.3)
Gleason score at initial diagnosis		
N	784	387
<7	19.4%	18.6%
7	37.1%	37.7%
3+4	20.0%	16.8%
4+3	15.9%	19.9%
>7	43.5%	43.7%
IVRS PSA Doubling Time (months)		
N	806	401
≤ 6 months	72.1%	71.6%
>6 months	27.9%	28.4%
Median (range)	4.40 (0.8; 10.0)	4.50 (0.7; 10.0)
PSA (ng/mL) at study entry (N)		
N	806	401
Mean (SD)	14.90 (22.5)	15.93 (23.8)
Median	7.78	7.96
Range	0.1, 294.8	1.1, 291.8
Loco-regional disease at study entry (N)		
N	806	401
N0	76.6%	77.3%
N1	23.4%	22.7%
ECOG Performance Status Score		
N	806	400
0	77.3%	77.8%
1	22.7%	22.3%

Table 10: Key Baseline Disease Characteristics; Intent-to-Treat Population (SPARTAN)		
	ERLEADA®	Placebo
Bone-sparing Agent Use	806	401
Yes	9.6%	9.7%
No	90.4%	90.3%

14.4 Study Results (SPARTAN: nmCRPC)

The primary endpoint was Metastasis-Free Survival (MFS), defined as the time from randomization to the time of first evidence of BICR-confirmed bone or soft tissue distant metastasis or death due to any cause, whichever occurred first. The median treatment duration for the primary analysis was 17 months in the ERLEADA arm and 11 months in the placebo (ADT alone) arm. The median treatment duration for the final analysis was 33 months in the ERLEADA® arm and 12 months in the placebo (ADT alone) arm.

At the primary analysis, treatment with ERLEADA® plus ADT significantly improved MFS over ADT alone. ERLEADA® decreased the risk of distant metastasis or death by 70%. The median MFS for ERLEADA® was 41 months and was 16 months for placebo (Table 11, Figure 6).

The primary endpoint (MFS) was supported by significant improvements in patients treated with ERLEADA over those treated with ADT alone for the key secondary endpoints of time to metastasis (TTM), progression-free survival (PFS), time to symptomatic progression (TTSP), overall survival (OS) and time to initiation of cytotoxic chemotherapy (TTICC) (Table 11).

The final analysis of OS and TTICC was conducted 32 months after the primary analysis of MFS, TTM, PFS and TTSP. At the time of primary analysis, patients treated with ADT alone were given the opportunity to cross-over to treatment with ERLEADA® at the time of unblinding. After unblinding, 19% of the randomized placebo population crossed over to ERLEADA®.

Patients who had crossed over had a median treatment duration of 26 months with ERLEADA® treatment.

Table 11: Summary of Efficacy Results in the ITT Population (Study SPARTAN)

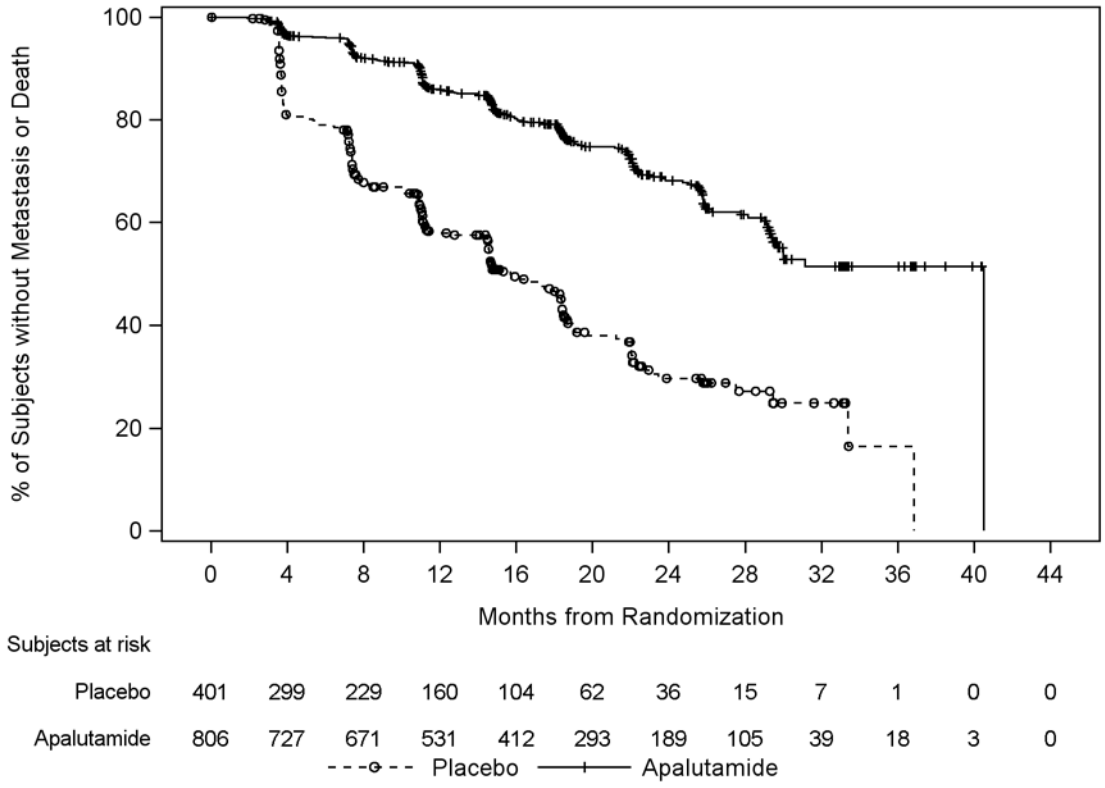
Endpoint	Number of Events (%)		Median [Months (95% CI)]		HR (95% CI) p-value (log-rank test)[a]
	ERLEADA® +ADT (N=806)	Placebo +ADT (N=401)	ERLEADA® +ADT	Placebo+ ADT	
Primary Endpoint					
Metastasis Free Survival (MFS)[b]	209 (25.9%)	210 (52.4%)	40.51 (29.70, 40.51)	15.70 (14.55, 18.40)	0.30 (0.24, 0.36) <0.0001
Key Secondary Efficacy Endpoints					
Time to Metastasis (TTM)[b,c]	188 (23.3%)	204 (50.9%)	40.51 (31.15, 40.51)	15.70 (14.55, 18.40)	0.28 (0.23,0.34) <0.0001
Progression-Free Survival (PFS)[b,d]	220 (27.3%)	219(54.6%)	40.51 (29.40, 40.51)	14.65 (11.27, 17.97)	0.30 (0.25, 0.36) <0.0001
Time to Symptomatic Progression (TTSP)[e]	63 (16%)	64 (8%)	NE (NE,NE)	NE (NE, NE)	0.45 (0.315-0.634)<0.0001

Endpoint	Number of Events (%)		Median [Months (95% CI)]		HR (95% CI) p-value (log-rank test)[a]
	ERLEADA® +ADT (N=806)	Placebo +ADT (N=401)	ERLEADA® +ADT	Placebo+ ADT	
Overall Survival (OS)	274 (34%)	154 (38%)	73.86 (61.2,NE)	59.89 (52.80, NE)	0.78 (0.64-0.96) 0.0161
Time to Initiation of Cytotoxic Chemotherapy(TTICC)[f]	155 (19%)	103 (26%)	NE (NE,NE)	NE (NE, NE)	0.44 (0.29-0.66) <0.0001

[a] All analyses stratified by PSA doubling time, bone-sparing agent use, and locoregional disease status.
[b] Determined using Ex-US Censoring rules,
[c] Time to Metastasis was defined as the time from randomization to the time of first evidence of BICR-confirmed radiographically detectable metastasis
[d] Progression free survival was defined as the time from randomization to the time of first evidence of BICR-confirmed radiographic progressive disease or death due to any cause (whichever occurs first)
[e] Time to symptomatic progression was defined as the time from randomization to development of either a skeletal-related event, pain progression or surgical intervention/radiation therapy
[f] Time to initiation of cytotoxic chemotherapy was defined as time from randomization to start of a new cytotoxic chemotherapy

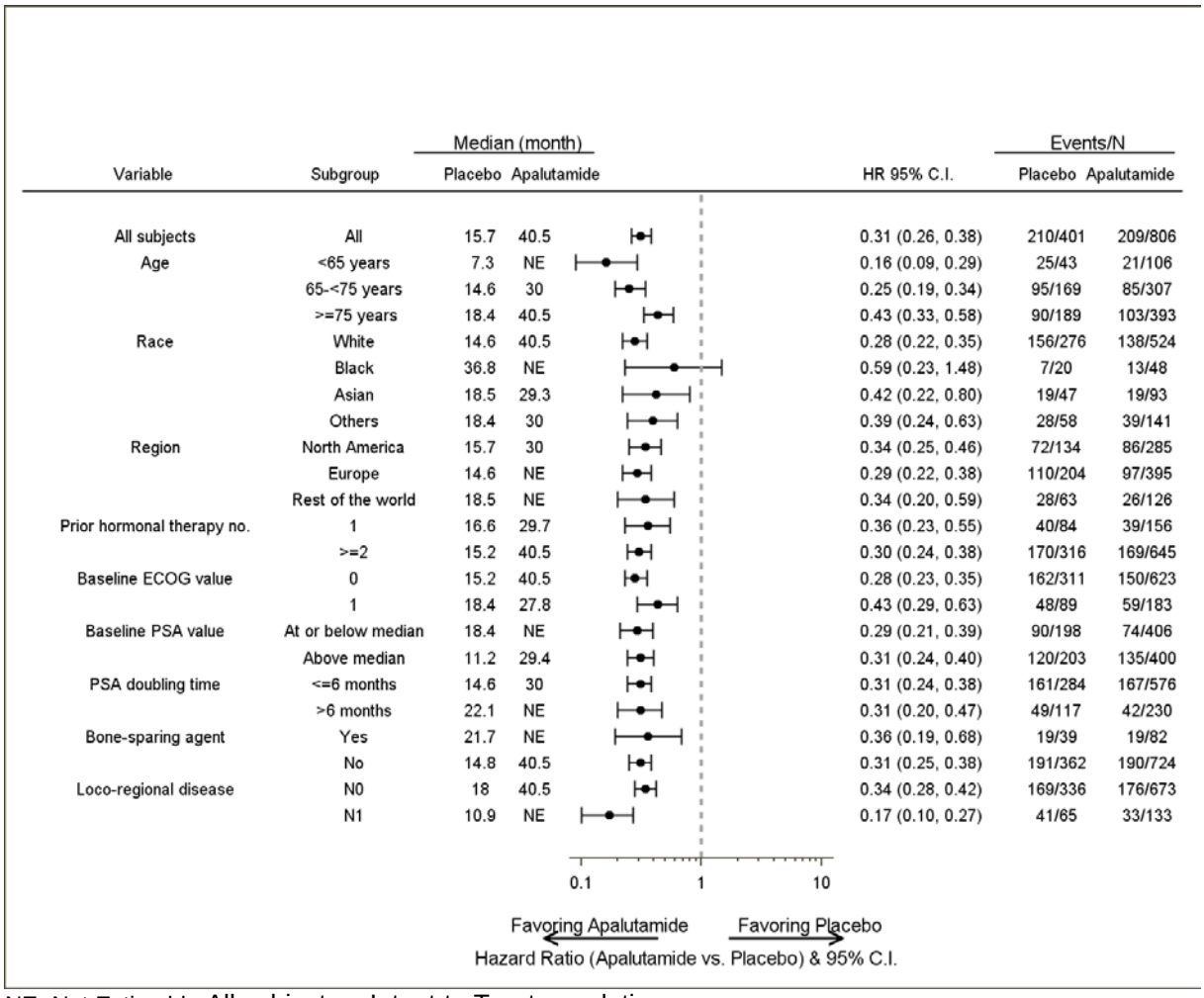
NE=Not Estimable

Figure 6: Kaplan-Meier Plot of Blinded Independent Central Review (BICR) Metastasis-Free Survival (MFS); Intent-to-treat Population (Study SPARTAN) (Ex-US Censoring rules)



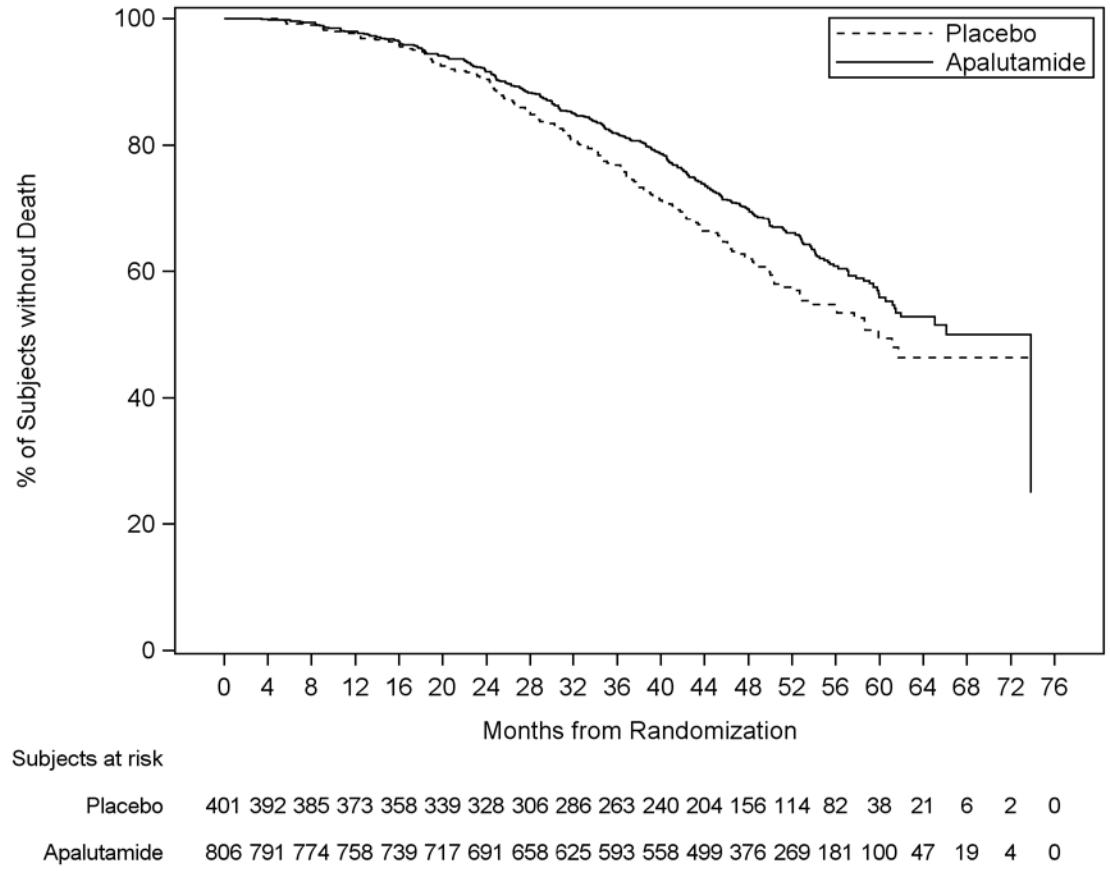
The treatment effect of ERLEADA® on MFS was favorable across all subgroups and consistent with results for the total population. The non-stratified analysis of MFS by BICR for all patients and subgroups is presented in Figure 7.

Figure 7: Forest Plot of BICR MFS by Subgroups (Non-stratified) Defined by Baseline Disease Characteristics (Study SPARTAN) (Ex-US Censoring rules)



NE=Not Estimable All subjects = Intent-to Treat population

Figure 8: Kaplan-Meier Plot of Overall Survival, Intent-to-treat Population (Study SPARTAN)



The treatment effect of ERLEADA® on OS was favorable (Figure 8) and consistent across all subgroups for the total population.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Repeat-dose toxicity studies were conducted in rats (up to 26 weeks) and dogs (up to 39 weeks). Most toxicities were related to apalutamide interference with androgen signaling and affected the male and female reproductive system, mammary glands, pituitary gland, adrenal glands and/or thymus at ≥ 25 mg/kg/day in rats (≥0.5 times the human exposure based on AUC) and/or at ≥ 2.5 mg/kg/day in dogs (≥0.5 times the human exposure based on AUC).

Seizures/convulsions were observed in male dogs at ≥ 25 mg/kg/day (≥ 5 and 3 times human exposure to apalutamide and N-desmethyl apalutamide, respectively, based on C_{max}) and considered to be mediated by off-target inhibition of $GABA_A$ current by both apalutamide and

metabolite N-desmethyl apalutamide. In vitro, apalutamide and N-desmethyl apalutamide inhibited ligand binding to the $GABA_A$-gated chloride channel with IC50 values of 3.0 and 3.2μM, respectively. In a tissue-based functional assay for the $GABA_A$ receptor, an apalutamide IC50 of 0.88 μM was determined. Distribution of apalutamide and N-desmethyl apalutamide to brain was demonstrated in mice, rats and dogs.

Hepatocellular and thyroid hypertrophy, related to hepatic enzyme induction, were observed in rats, and bile duct/oval cell hyperplasia was observed in the liver in male dogs with concomitant increases in serum alkaline phosphatase (ALP) at doses ≥0.5 times the human dose based on AUC comparison.

Carcinogenesis, Mutagenesis
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of apalutamide. Apalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either in vitro chromosome aberration test in human lymphocytes, the in vivo rat micronucleus assay or the in vivo rat Comet assay.

Reproductive and Developmental Toxicology
Male fertility is likely to be impaired by treatment with apalutamide based on findings in repeat-dose and fertility studies which were consistent with the pharmacological activity of apalutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), atrophy, aspermia/hypospermia, degeneration and/or hyperplasia or hypertrophy in the reproductive system were observed at ≥ 25 mg/kg/day in rats (≥0.5 times the human exposure based on AUC) and ≥ 2.5 mg/kg/day in dogs (≥0.5 times the human exposure based on AUC).

In a fertility study, male rats were given apalutamide for 4 weeks prior to mating. A decrease in sperm concentration and motility, copulation and fertility rates (upon pairing with untreated females) along with reduced weights of the secondary sex glands and epididymis were observed at ≥ 25 mg/kg/day (≥0.5 times human exposure based on AUC). A reduced number of live fetuses, as a result of increased pre- and/or post-implantation losses in pregnant females, were observed at 150 mg/kg/day (2 times human exposure based on AUC). Effects on male rats were reversible after 8 weeks from the last apalutamide administration.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]ERLEADA®
apalutamide tablets

Read this carefully before you start taking **ERLEADA®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ERLEADA®**.

What is ERLEADA® used for?

ERLEADA® is used to treat prostate cancer that

- has spread to other parts of the body and still responds to a medicine or surgery that lowers testosterone
- has not spread to other parts of the body, and no longer responds to a medicine or surgery that lowers testosterone.

ERLEADA® has not been studied in patients with low risk of the cancer spreading to other parts of the body. Talk to your healthcare professional if you have questions about this.

How does ERLEADA® work?

ERLEADA® contains apalutamide. Apalutamide blocks the activity of androgens (hormones like testosterone) to slow the spread of your prostate cancer and the start of your disease symptoms.

What are the ingredients in ERLEADA®?

Medicinal ingredients: apalutamide
Non-medicinal ingredients: colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl methylcellulose-acetate succinate, iron oxide black, iron oxide yellow, magnesium stearate, microcrystalline cellulose, microcrystalline cellulose (silicified), polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

ERLEADA® comes in the following dosage forms:

tablet, 60 mg

Do not use ERLEADA® if:

- you are allergic to apalutamide or to any ingredient in the medicine, including any non-medicinal ingredient, or component of the container.
- you are pregnant or can get pregnant. ERLEADA® may harm your unborn baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ERLEADA®. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure, high blood sugar levels or high levels of fat in your blood (called dyslipidemia).
- have a history of heart disease including a known history of an abnormal electrical signal called “QT interval prolongation”. Your healthcare professional will monitor you for signs of heart disease during treatment with ERLEADA®.

- have a risk of falls or broken bones. Your healthcare professional will monitor your risks for falls and broken bones during treatment with ERLEADA®.
- have a history of seizures, brain injury, stroke, or brain tumors (non-cancerous or cancerous). Your healthcare professional will monitor you for signs of brain problems (stroke or mini-stroke) during treatment with ERLEADA®.
- have a partner who is pregnant or may become pregnant.
    - ERLEADA® can harm your unborn baby or can make your partner lose the baby. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after the last dose.
    - If your sexual partner may become pregnant, a condom and another form of highly effective birth control must be used during and for 3 months after treatment. Talk with your healthcare professional if you have questions about birth control. If your sexual partner becomes pregnant while you are taking ERLEADA®, tell your healthcare professional right away.
- You must not donate sperm during your treatment and for 3 months after your last dose of ERLEADA®.

Other warnings you should know about:

Women, infants, and children: ERLEADA® is not for use in women and children.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

- You should not start; or stop; any other medications that you take, before you talk with the healthcare professional who prescribed ERLEADA®.

The following may interact with ERLEADA®:
- Gemfibrozil, used to treat high fat levels in the blood
- Itraconazole, ketoconazole, used to treat fungal infections
- Midazolam, used to treat anxiety
- Omeprazole, used to treat gastroesophageal reflux disease (conditions where there is too much acid in the stomach)
- Warfarin, used to prevent blood clots
- Fexofenadine, used to treat allergies
- Rosuvastatin, used lower cholesterol levels
- Levothyroxine, used to treat thyroid conditions

How to take ERLEADA®:
- Take exactly as your healthcare professional tells you.
- Take at about the same time once a day.
- Swallow tablets whole.
- Take ERLEADA® with or without food.

If you have trouble swallowing the tablets whole:
1. Place your dose of ERLEADA® tablets in a container that contains 4 ounces (120 mL) of applesauce and stir the whole tablets. **Do not crush the tablets**.
2. Wait 15 minutes and stir the mixture again.
3. Wait another 15 minutes and stir the mixture again. Continue stirring until tablets are well mixed with no chunks remaining.

4. Swallow the mixture right away using a spoon.
5. Rinse the container with 2 ounces (60 mL) of water and drink the water mixture.
6. Repeat the rinse with 2 ounces (60 mL) of water one more time to make sure 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 in applesauce.

Usual Adult dose: 240 mg (four 60 mg tablets) once a day.

- Your healthcare professional may change your ERLEADA® dose if needed.
- Do not stop taking your ERLEADA® without talking to your healthcare professional first.

You should start or continue a gonadotropin-releasing hormone (GnRH) analog therapy during your treatment with ERLEADA® unless you had surgical castration. This is a surgery to remove your testicles to lower the amount of testosterone in your body.

Overdose:

If you think you have taken too much ERLEADA®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of ERLEADA®, take your normal dose as soon as possible on the same day. Go back to your regular schedule on the following day. You should not take extra tablets to make up the missed dose.

What are possible side effects from using ERLEADA®?
These are not all the possible side effects which you may feel when taking ERLEADA®. If you experience these or any side effects not listed here, contact your healthcare professional.

Side effects of ERLEADA® include:
- feeling tired
- high blood pressure
- skin rash
- itching
- diarrhea
- nausea
- decreased appetite
- changes in the way things taste
- underactive thyroid gland (symptoms may include unexplained weight gain, dry skin, hair loss, hoarseness, constipation, fatigue, joint pain, muscle weakness, puffy face, feeling cold, heavier than normal or irregular menstrual periods)
- weight loss
- joint pain
- muscle spasm
- falls
- hot flash
- swelling in hands, ankles or feet

ERLEADA® can cause abnormal blood test results. Your healthcare professional may do blood tests to check for side effects. Tell your healthcare professional if you have any side effect that bothers you or that does not go away.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Fracture (broken bone)		✓	
COMMON			
Cardiac problems (including heart attack, heart disease, heart failure): pressure or pain in your chest or arms that may spread to neck, jaw or back, chest pain or discomfort or shortness of breath at rest or with activity, changes in heart rate, dizziness or lightheadedness, nausea			✓
Stroke or mini-stroke (bleeding or blood clot in the brain): Sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body; sudden confusion, difficulty speaking or understanding others, sudden difficulty in walking or loss of balance or coordination, suddenly feeling dizzy or sudden severe headache with no known cause.			✓
RARE			
Seizure (convulsion)**:** muscle twitching, changes in emotions, confusion, loss of consciousness with uncontrollable shaking			✓
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (severe skin reactions): Redness, blistering and/or peeling of large areas of the skin and/or inside of the lips,			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			
VERY RARE			
Interstitial lung disease (disorders that inflame or scar the lung tissue): Respiratory symptoms such as shortness of breath at rest or aggravated by effort, dry cough			✓
QT prolongation (an abnormal heart electrical signal): irregular heartbeat, dizziness, fainting, loss of consciousness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store ERLEADA® at 15°C to 30°C, in the original package to protect from light and moisture.
- If your ERLEADA® tablets are provided to you in a bottle, the bottle contains silica gel desiccant to help keep your medication dry. Do not remove desiccant from the bottle.

Keep out of reach and sight of children.

Do not use ERLEADA® after the expiry date which is stated on the label. The expiry date refers to the last day of the month.

Proper disposal:
Medicines should not be discarded in the toilet or household garbage. Follow your local rules for discarding unused medicine. If you are not sure, ask your pharmacist how to throw away medicines you no longer need. This will help to protect the environment.

If you want more information about ERLEADA®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html);
- For questions, concerns, or the full Product Monograph go to: www.janssen.com/canada or contact the manufacturer, Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc.
Toronto, Ontario M3C 1L9

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