PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ERLEADA™

apalutamide tablets

tablet, 60 mg, oral

ATC Code: L02BB05

Anti-androgen

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Date of Preparation:
July 3, 2018

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Submission Control No: 211942

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

ERLEADA™ has not been studied in patients with NM-CRPC 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 effectiveness of ERLEADA™ in children have not been evaluated.

1.2 Geriatrics (> 65 years of age)

No overall differences in effectiveness were observed between geriatric patients and younger patients. (see **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 DOSAGE AND ADMINISTRATION

3.1 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.

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 to 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 effectiveness of ERLEADA™ in pediatric patients have not been evaluated.

Geriatrics ≥65 years of age): No dose adjustment is necessary for elderly patients. Patients ≥ 65 years treated with ERLEADA™ experienced higher toxicity and lower tolerance in SPARTAN (see **WARNINGS AND PRECAUTIONS, Geriatrics**). In SPARTAN, treatment discontinuation due to adverse events was reported in 12% of patients ≥ 65 years and 2.8% of those < 65 years. 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**).

3.2 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.

4 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.

5 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 or in a blister package of 56 tablets. Each bottle contains silica gel desiccant.

6 WARNINGS AND PRECAUTIONS

Cardiovascular

Cardiac disorders

In SPARTAN, higher incidences of ischemic heart disease and cardiac failure were reported in patients treated with ERLEADA™ (see **ADVERSE REACTIONS**). 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, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias were excluded from the SPARTAN clinical trial. Patients with a cardiac history should be assessed for active cardiac disease before starting therapy with ERLEADA™.

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 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.

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.

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 weight bearing bones (see **Clinical Trials Adverse Drug Reactions**, Table 2 footnote). Falls were not associated with loss of consciousness or seizure. 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.

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

Seizures

Permanently discontinue ERLEADA™ in patients who develop a seizure during treatment.

In SPARTAN, two patients (0.2%) treated with ERLEADA™ experienced a seizure. Patients with a history of seizure or predisposing factors for seizure were excluded from 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™ may be harmful to a developing fetus and has potential to increase risk for 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**).

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 starting 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.

6.1 Special Populations

6.1.1 Pregnant Women

ERLEADA™ is contraindicated in women who are or may become pregnant (see **CONTRAINDICATIONS**). Based on its mechanism of action, ERLEADA™ may 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™.

6.1.2 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.

6.1.3 Pediatrics

Safety and effectiveness of ERLEADA™ in pediatric patients have not been evaluated. There is no relevant use of ERLEADA™ in pediatric patients aged 17 years and younger.

6.1.4 Geriatrics

Of the 803 patients who received ERLEADA™ in SPARTAN, 87% of patients were 65 years and over and 49% were 75 years and over. In patients ≥ 65 years, Grade 3-4 adverse reactions occurred in 46% of patients treated with ERLEADA and 35% of patients treated with placebo. In patients ≥ 75 years, Grade 3-4 adverse reactions occurred in 51% of patients treated with ERLEADA and in 37% of patients treated with placebo. No overall differences in effectiveness were observed between these patients and younger patients.

7 ADVERSE REACTIONS

7.1 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 (NM-CRPC), (see **CLINICAL TRIALS**).

7.2 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.

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. 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. At the time of the analysis, 61% of patients were still on ERLEADA™ and 30% of patients were still on placebo.

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 11 (1.4%) patients in the ERLEADA™ arm and 2 patients (0.5%) in the placebo arm. The causes of death in the ERLEADA™ arm were infection (n = 6: sepsis or pneumonia), myocardial infarction (n = 3), and one case each of cerebral hemorrhage and cerebrovascular accident.

Treatment discontinuations due to adverse events were reported for 11% of patients treated with ERLEADA™ and 7% of patients treated with placebo. Adverse events leading to dose interruption were reported for 30% of patients treated with ERLEADA™ and 18% treated with placebo. Dose reduction due to adverse events was reported for 9.6% of patients treated with ERLEADA™ and 1.8% of patients treated with placebo. The most frequently reported adverse events led to dose modifications were rash and fatigue.

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

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 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	20.3	1.0	15.1	0.5
Nausea	18.1	0	15.8	0
General disorders and administration site Conditions				
Fatigue[1,6]	39.0	1.4	27.6	0.3
Injury, poisoning and procedural complications				
Fall[6]	15.6	1.7	9.0	0.8
Fracture[2]	11.7	2.7	6.5	0.8
Investigations				
Weight decreased[6]	16.1	1.1	6.3	0.3
Metabolism and nutrition disorders				
Decreased appetite[3]	12.3	0.1	9.3	0
Peripheral edema[4]	10.7	0	8.5	0
Musculoskeletal and connective tissue disorders				
Arthralgia[6]	15.9	0	7.5	0
Skin and subcutaneous tissue disorders				
Rash[5]	23.8	5.2	5.5	0.3
Vascular disorders				
Hypertension	24.8	14.3	19.8	11.8
Hot flush	14.1	0	8.5	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, and rash vesicular

6 Grade 4 definitions do not exist for these reactions

Rash

In SPARTAN, rash associated with ERLEADA™ was most commonly described as macular or maculo-papular. Adverse events of rash were reported for 24% of patients treated with ERLEADA™ versus 5.5% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA™ treatment (5.2%) versus placebo (0.3%). There were no reported events of toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) at the time of the safety analysis.

The onset of rash occurred at a median of 82 days of ERLEADA™ treatment and resolved within a median of 60 days from onset of rash for 81% of patients. Medications utilized to treat rash included topical corticosteroids, systemic corticosteroids and oral anti-histamines. Among patients with skin rash, dose interruption occurred in 28%, dose reduction occurred in 12% and discontinuation in 9% of patients (see **DOSAGE AND ADMINISTRATION**). Rash recurred in

approximately half of patients who were re-challenged, with no serious allergic reactions.

Hypothyroidism
Hypothyroidism was reported for 8.1% of patients treated with ERLEADA™ and 2.0% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. There were no grade 3 or 4 adverse events. Hypothyroidism occurred in 28% of patients already receiving thyroid replacement therapy in the ERLEADA™ arm and in 5.9% of patients in the placebo arm. In patients not receiving thyroid replacement therapy, hypothyroidism occurred in 5.7% of patients treated with ERLEADA™ and in 0.8% of patients treated with placebo. The median onset was day 113. 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**).

7.3 Less Common Clinical Trial Adverse Reactions

The following are selected clinically significant adverse reactions reported in less than 10% of patients receiving ERLEADA™ and with higher incidences reported than the placebo arm.

Cardiac disorders: ischemic heart disease (3.7% versus 2% on placebo), heart failure (2.2% versus 1% on placebo)
Endocrine disorders: Hypothyroidism (8.1% vs 2.0% on placebo)
Nervous system disorders: Seizure (0.2%)
Skin and subcutaneous tissue disorders: Pruritis (6.2% vs 2.0% on placebo)

7.4 Abnormal Laboratory Findings: Hematologic and Clinical Chemistry

Table 3 shows laboratory abnormalities in the SPARTAN study.

Table 3: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA™-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN

	ERLEADA N=803		Placebo N=398	
Laboratory Abnormality	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

8 DRUG INTERACTIONS

8.1 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-gp but not BCRP, 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-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (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).

8.2 Drug-Drug Interactions

The drugs listed in Table 4 below are based on either drug interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 4: 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**).

Drug Common name	Source of Evidence	Effect	Clinical comment
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**).
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:			

Drug Common name	Source of Evidence	Effect	Clinical comment
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)

8.3 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.

8.4 Drug-Herb Interactions

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

8.5 Drug-Laboratory Test Interactions

No Drug-Laboratory Test Interactions have been identified.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 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.

9.2 Pharmacodynamics

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**)

9.3 Pharmacokinetics

Table 5: 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 t_{max} was delayed about 2 hours with food (see **DOSAGE AND ADMINISTRATION**).

Absorption:
After oral administration, median time to achieve peak plasma concentration (t_{max}) was 2 hours. Mean absolute oral bioavailability is approximately 100% in healthy subjects, indicating that apalutamide is completely absorbed after oral 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/1.73m2) or moderate renal impairment (eGFR 30-59 mL/min/1.73m2), 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 803 patients who received ERLEADA™ in SPARTAN, 77% of patients were 65 years and over and 26% were 80 years and over. 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™ may 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:
The 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.

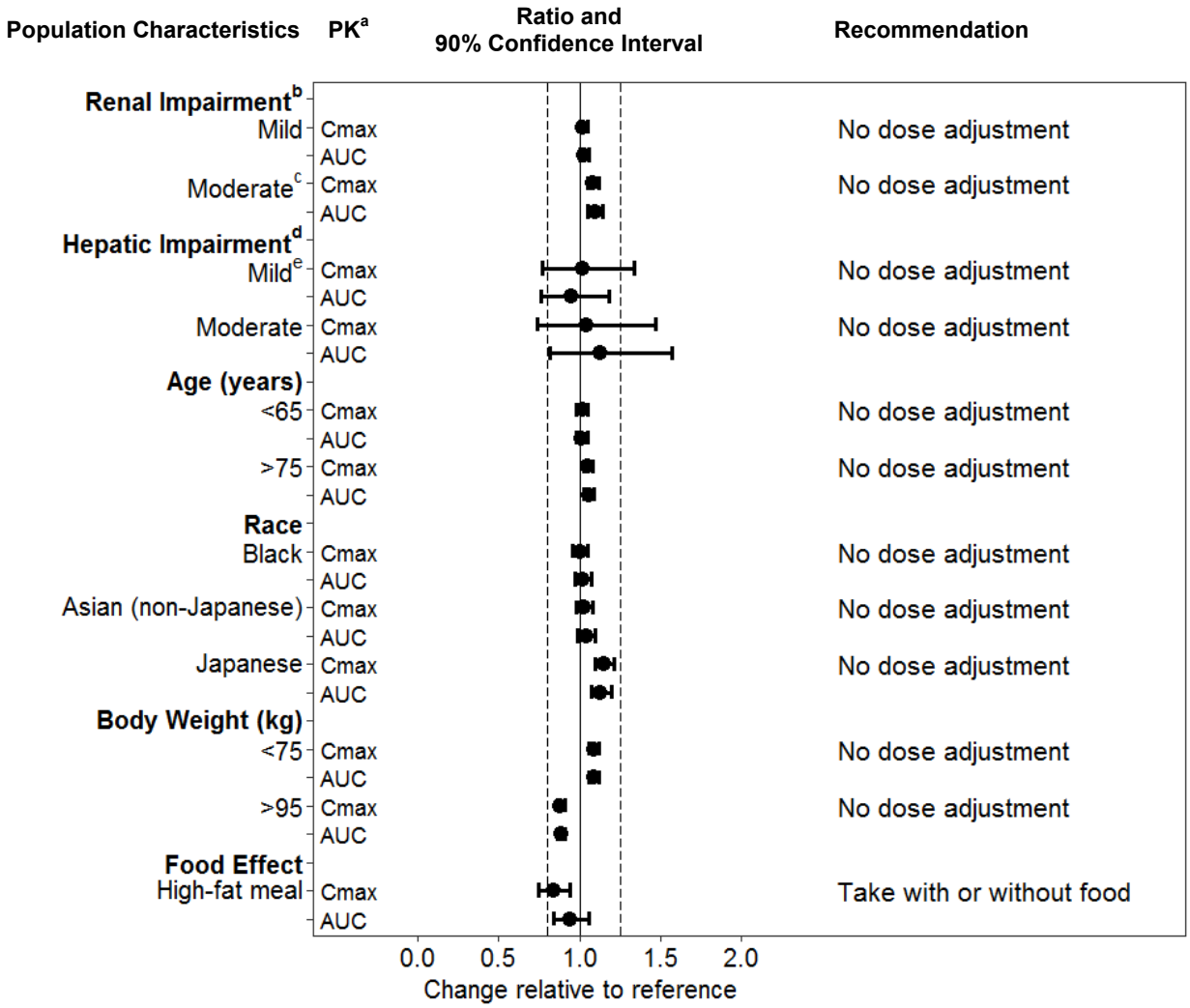
Hepatic Insufficiency:
In a dedicated Phase I hepatic impairment study systemic exposure of apalutamide and N-desmethyl apalutamide was similar in subjects with mild or moderate baseline hepatic impairment (Child-Pugh Class A or B, respectively) compared to subjects with normal hepatic function. No dosage 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

10 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.

11 SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for this product.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

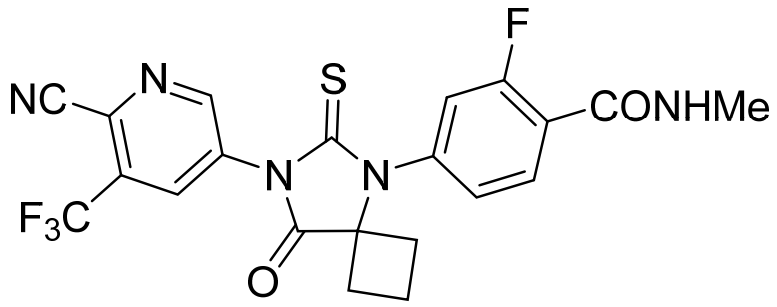
Drug Substance

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).

13 CLINICAL TRIALS

13.1 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 of 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 6 below.

Table 6: 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%
Bone-sparing Agent Use	806	401
Yes	9.6%	9.7%
No	90.4%	90.3%

13.2 Study Results

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. 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 7, Figure 2).

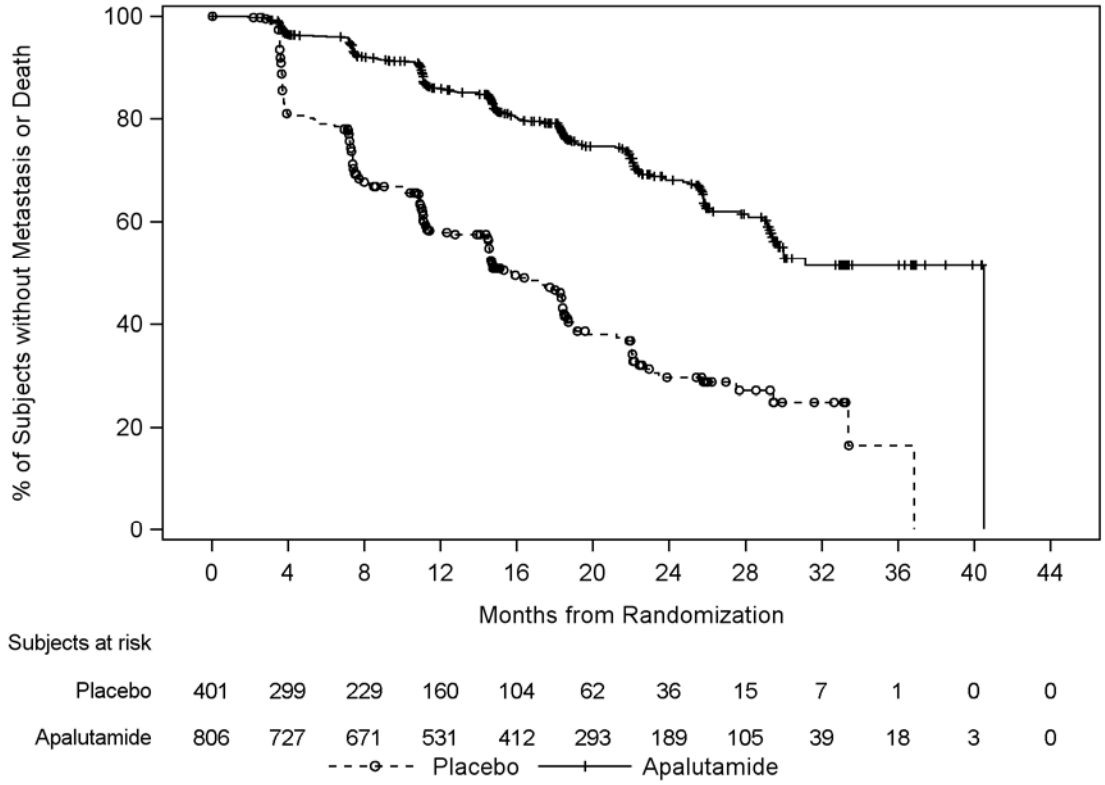
As of the clinical cut-off date of 19 May 2017 for this analysis, 61% of patients in the ERLEADA™ arm and 30% of patients in the placebo arm were continuing study treatment. The median treatment duration was 16.9 months in the ERLEADA™ arm and 11.2 months in the placebo arm.

Table 7: Summary Results of Primary and Secondary Endpoints by BICR 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	
Metastasis Free Survival[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
Time to Metastasis[b]	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[b]	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	64 (7.9%)	63 (15.7%)	NE (NE, NE)	NE (36.83, NE)	0.45 (0.32,0.63) <.0001[b]

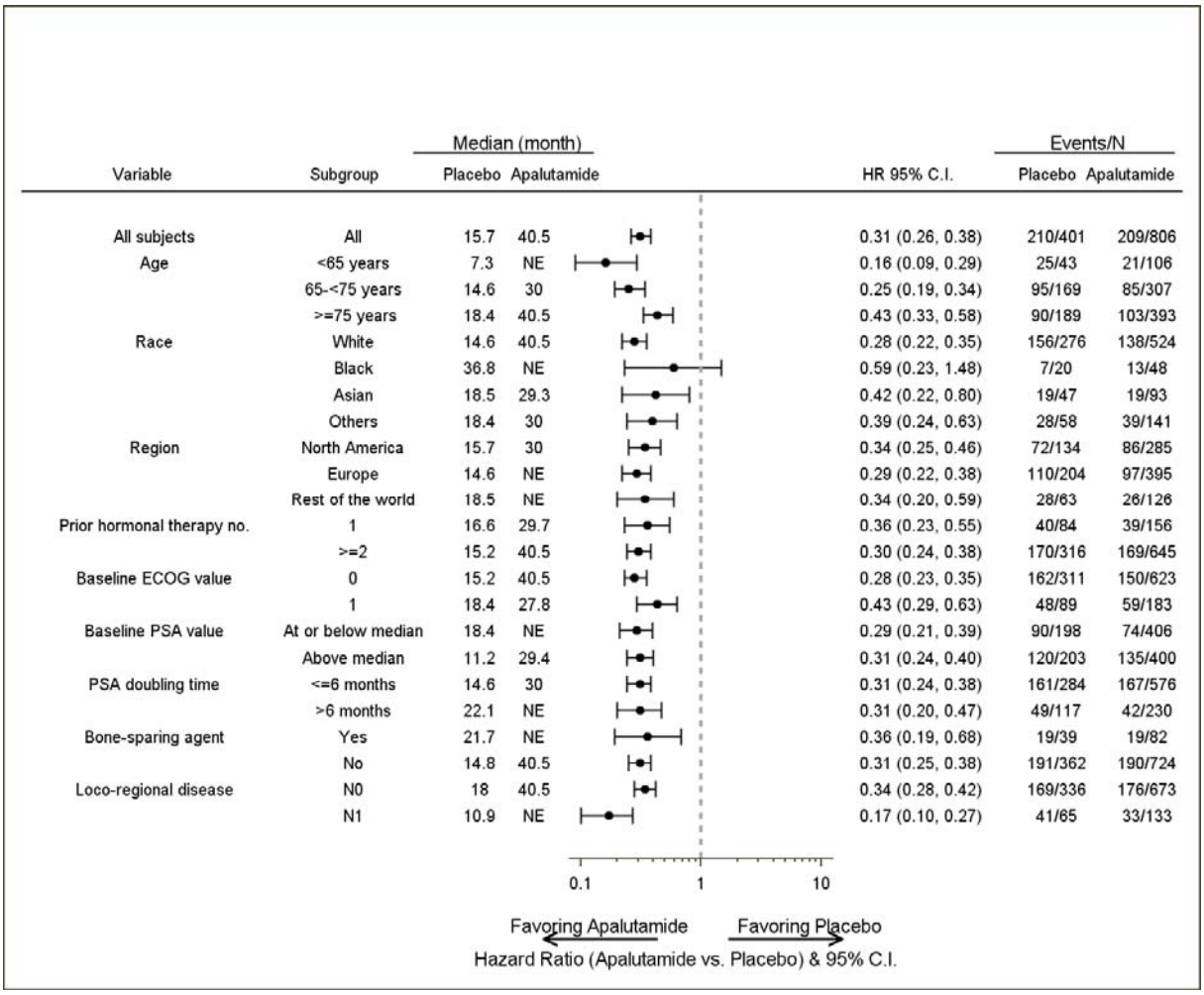
[a] All analyses stratified by PSA doubling time, bone-sparing agent use, and locoregional disease status.
[b] Determined using Ex-US Censoring rules
NE=Not Estimable

Figure 2: 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 3.

Figure 3: Forest Plot of BICR MFS by Subgroups (Non-stratified) Defined by Baseline Disease Characteristics (Study SPARTAN) (Ex-US Censoring rules)



All subjects = Intent-to Treat population

Patients treated with ERLEADA™ plus ADT showed significant improvement over those treated with ADT alone for the following secondary endpoints of time to metastasis (TTM), progression-free survival (PFS), and time to symptomatic progression. (Table 7). At the time of the analysis of MFS, overall survival (OS) data were not mature (24% of the required number of events) and the p-value did not reach the prespecified statistical significance level. Time to initiation of cytotoxic chemotherapy could not be evaluated based on the hierarchical testing scheme.

14 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 Cmax) 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 3.2 µM, 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

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 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 a history of heart disease including a known history of an abnormal electrical signal called “QT interval prolongation”
- 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)
- have a partner who is pregnant or may become pregnant. ERLEADA™ may harm your unborn baby or may 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.

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 medicine 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.

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 in order 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 you may feel when taking ERLEADA™. If you experience any side effects not listed here, contact your healthcare professional.

Side effects of ERLEADA™ include:
- feeling very tired
- high blood pressure
- skin rash
- diarrhea
- nausea
- decreased appetite
- underactive thyroid gland
- weight loss
- joint pain
- falls
- broken bones
- 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, ischemic heart disease and heart failure): pressure or pain in your chest or arms that may spread to neck, jaw or back, shortness of breath, changes in heartrate dizziness or lightheadedness, nausea			✓
RARE			✓

Seizure: muscle twitching, changes in emotions, confusion, loss of consciousness with uncontrollable shaking			
VERY RARE **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 (http://hc-sc.gc.ca/index-eng.php);

- 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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Last Revised: July 3, 2018