janssen

PRODUCT NAME
ERLEADA® (apalutamide) tablets.

DOSAGE FORMS AND STRENGTHS
ERLEADA 60 mg tablets contain 60 mg of apalutamide.
Slightly yellowish to greyish green, oblong-shaped, film-coated (FC) tablets, debossed with "AR 60" on one side.
For excipients, see *PHARMACEUTICAL INFORMATION - List of Excipients.*

CLINICAL INFORMATION
Indications
ERLEADA is indicated in adult men for the treatment of non-distant metastatic castration resistant prostate cancer (nm-CRPC) who are at high risk of developing metastatic disease.
ERLEADA is indicated for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) in combination with androgen deprivation therapy (ADT).

Dosage and Administration
For nm-CRPC, ERLEADA should only be administered to patients who:
- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, with high risk for development of metastases, defined as PSADT ≤ 10 months. PSADT is calculated using at least 3 PSA values obtained during continuous ADT;
- Castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 PSA rises at least 1 week apart, with the last PSA > 2 ng/mL;
- Surgically or medically castrated, with testosterone levels of < 50 ng/dL. If the patient is medically castrated, dosing with a GnRH analogue;
- Are absence of **distant metastases**, including central nervous system (CNS) and vertebral or meningeal involvement, or history of distant metastases (with exception: pelvic lymph nodes < 2 cm in short axis (N1) located below the iliac bifurcation are included).

Dosage
The recommended dose of ERLEADA is 240 mg (four 60 mg tablets) administered orally once daily. Swallow the tablets whole. ERLEADA can be taken with or without food.
Patients should also receive a gonadotropin-releasing hormone (GnHR) analog concurrently or should have had bilateral orchidectomy.

Alternative Method of Administration
For patients who have difficulty swallowing tablets whole, the recommended dose of ERLEADA tablets may be mixed with 4 ounces (120 mL) of applesauce. Do not crush the tablets. Stir applesauce upon introduction of whole tablets as well as at 15 minutes and 30 minutes afterwards until tablets are 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 *PHARMACOLOGICAL PROPERTIES - Pharmacokinetic Properties*).

Dose modification
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.

Missed dose(s)
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.

Special populations
Pediatrics (17 years of age and younger)
The safety and effectiveness of ERLEADA in children have not been evaluated.
There is no relevant use of ERLEADA in pediatric patients aged 17 years and younger.

Elderly (65 years of age and older)
Of the 1327 subjects who received ERLEADA in clinical studies, 19% of subjects were less than 65 years, 41% of subjects were 65 years to 74 years, and 40% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Renal impairment
A dedicated renal impairment study for ERLEADA has not been conducted. Based on the population pharmacokinetic analysis using data from clinical studies in subjects with castration-resistant prostate cancer (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 $\geq$ 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 $\leq$ 29 mL/min/1.73m^2).

Hepatic impairment
A dedicated hepatic impairment study compared the systemic exposure of apalutamide and N-desmethyl apalutamide in subjects with baseline mild or moderate hepatic impairment (Child-Pugh Class A or B, respectively) versus healthy controls with normal hepatic function. The systemic exposure of apalutamide and N-desmethyl apalutamide was similar in subjects with mild or moderate baseline hepatic impairment 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).

Administration
ERLEADA should be administered orally once daily, with or without food. Swallow the tablets whole.
ERLEADA should be prescribed by physicians experienced in the use of anti-cancer therapies.

Contraindications
ERLEADA is contraindicated in women who are or may become pregnant (*see Pregnancy, Breast-feeding and Fertility - Pregnancy*).
Patients who are hypersensitive to this drug or to any excipients.

Warnings and Precautions
Falls and fractures
Falls and fractures occurred in patients receiving ERLEADA. Patients should be evaluated for fractures and fall risk before starting ERLEADA and should continue to be monitored and managed for fractures according to established treatment guidelines and use of bone-targeted agents should be considered.
Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.
In SPARTAN, a randomized study of patients with nmCRPC, fracture was reported for 11.7% of subjects treated with ERLEADA and 6.5% of subjects treated with placebo. Half of the subjects experienced a fall within 7 days before the fracture event in both treatment groups. Falls were reported for 15.6% of subjects treated with ERLEADA versus 9.0% of subjects treated with placebo. Evaluate patients for fracture and fall risk. In TITAN, a randomized study of patients with mCSPC, nonpathological fractures occurred in 6% of patients treated with ERLEADA and in 5% of patients treated with placebo.

Ischemic heart disease and ischemic cerebrovascular disorders
Ischemic heart disease and ischemic cerebrovascular disorders, including events leading to death, occurred in patients treated with ERLEADA. Monitor for signs and symptoms of ischemic heart disease and ischemic cerebrovascular disorders. Optimize management of risk factors, such as hypertension, diabetes, or dyslipidemia.
In a randomized study SPARTAN, ischemic heart disease occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study TITAN, ischemic heart disease occurred in 4% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA and 2 patients (0.2%) treated with placebo died from ischemic heart disease.

In the SPARTAN study, with a median exposure of 32.9 months for ERLEADA and 11.5 months for placebo, ischemic cerebrovascular disorders occurred in 4% of patients treated with ERLEADA and 1% of patients treated with placebo (*see Adverse Reactions*). In the TITAN study, ischemic cerebrovascular disorders occurred in a similar proportion of patients in the ERLEADA (1.5%) and placebo (1.5%) groups. Across the SPARTAN and TITAN studies, 2 patients (0.2%) treated with ERLEADA and no patients treated with placebo died from an ischemic cerebrovascular disorder.
Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within six months of randomization were excluded from the SPARTAN and TITAN studies.

Seizure
ERLEADA is not recommended in patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, recent stroke (within one year), primary brain tumours or brain metastases. If a seizure develops during treatment with ERLEADA, treatment should be discontinued permanently. The risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold.
In two randomized studies, SPARTAN and TITAN, five subjects (0.4%) treated with ERLEADA and two subjects (0.2%) treated with placebo experienced a seizure. In these studies, subjects with a history of seizure or predisposing factors for seizure were excluded. No seizures occurred in two other studies that enrolled 145 subjects. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

Severe Cutaneous Adverse Reactions (SCAR)
Rare postmarketing cases of SCAR (including drug reaction with eosinophilia and systemic symptoms [DRESS] and Stevens Johnson syndrome/toxic epidermal necrolysis [SJS/TEN]), which can be life-threatening or may lead to death, have been reported with androgen receptor inhibitors including ERLEADA. SCAR was not reported in clinical trials TITAN and SPARTAN. Discontinue ERLEADA immediately if signs or symptoms of SCAR develop (see *Adverse Reactions – Postmarketing data*).

Interstitial Lung Disease (ILD)
Postmarketing cases of ILD, including fatal cases, have been observed in patients treated with anti androgens, including apalutamide. In case of acute onset and/or unexplained worsening of pulmonary symptoms, treatment with apalutamide should be interrupted pending further investigation of these symptoms. If ILD is diagnosed, apalutamide should be discontinued and further treatment with anti androgens should be withheld (see *Adverse Reactions – Postmarketing data*).

Concomitant use with other medicinal products
Apalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. A review of concomitant medicinal products should therefore be conducted when apalutamide treatment is initiated. Concomitant use of apalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.
Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If ERLEADA is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

Recent cardiovascular disease
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 clinical studies. Therefore, the safety of apalutamide in these patients has not been established.

Androgen deprivation therapy may prolong the QT interval
QT Prolongation: In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating Erleada.

Interactions
Medications that inhibit CYP2C8

CYP2C8 plays a role in the elimination of apalutamide and in the formation of its active metabolite. In a drug-drug interaction study, the Cmax of apalutamide decreased by 21% while AUC increased by 68% following co-administration of apalutamide 240 mg single dose with gemfibrozil (strong CYP2C8 inhibitor). For the active moieties (sum of apalutamide plus the potency adjusted active metabolite), Cmax decreased by 21% while AUC increased by 45%. No initial dose adjustment is necessary when ERLEADA is co-administered with a strong inhibitor of CYP2C8 (e.g., gemfibrozil, clopidogrel) however, a reduction of the Erleada dose based on tolerability should be considered. Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of apalutamide.

Medications that inhibit CYP3A4
CYP3A4 plays a role in the elimination of apalutamide and in the formation of its active metabolite. In a drug-drug interaction study, the C_{max} of apalutamide decreased by 22% while AUC was similar following co-administration of Erleada as a 240 mg single dose with itraconazole (strong CYP3A4 inhibitor). For the active moieties (sum of apalutamide plus the potency adjusted active metabolite), C_{max} decreased by 22% while AUC was again similar. No initial dose adjustment is necessary when Erleada is co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) however, a reduction of the Erleada dose based on tolerability should be considered. Mild or moderate inhibitors of 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. Based on the drug-drug interaction study results with strong CYP3A4 inhibitor or strong CYP2C8 inhibitor, CYP3A4 or CYP2C8 inducers are not expected to have clinically relevant effects on the pharmacokinetics of apalutamide and the active moieties therefore no dose adjustment is necessary when Erleada is co-administered with inducers of CYP3A4 or CYP2C8.

Acid lowering agents
Apalutamide is not ionizable under relevant physiological pH condition, therefore acid lowering agents (e.g. proton pump inhibitor, H_2-receptor antagonist, antacid) are not expected to affect the solubility and bioavailability of apalutamide.

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

Effect of ERLEADA on 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.
The effect of apalutamide on CYP2B6 substrates has not been evaluated in vivo and the net effect is presently unknown. When substrates of CYP2B6 (e.g., efavirenz) are administered with ERLEADA, monitoring for an adverse reaction and evaluation for loss of efficacy of the substrate should be performed and dose adjustment of the substrate may be required to maintain optimal plasma concentrations.

In humans, ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. In a drug-drug interaction study using a cocktail approach, co-administration of ERLEADA with single oral doses of sensitive CYP substrates resulted in a 92% decrease in the AUC of midazolam (CYP3A4 substrate), 85% decrease in the AUC of omeprazole (CYP2C19 substrate), and 46% decrease in the AUC of S-warfarin (CYP2C9 substrate). ERLEADA did not cause clinically meaningful changes in exposure to the CYP2C8 substrate. 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. If given with warfarin, monitor International Normalized Ratio (INR) during ERLEADA treatment.

Induction of CYP3A4 by apalutamide suggests that UDP-glucuronosyl transferase (UGT) may also be induced via activation of the nuclear pregnane X receptor (PXR). Concomitant administration of ERLEADA with medications

that are substrates of UGT can result in lower exposure to these medications. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of efficacy.

Effect of Apalutamide on drug transporters
Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. A drug-drug interaction study using a cocktail approach showed that co-administration of ERLEADA with single oral doses of sensitive transporter substrates resulted in a 30% decrease in the AUC of fexofenadine (P-gp substrate) and 41% decrease in the AUC of rosuvastatin (BCRP/OATP1B1 substrate) but had no impact on C_{max}. 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.

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.

Pregnancy, Breast-feeding and Fertility
Pregnancy
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 data available with the use of ERLEADA during pregnancy.

Contraception
ERLEADA may be harmful to a developing fetus. 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 (*see Pregnancy, Breast-feeding and Fertility - Pregnancy*).

Breast-feeding
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.
It is unknown whether apalutamide/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Erleada should not be used during breast-feeding.

Fertility
Based on animal studies, ERLEADA may impair fertility in males of reproductive potential (*see NON-CLINICAL INFORMATION*).

Effects on Ability to Drive and Use Machines
No studies on the effects of ERLEADA on the ability to drive or use machines have been performed. It is not anticipated that ERLEADA will affect the ability to drive and use machines. However, seizures have been reported in patients taking Erleada. Patients should be advised of this risk in regards to driving or operating machines.

Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of apalutamide based on the comprehensive assessment of the available adverse event information. A causal relationship with apalutamide cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Metastatic Castration -Sensitive Prostate Cancer (mCSPC)
TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral

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.

The most common adverse reactions (≥15%) reported in the randomized clinical study that occurred more commonly (≥2%) in the ERLEADA arm were arthralgia, fatigue, rash, hypertension, and hot flush.

Ten patients (2%) who were treated with ERLEADA and 16 patients (3%) treated with placebo died from adverse events (within 30 days of last dose). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%).

Table 1 shows adverse reactions on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. ARs are also listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), and rare (≥ 1/10000 to < 1/1000). Within each frequency grouping, ARs are presented in order of decreasing frequency.

Table 1: Adverse Reactions in TITAN (mCSPC)

System/Organ Class		**ERLEADA N=524**		**Placebo N=527**	
Adverse Reaction	**Frequency Category[a]**	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and administration site conditions					
Fatigue[c]	very common	19.7	1.5	16.7	1.1
Musculoskeletal and connective tissue disorders					
Arthralgia[c]	very common	17.4	0.4	14.8	0.9
Muscle spasm	Common	3.1	0	1.9	0
Skin and subcutaneous tissue disorders					
Rash[b]	very common	27.9	6.3	8.9	0.8
Pruritus	very common	10.7	0.2	4.6	0.2
Nervous system disorders					
Dysgeusia	Common	3.2	0	0.6	0
Ischemic cerebrovascular disorders[g]	Common	1.5	0.6	1.5	0.2
Seizure	Uncommon	0.6	0.2	0.4	0
Metabolism and nutrition disorders					
Hypercholesterolemia	Common	4.6	0.4	0.8	0
Hypertriglyceridemia	Common	3.4	0.6	1.3	0.4
Cardiac disorders					
Ischemic Heart Disease[d]	Common	4.4	2.3[e]	1.5	0.6[e]
Vascular disorders					
Hot flush	very common	22.7	0	16.3	0
Hypertension	very common	17.7	8.4	15.6	9.1
Gastrointestinal disorders					
Diarrhea	Common	9.4	0.2	6.1	0.2
Endocrine disorders					
Hypothyroidism[f]	Common	6.5	0	1.1	0

[a] Adverse reaction frequencies presented are based on the placebo-controlled period of the clinical study

[b] 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

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

[d] Includes angina pectoris, angina unstable, myocardial infarction, acute myocardial infarction, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, arteriosclerosis coronary artery, cardiac stress test abnormal, troponin increased, myocardial ischemia

[e] Includes Grades 3-5

[f] Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine decreased, autoimmune thyroiditis, thyroxine free decreased, tri-iodothyronine decreased

[g] Includes transient ischemic attack, cerebrovascular accident, cerebrovascular disorder, ischemic stroke, carotid arteriosclerosis, carotid artery stenosis, hemiparesis, lacunar infarction, lacunar stroke, thrombotic cerebral infarction, vascular encephalopathy, cerebellar infarction, cerebral infarction, and cerebral ischemia

At the time of final study analysis with a median treatment duration of 39 months, no new safety concerns were identified.

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)
SPARTAN, a randomized double-blind, placebo-controlled, multi-center clinical study, enrolled subjects who had nm-CRPC. In this study, subjects received ERLEADA at a dose of 240 mg daily in combination with androgen deprivation therapy (ADT) in the treatment arm and placebo with ADT in the control arm.
The most common adverse reactions (≥15%) reported in the randomized clinical study that occurred more commonly (≥2%) in the ERLEADA arm were fatigue, skin rash, weight decreased, arthralgia, and fall.
Discontinuations due to adverse events were reported for 11% of subjects treated with ERLEADA and 7% of subjects treated with placebo. At the time of the analysis, 23.6% of subjects were still on ERLEADA.

Table 2 shows adverse reactions on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. ARs are also listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), and rare (≥ 1/10000 to < 1/1000). Within each frequency grouping, ARs are presented in order of decreasing frequency.

Table 2: Adverse Reactions due to ERLEADA in SPARTAN

System/Organ Class		ERLEADA N=803		Placebo N=398	
Adverse Reaction	**Frequency Category[a]**	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
General disorders and administration site conditions					
Fatigue[e]	very common	30.4	0.9	21.1	0.3
Musculoskeletal and connective tissue disorders					
Arthralgia[e]	very common	15.9	0	7.5	0
Skin and subcutaneous tissue disorders					
Skin rash[b]	very common	24.7	5.2	6	0.3
Pruritus[e]	Common	6.2	0.2	1.5	0
Nervous system disorders					
Ischemic cerebrovascular disorders[f]	Common	4.0	1.6	1.0	0.8
Seizure	Uncommon	0.2	0	0	0
Metabolism and nutrition disorders					
Hypercholesterolemia	Common	6.1	0	1.5	0
Hypertriglyceridemia	Common	3.5	0.6	0.8	0.3
Injury, poisoning and procedural complications					
Fall[e]	very common	15.6	1.7	9.0	0.8
Fracture[c]	very common	11.7	2.7	6.5	0.8
Investigations					
Weight decreased[e]	very common	16.1	1.1	6.3	0.3
Endocrine disorders					
Hypothyroidism[d]	Common	8.1	0	2.0	0

a.	Adverse reaction frequencies presented are based on the placebo-controlled period of the clinical study
b.	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
c.	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
d.	Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine decreased, autoimmune thyroiditis, thyroxine free decreased, tri-iodothyronine decreased
e.	Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
f.	Includes transient ischemic attack, cerebrovascular accident, cerebrovascular disorder, ischemic stroke, carotid arteriosclerosis, carotid artery stenosis, hemiparesis, lacunar infarction, lacunar stroke, thrombotic cerebral infarction, vascular encephalopathy, cerebellar infarction, cerebral infarction, and cerebral ischemia. Addition of adverse reaction was based on data of the final analysis with a median exposure of 32.9 months for ERLEADA and 11.5 months for placebo

Skin rash

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, skin rash associated with ERLEADA was most commonly described as macular or maculo-papular. Skin rash included rash, rash maculo-papular, rash generalised, 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. Adverse reactions of skin rash were reported for 26% of subjects treated with ERLEADA versus 8% of subjects treated with placebo. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA treatment (6%) versus placebo (0.5%). There were no reported events of drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) in clinical trials.

The onset of skin 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 subjects. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of subjects received systemic corticosteroids. Among subjects with skin rash, dose interruption occurred in 28% and dose reduction occurred in 14% (*see Dosage and Administration – Dose modification*). Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA. Skin rash led to ERLEADA treatment discontinuation in 7% of subjects who experienced skin rash.

Hypothyroidism

In the combined data of two randomized, placebo-controlled studies, SPARTAN and TITAN, hypothyroidism was reported for 8% of subjects treated with ERLEADA and 2% of subjects 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 subjects already receiving thyroid replacement therapy in the ERLEADA arm and in 3% of subjects in the placebo arm. In subjects not receiving thyroid replacement therapy, hypothyroidism occurred in 7% of subjects treated with ERLEADA and in 2% of subjects treated with placebo. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted (*see Interactions - Effect of ERLEADA on drug metabolizing enzymes*).

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 3). Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their

frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10 (≥10%)
Common	≥ 1/100 and < 1/10 (≥1% and < 10%)
Uncommon	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10000 and < 1/1000 (≥0.01 and < 0.1%)
Very rare	< 1/10000, including isolated reports (< 0.01%)
Not known	Cannot be estimated from the available data

In Table 3, adverse reactions are presented by frequency category based on spontaneous reporting rates and by frequency category based on incidence in clinical trials or epidemiology studies, when known.

Table 3: Adverse Reactions Identified During Postmarketing Experience with Apalutamide

System Organ Class Adverse Reaction	**Frequency Category Estimated from Spontaneous Reporting Rates**[c]	**Frequency Category Calculated from Clinical Trials with ERLEADA**
Metabolism and nutrition disorders		
Decreased appetite	Uncommon	Very common
Nervous system disorders		
Restless legs syndrome	Very rare	Uncommon
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease[a]	Uncommon	Rare[d]
Skin and subcutaneous tissue disorders		
Drug reaction with eosinophilia and systemic symptoms[a,b]	Rare	Rare[d]
Stevens-Johnson syndrome/Toxic epidermal necrolysis[a, b]	Rare	Rare[d]

[a] The adverse reaction was not identified from clinical trials and the frequency was not known. Frequency is calculated by "Rule of 3"
[b] See Warnings and Precautions section
[c] Postmarketing spontaneous reporting rates were based on estimated exposure of person-years of treatment
[d] Frequency calculated using the "Rule of 3" (upper limit of 95% Confidence Interval is not higher than 3/X, where X=4483, total sample size in clinical trials)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat Narkotika, Psikotropika, Prekursor, dan Zat Adiktif
Badan Pengawas Obat dan Makanan Republik Indonesia
Address: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/

Overdose
There is no known specific antidote for apalutamide overdose. In the event of an overdose, ERLEADA should be stopped and general supportive measures should be undertaken until clinical toxicity has been diminished or resolved. Adverse reactions in the event of an overdose has not yet been observed, it is expected that such reactions would resemble the adverse reactions listed above.

Treatment
In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Anti-androgens, ATC code: L02BB05 apalutamide.

Mechanism of action
Apalutamide is an orally administered, selective 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 tumor cell proliferation and increased apoptosis leading to potent antitumor activity. A major metabolite, N-desmethyl apalutamide, exhibited one-third the in vitro activity of apalutamide.

Pharmacodynamic effects

Prostate Specific Antigen (PSA) Reduction
Apalutamide 240 mg daily in addition to ADT in patients with mCSPC (TITAN) reduced PSA to undetectable levels (<0.2 ng/mL) in 68% of patients compared to 32% of patients taking ADT alone.

Apalutamide 240 mg daily in addition to ADT in patients with nmCRPC (SPARTAN) reduced PSA to undetectable levels (<0.2 ng/mL) in 38% of patients compared to no patients (0%) taking ADT alone.

The exposure response relationship and time course of pharmacodynamic response for the safety and effectiveness of apalutamide have not been fully characterized.

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

Clinical studies
The efficacy of ERLEADA was established in two randomized placebo-controlled multicenter Phase 3 clinical studies of subjects with mCSPC (TITAN) or nmCRPC (SPARTAN). All subjects in these studies received concomitant GnRH analog or had prior bilateral orchiectomy.

TITAN: Metastatic Castration -Sensitive Prostate Cancer (mCSPC)
TITAN was a randomized, double-blind, placebo-controlled, multinational, multicenter clinical trial in which 1052 subjects 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 subjects in the TITAN trial received concomitant GnRH analog or had prior bilateral orchiectomy. Subjects were stratified by Gleason score at diagnosis, prior docetaxel use, and region of the world. Subjects 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 subjects were 75 years of age or older. The racial distribution was 68% Caucasian, 22% Asian, and 2% Black. Sixty-three percent (63%) of subjects had high-volume disease and 37% had low-volume disease. Sixteen percent (16%) of subjects had prior surgery, radiotherapy of the prostate or both. A majority of subjects had a Gleason score of 7 or higher (92%). Sixty-eight percent (68%) of subjects received prior treatment with a first-generation anti-androgen in the non-metastatic setting. All subjects except one in the placebo group, had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry. Among the subjects who discontinued study treatment (N = 271 for placebo and N = 170 for ERLEADA), the most common reason for discontinuation in both arms was disease progression. A greater proportion (73%) of subjects treated with placebo received subsequent anti-cancer therapy compared to subjects treated with ERLEADA (54%).
The major efficacy outcome measures of the study were overall survival (OS) and radiographic progression-free survival (rPFS). An updated OS analysis was conducted at the time of final study analysis when 405 deaths were observed with a median follow-up of 44 months. Results from this updated analysis were consistent with those from the pre specified interim analysis. Efficacy results of TITAN are summarized in Table 4 and Figures 1 and 2.

Table 4: Summary of Efficacy Results – Intent-to-treat mCSPC Population (TITAN)		
Endpoint	**ERLEADA N=525**	**Placebo N=527**
Primary Overall Survival[a]		
Deaths (%)	83 (16%)	117 (22%)
Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[b]	0.671 (0.507, 0.890)	
p-value[c]	0.0053	
Updated Overall Survival[d]		
Deaths (%)	170 (32%)	235 (45%)
Median, months (95% CI)	NE (NE, NE)	52 (42, NE)
Hazard ratio (95% CI)[b]	0.651 (0.534, 0.793)	
p-value[c]	<0.0001	
Radiographic Progression-free Survival		
Disease progression or death (%)	134 (26%)	231 (44%)
Median, months (95% CI)	NE (NE, NE)	22.08 (18.46, 32.92)
Hazard ratio (95% CI)[b]	0.484 (0.391, 0.600)	
p-value[c]	<0.0001	

a. This is based on the pre-specified interim analysis with a median follow-up time of 22 months.
b. Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors active treatment.
c. p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
d. Median follow-up time of 44 months.
NE=Not Estimable

A statistically significant improvement in OS and rPFS was demonstrated in subjects randomized to receive ERLEADA compared with subjects randomized to receive placebo in the primary analysis. The improvement in OS was demonstrated even though 39% of subjects in the placebo arm crossed over to receive ERLEADA, with a median treatment of 15 months on ERLEADA crossover.
Consistent improvement in rPFS was observed across the following subject subgroups: disease volume (high vs low), previous treatment for localized disease (yes or no), prior docetaxel use (yes or no), and Gleason score at diagnosis (≤7 vs. >7).
Consistent improvement in OS was observed across the following subject subgroups: disease volume (high vs low), previous treatment for localized disease (yes or no), and Gleason score at diagnosis (≤7 vs. >7).

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

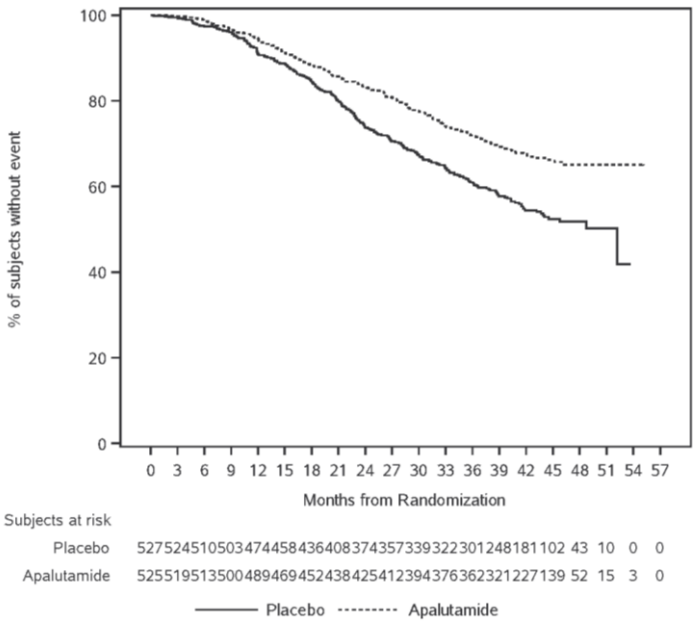
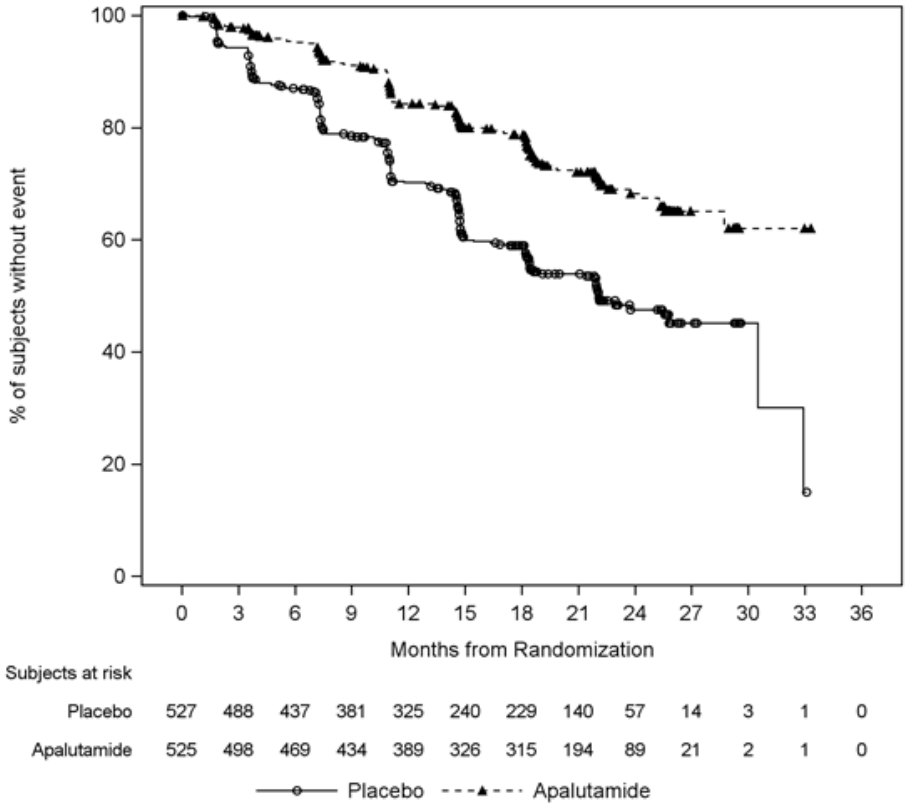
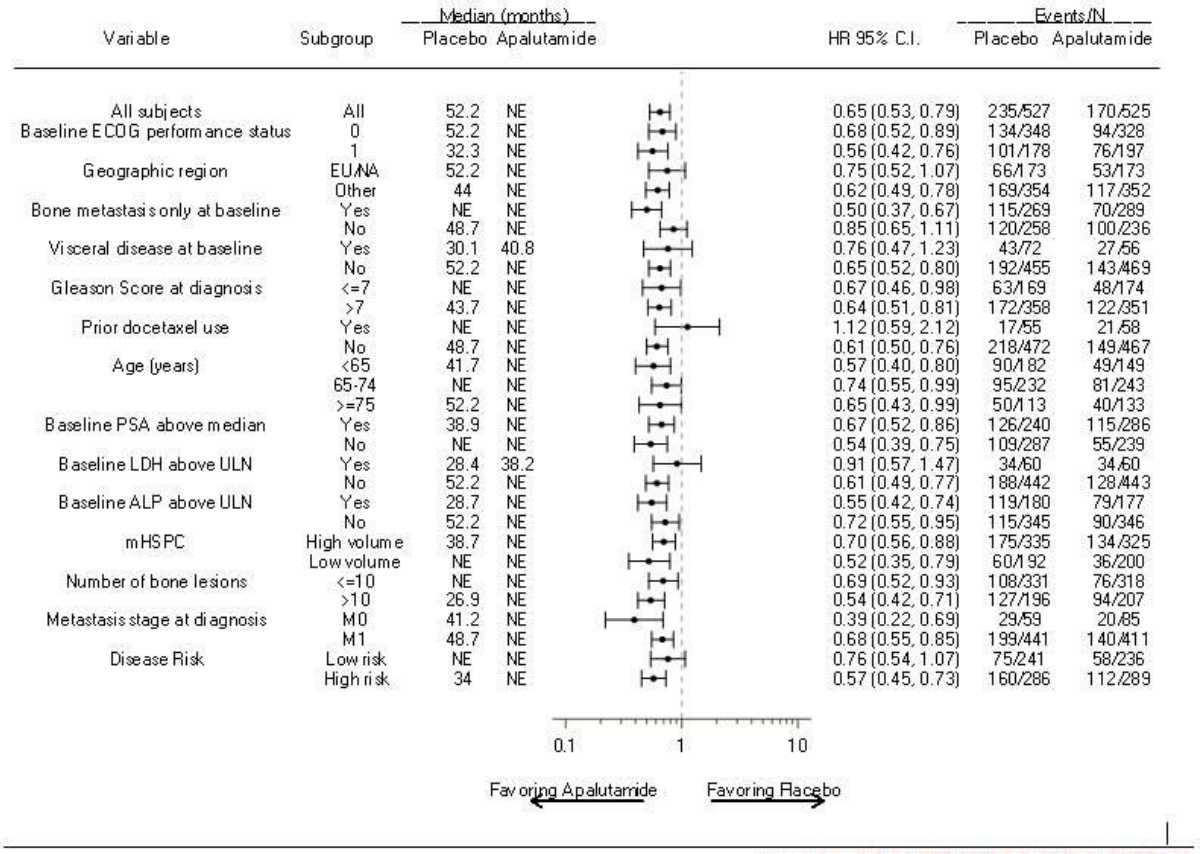


Figure 2: Kaplan-Meier Plot of Radiographic Progression-Free Survival (rPFS); Intent-to-treat mCSPC Population (TITAN)



Subgroup analysis in patients who had used docetaxel before did not show a statistically significant improvement in overall survival with ERLEDA compared to placebo (median overall survival NE vs NE; HR = 1.12; 95% CI:0.59-2.12).

Figure 3: Forest Plot of Overall Survival Defined by Baseline Clinical Disease Characteristics; Intent-to-treat Population (Study 56021927PCR3002)



Treatment with ERLEADA statistically significantly delayed the initiation of cytotoxic chemotherapy (HR = 0.391, 95% CI = 0.274, 0.558; p < 0.0001), resulting in a 61% reduction of risk for subjects in the treatment arm compared to the placebo arm.

There were no significant detrimental effects to overall health-related quality of life, as measured by the FACT-P total score change from baseline, with the addition of ERLEADA to ADT. The addition of ERLEADA to ADT did not worsen the FACT-P item level score for fatigue or patient reported bother due to side effects.

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

A total of 1207 subjects with nm-CRPC were randomized 2:1 to receive either ERLEADA orally at a dose of 240 mg once daily in combination with ADT (medical castration or surgical castration) or placebo with ADT in a multicenter, double-blind, clinical trial (SPARTAN). Subjects enrolled had a Prostate Specific Antigen (PSA) Doubling Time (PSADT) ≤ 10 months. All subjects who were not surgically castrated received ADT continuously throughout the study. Seventy-three percent (73%) of subjects received prior treatment with a first generation anti-androgen; 69% of subjects received bicalutamide and 10% of subjects received flutamide. Systemic corticosteroids were not allowed at study entry. PSA results were blinded and were not used for treatment discontinuation. Subjects randomized to either arm were to continue treatment until disease progression defined by blinded central imaging review (BICR), initiation of new treatment, unacceptable toxicity or withdrawal. Upon development of distant metastatic disease, subjects were offered ZYTIGA as an option for the first subsequent treatment after study treatment discontinuation.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 74 years (range 48-97) and 26% of subjects 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 subjects in both treatment arms had prior surgery or radiotherapy of the prostate. A majority of subjects had a Gleason score of 7 or higher (81%). Fifteen percent (15%) of subjects had <2 cm pelvic lymph nodes at study entry. All

subjects enrolled were confirmed to be non-metastatic by blinded central imaging review and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) performance status score of 0 or 1 at study entry.

Metastasis-free survival (MFS) is 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 significantly improved MFS. ERLEADA decreased the risk of distant metastasis or death by 72%. The median MFS for ERLEADA was 41 months and was 16 months for placebo (see Figures 4 and 5).

Figure 4: Kaplan-Meier Metastasis-Free Survival (MFS) Curve in SPARTAN

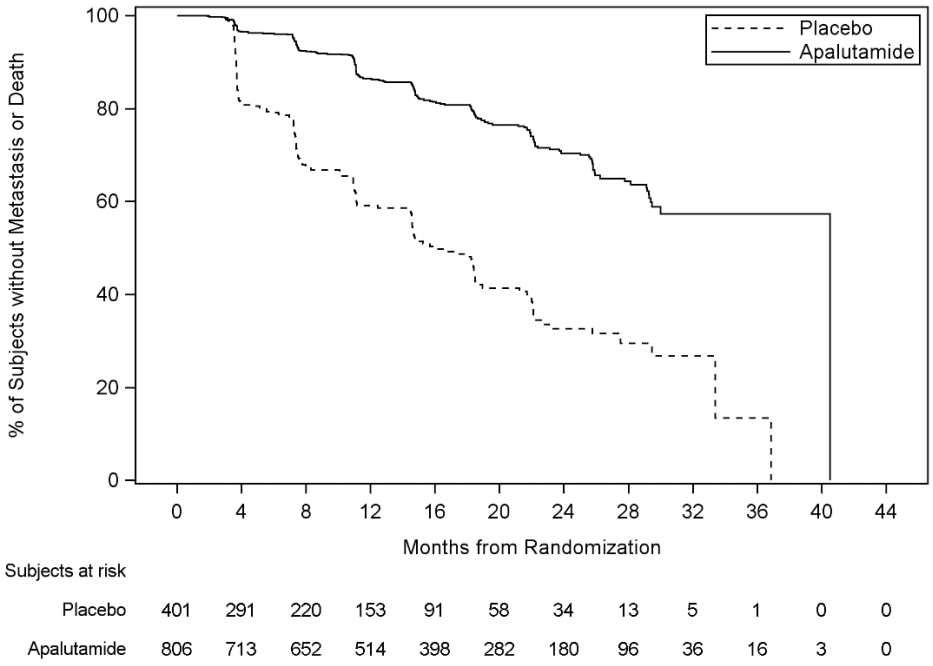
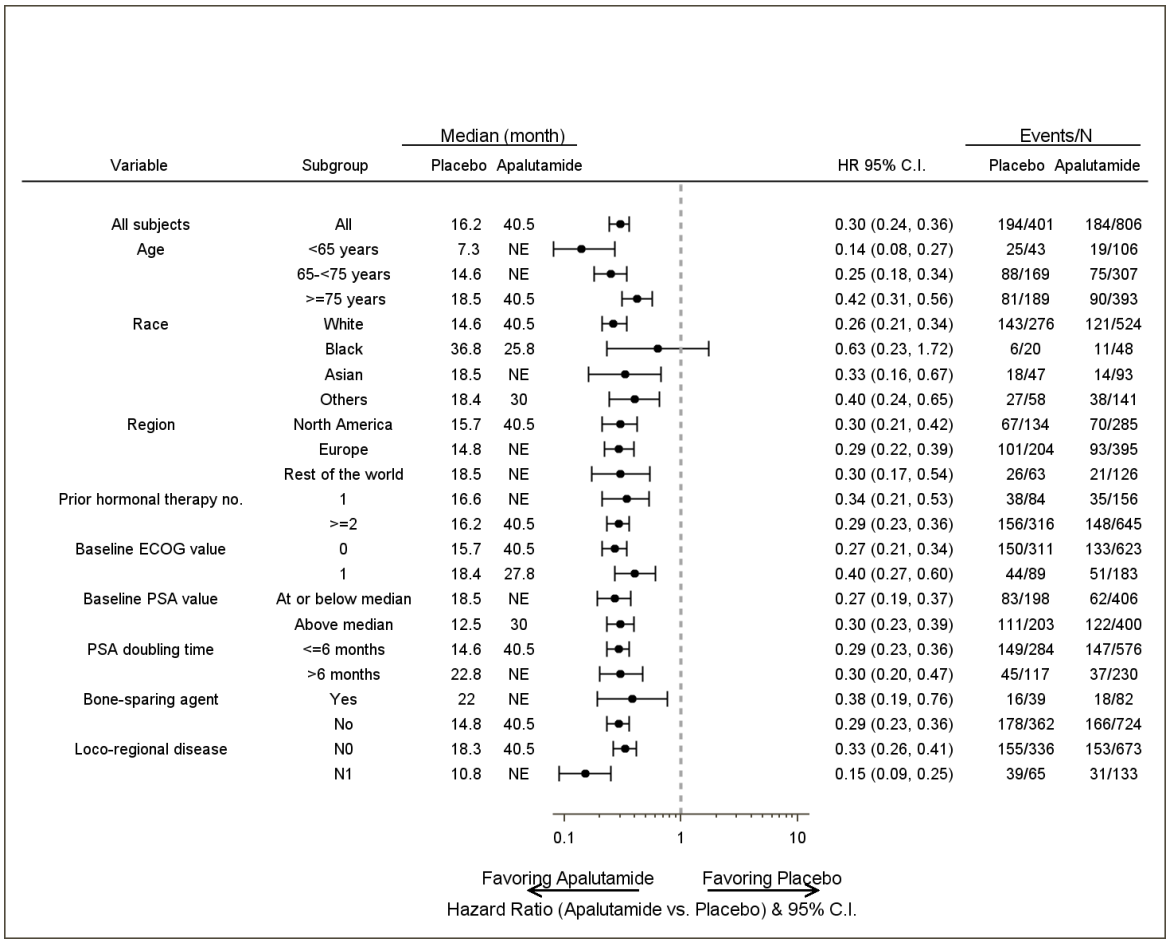


Figure 5: Metastasis-free Survival by Subgroups in SPARTAN



- All subjects = Intent-to Treat population
- The non-stratified analysis is presented in Figure 5

Subjects treated with ERLEADA and 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. In addition, overall survival (OS) and time to initiation of cytotoxic chemotherapy were also significantly improved (see Table 5 for Interim Analysis and Table 6 for Final Analysis).

Table 5: Summary of Efficacy Analysis (SPARTAN) at Interim Analysis[a]

Endpoint	ERLEADA (N=806) Median (months)	Placebo (N=401) Median (months)	HR (95% CI) p value[b]
Metastasis Free Survival (MFS)[c]	40.5	16.2	0.28 (0.23-0.35) < 0.0001
Time to Metastasis (TTM)[c]	40.5	16.6	0.27 (0.22-0.34) < 0.0001
Progression-free Survival (PFS)[c]	40.5	14.7	0.29 (0.24-0.36) < 0.0001
Time to Symptomatic Progression	NR	NR	0.45 (0.32-0.63) < 0.0001[d]
Overall Survival (OS)	NR	39.0	0.70 (0.47-1.04) 0.0742
Time to Initiation of Cytotoxic Chemotherapy	NR	NR	0.44 (0.29-0.66) < 0.0001

NR = Not reached

a. Median follow-up time of 20.3 months
b. p value from stratified log-rank test
c. Assessed by BICR and unchanged for final analysis
d. Actual p value – 0.00000356; hence, OBF-type efficacy boundary of 0.00008 is crossed in the interim analysis for Symptomatic Progression

Table 6: Summary of Efficacy Analysis (SPARTAN) at Final Analysis[a]			
Endpoint	**ERLEADA (N=806) Median (months)**	**Placebo (N=401) Median (months)**	**HR (95% CI) p value[b]**
Overall Survival (OS)	73.9	59.9	0.78 (0.64-0.96) 0.0161
Time to Symptomatic Progression	NR	NR	0.57 (0.44-0.73) < 0.0001[c]
Time to Initiation of Cytotoxic Chemotherapy	NR	NR	0.63 (0.49-0.81) 0.0002

NR = Not reached

[a] Median follow-up time of 52.0 months

[b] p value from stratified log-rank test

[c] Actual p value – 0.00000356 at the first interim analysis; hence, OBF-type efficacy boundary of 0.00008 is crossed for Symptomatic Progression

At the interim analysis, treatment with ERLEADA significantly decreased the risk of symptomatic progression by 55% compared with placebo. (see Table 5 and Figure 6). The final analysis corroborated that treatment with ERLEADA decreased the risk of symptomatic progression by 43% compared with placebo. (see Table 6 and Figure 7).

Figure 6: Kaplan-Meier Plot of Time to Symptomatic Progression; Intent-to-treat Population in SPARTAN at Interim Analysis

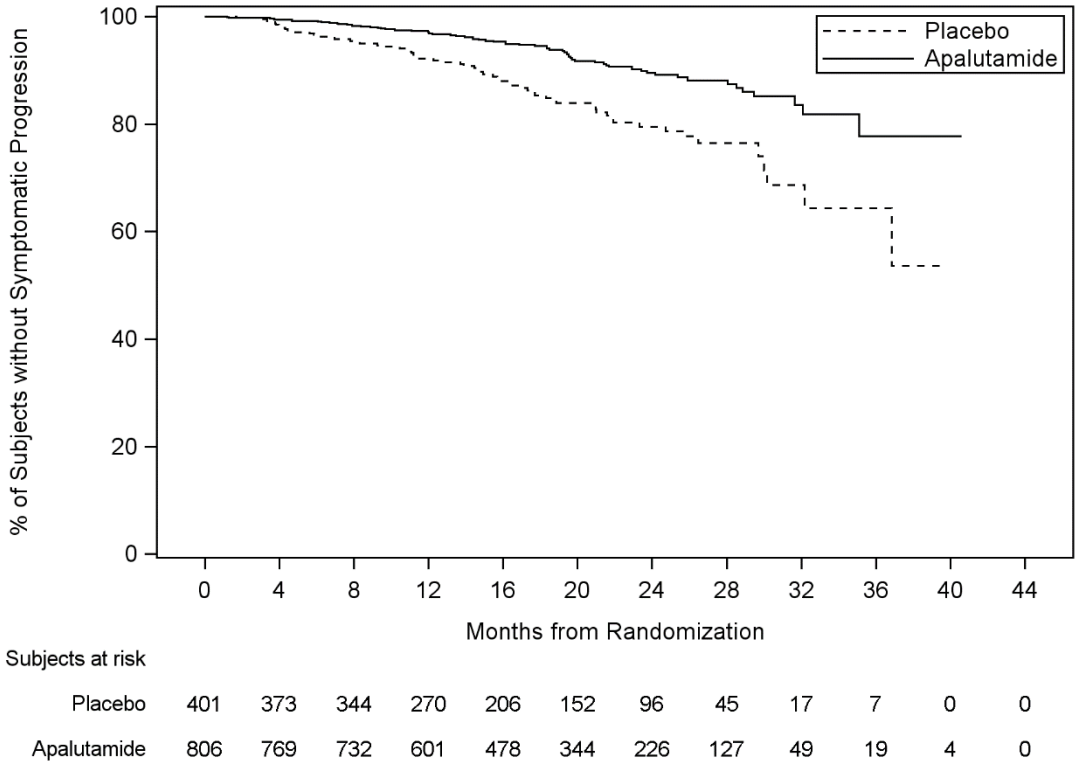
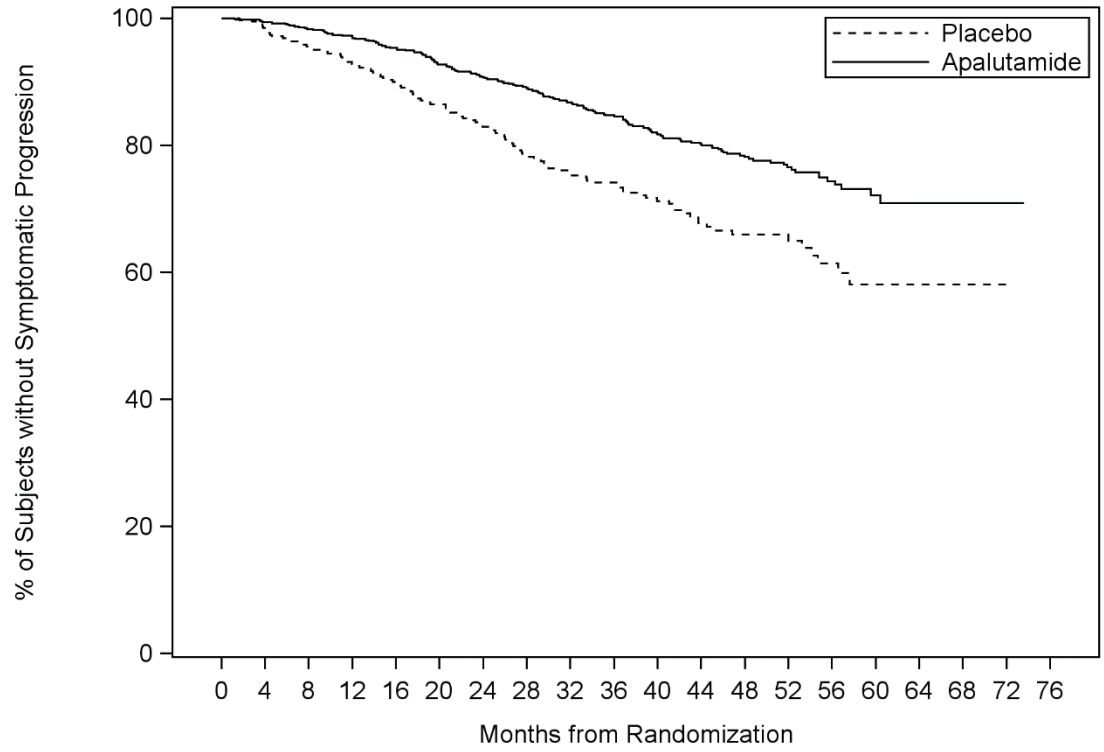


Figure 7: Kaplan-Meier Plot of Time to Symptomatic Progression; Intent-to-treat Population in SPARTAN at Final Analysis



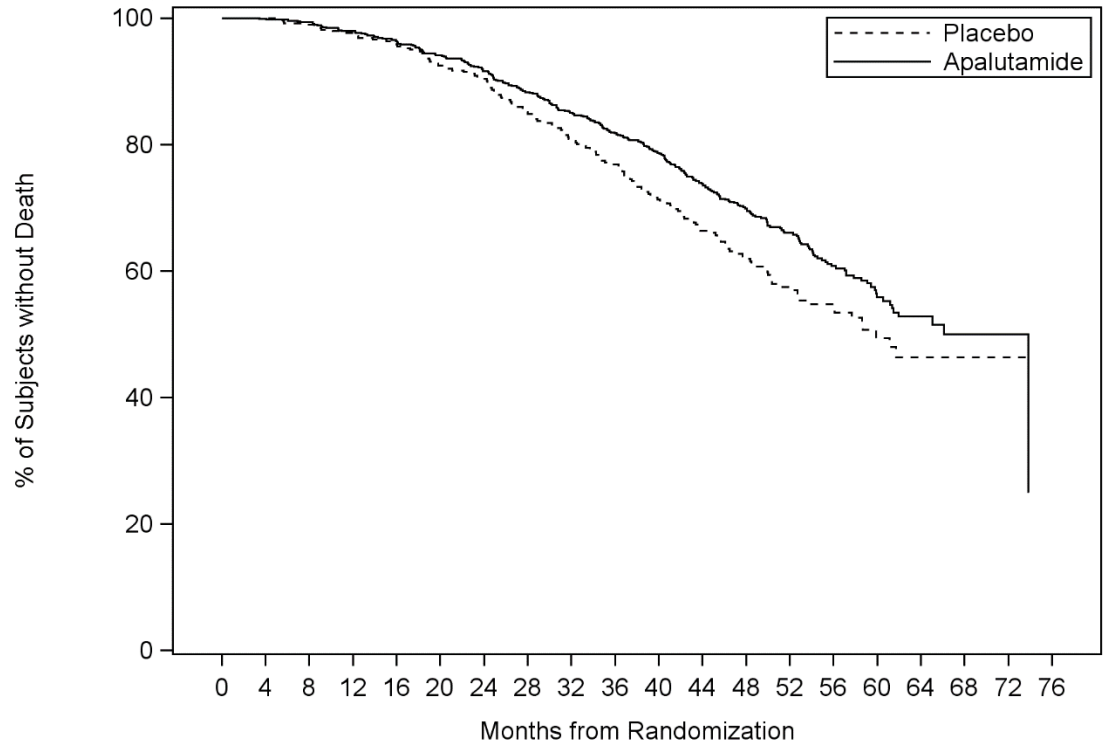
Subjects at risk

Placebo	401	377	355	331	308	279	253	223	206	185	158	126	90	66	45	17	11	5	1	0
Apalutamide	806	771	749	721	693	658	620	589	553	520	476	413	286	206	132	65	22	6	1	0

At the interim analysis, with median follow-up time of 20.3 months, the OS was longer for ERLEADA than placebo with a hazard ratio (HR) of 0.700 (95% CI: 0.472, 1.038). The p-value was 0.0742 which did not meet the pre-specified value for statistical significance. At the final analysis, with median follow-up time of 52.0 months, results showed that treatment with ERLEADA significantly decreased the risk of death by 22% compared with placebo (HR=0.784; 95% CI: 0.643, 0.956; 2-sided p=0.0161). The median OS was 73.9 months for the ERLEADA

arm and 59.9 months for the placebo arm. The pre specified alpha boundary (p≤0.046) for this final analysis was crossed and statistical significance was achieved.

Figure 8: Kaplan-Meier Plot of Time to Overall Survival (OS); Intent-to-treat Population in SPARTAN at Final Analysis



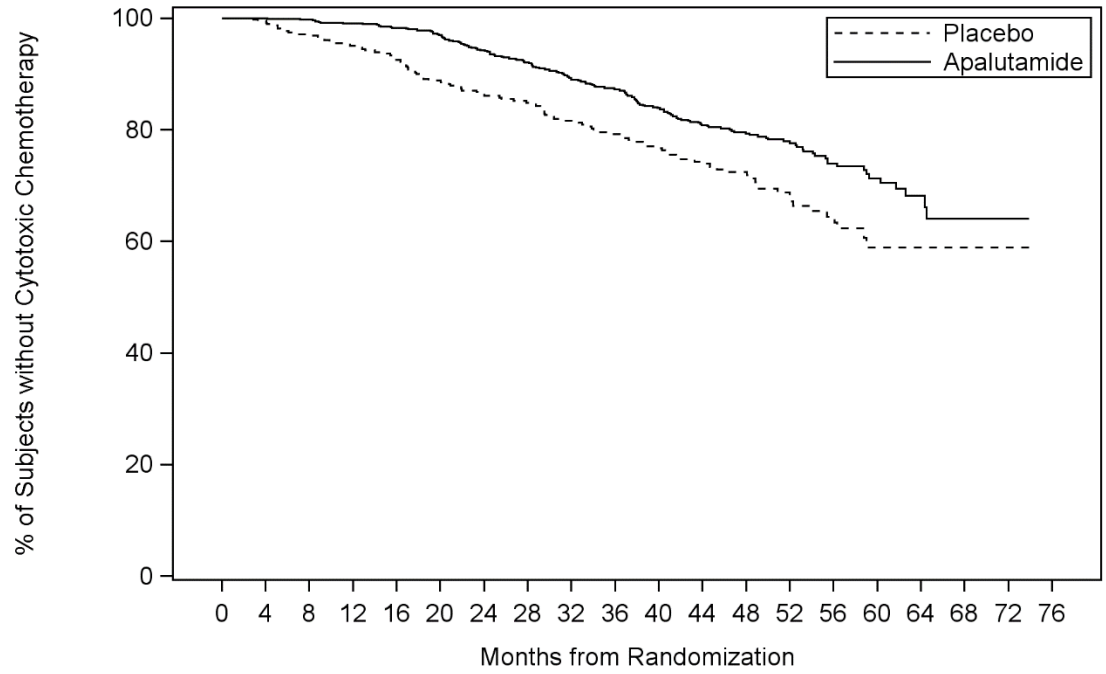
Subjects at risk

Placebo	401	392	385	373	358	339	328	306	286	263	240	204	156	114	82	38	21	6	2	0
Apalutamide	806	791	774	758	739	717	691	658	625	593	558	499	376	269	181	100	47	19	4	0

At the final analysis, treatment with ERLEADA significantly decreased the risk of initiating cytotoxic chemotherapy by 37% compared with placebo (HR=0.629; 95% CI: 0.489, 0.808; p=0.0002) demonstrating

statistically significant improvement for ERLEADA versus placebo. The median time to the initiation of cytotoxic chemotherapy was not reached for either treatment arm.

Figure 9: Kaplan-Meier Plot of Time to Initiation of Cytotoxic Chemotherapy: Intent-to-treat Population in SPARTAN at Final Analysis



Subjects at risk

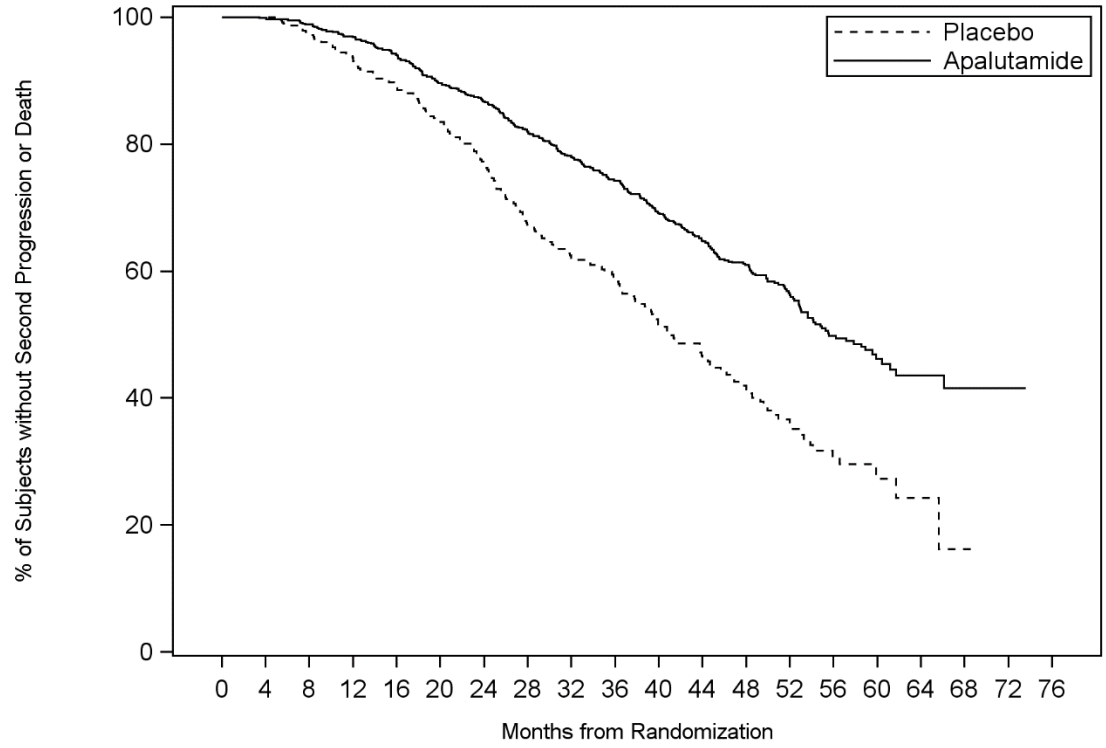
Placebo	401	388	371	352	327	302	283	266	247	224	200	173	128	89	63	26	16	4	2	0
Apalutamide	806	787	763	739	711	687	646	610	565	535	492	436	314	225	152	84	35	14	4	0

If eligible and without evidence of disease progression, subjects treated with placebo were given the opportunity to cross-over to treatment with ERLEADA at time of unblinding. After unblinding, 19% of the randomized placebo population crossed over to ERLEADA. Of all the randomized subjects, a greater proportion of subjects in the placebo arm received subsequent therapy (285/401, 71%) compared with the ERLEADA arm (386/806, 48%).

At the interim analysis, post-progression survival (PFS-2, defined as the time to death or disease progression by PSA, radiographic, or symptomatic progression on or after first subsequent therapy) was longer for subjects treated with ERLEADA compared to those treated with placebo (HR=0.489; 95%CI: 0.361, 0.662; p< 0.0001).

Final analysis of PFS-2 confirmed a 44% reduction in risk of PFS-2 with ERLEADA versus placebo (HR=0.565; 95% CI: 0.471, 0.677; p<0.0001).

Figure 10: Kaplan-Meier Plot of Second Progression-Free Survival (PFS-2); Intent-to-treat Population in SPARTAN at Final Analysis



There were no detrimental effects to overall health-related quality of life with the addition of ERLEADA to ADT and a small but not clinically meaningful difference in change from baseline in favor of ERLEADA observed in the analysis of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score and subscales.

Pharmacokinetic Properties

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. At steady-state, mean (CV%) C_{max} and AUC values for apalutamide were 6 µg/mL (28%) and 100 µg.h/mL (32%), respectively. Daily fluctuations in apalutamide plasma concentrations were low, with mean peak-to-trough ratio of 1.63. An increase in apparent clearance (CL/F) was observed with repeat dosing, likely due to induction of apalutamide's own metabolism.

At steady-state, the mean (CV%) C_{max} and AUC values for the major active metabolite, N-desmethyl apalutamide, were 5.9 µg/mL (18%) and 124 µg.h/mL (19%), respectively. N-desmethyl apalutamide is characterized by a flat concentration-time profile at steady-state with a mean peak-to-trough ratio of 1.27. Mean (CV%) AUC metabolite/parent drug ratio for N-desmethyl apalutamide following repeat-dose administration was about 1.3 (21%). Based on systemic exposure, relative potency, and pharmacokinetic properties, N-desmethyl apalutamide likely contributed to the clinical activity of apalutamide.

Absorption

After oral administration, median time to achieve peak plasma concentration (t_{max}) was 2 hours (range: 1 to 5 hours). Mean absolute oral bioavailability is approximately 100%, indicating that apalutamide is completely absorbed after oral administration.

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 Figure 4) (*see Dosage and Administration*).
Following oral administration of 4x60 mg apalutamide tablets dispersed in applesauce, Cmax 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*).

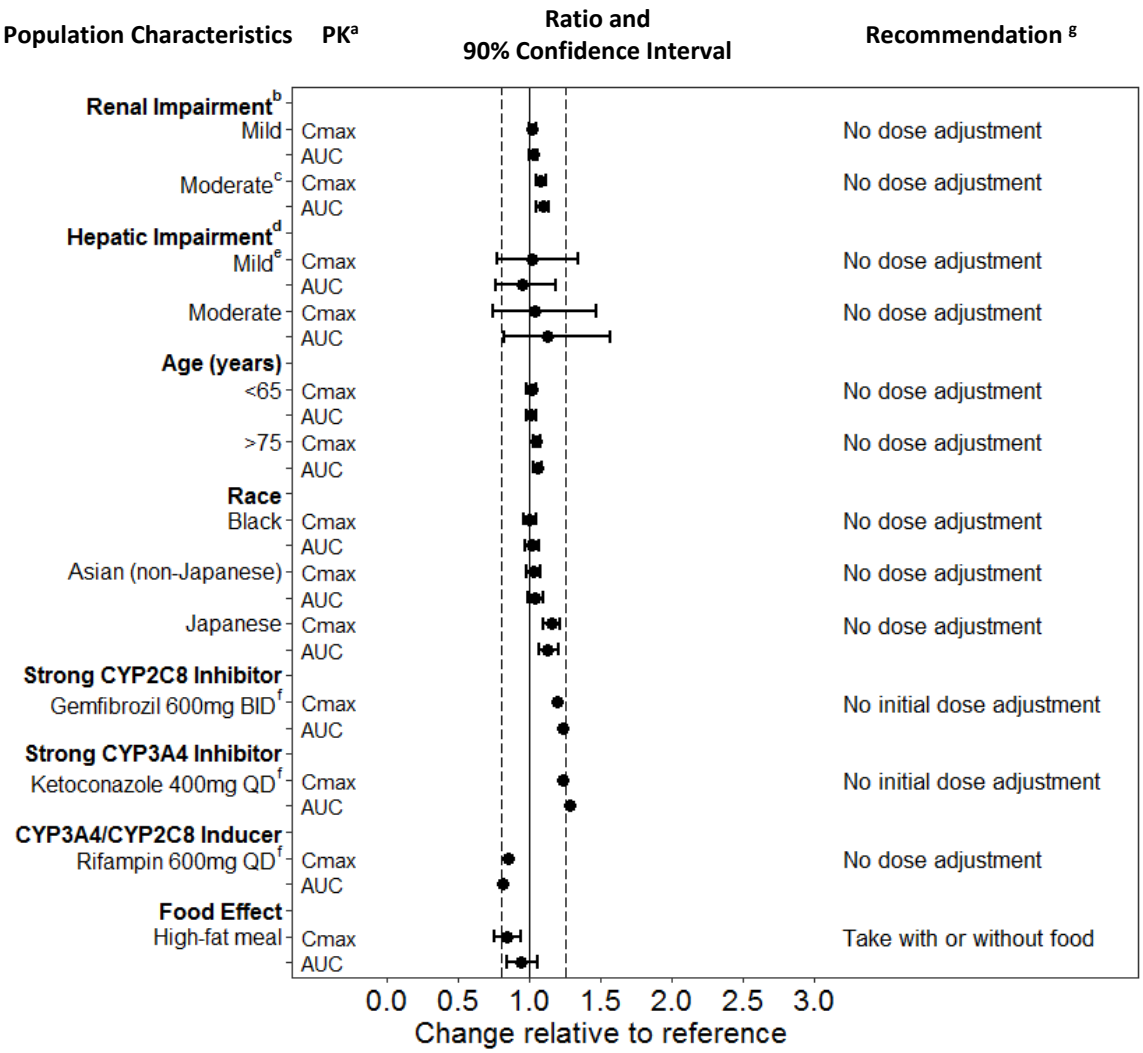
Distribution
The mean apparent volume of distribution at steady-state of apalutamide is about 276 L. The volume of distribution of apalutamide is greater than the volume of total body water, indicative of extensive extravascular distribution.
Apalutamide and N-desmethyl apalutamide are 96% and 95% bound to plasma proteins, respectively, and mainly bind to serum albumin with no concentration dependency.

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 45%, 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
The effects of renal impairment, hepatic impairment, age, race, and other extrinsic factors on the pharmacokinetics of apalutamide are summarized in Figure 11.

Figure 11: Effects of Intrinsic/Extrinsic Factors and Other Medications on ERLEADA



[a] Pharmacokinetic (PK) parameters (C_{max} and AUC) are for apalutamide, except in the drug interaction studies, where they are for active moieties (i.e., unbound apalutamide + potency adjusted unbound N-desmethyl 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

[f] Effects on steady-state PK of active moieties based on simulations

[g] See Dosage and Administration, Special population and Interactions.

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, or between different races.

The potential effect of severe renal impairment or end stage renal disease (eGFR ≤29 mL/min/1.73m^2) have not been established due to insufficient data. Clinical and pharmacokinetic data are not available for patients with severe hepatic impairment (Child-Pugh Class C).

NON-CLINICAL INFORMATION

Carcinogenicity and Mutagenicity

Apalutamide was not carcinogenic in a 6-month study in the male transgenic (Tg.rasH2) mouse.

In the 24-month oral carcinogenicity study in male Sprague-Dawley rats, apalutamide was administered by oral gavage at doses of 5, 15 and 50 mg/kg/day (0.2, 0.7, and 2.5 times the AUC in patients (human exposure at

recommended dose of 240 mg), respectively) for 100 weeks. Apalutamide-related neoplastic findings included an increased incidence of testicular Leydig cell adenoma and carcinoma at doses greater than or equal to 5 mg/kg/day, mammary adenocarcinoma and fibroadenoma at 15 mg/kg/day or 50 mg/kg/day, and thyroid follicular cell adenoma at 50 mg/kg/day. These findings were considered rat-specific and therefore of limited relevance to humans.
Apalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either in vitro chromosome aberration test, the in vivo rat micronucleus assay or the in vivo rat Comet assay.

Reproductive Toxicology
Male fertility is likely to be impaired by treatment with apalutamide based on findings in repeat-dose toxicology 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 (1.4 times the human exposure based on AUC) and ≥ 2.5 mg/kg/day in dogs (0.9 times the human exposure based on AUC).
In a fertility study in male rats, 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 following 4 weeks of dosing at ≥ 25 mg/kg/day (approximately equal to the human exposure based on AUC). Effects on male rats were reversible after 8 weeks from the last apalutamide administration.
In a development toxicity study in the rat, early embryonic loss was seen at 50 and 100 mg/kg/day. In addition, a disturbance of the normal embryo-fetal development was observed ≥ 25 mg/kg/day (2.3 times the human exposure based on AUC), evidenced by a shortening of the mean anogenital distance, a misshapen (rounded) pituitary gland and some skeletal variations.

PHARMACEUTICAL INFORMATION
List of Excipients
Tablet core
Colloidal anhydrous silica
Croscarmellose sodium
Hydroxypropyl methylcellulose-acetate succinate (HPMC-AS)
Magnesium stearate
Microcrystalline cellulose
Microcrystalline cellulose (silicified)

Film-coat
Iron oxide black (E172)
Iron oxide yellow (E172)
Polyethylene glycol
Polyvinyl alcohol (partially hydrolyzed)
Talc
Titanium dioxide

Incompatibilities
Not applicable.

Shelf Life
Shelf-life before opening: 24 months.
Shelf-life after opening: 6 weeks.
See expiry date on the outer pack.

Storage Conditions
Do not store above 30°C.
Keep out of the sight and reach of children.

Nature and Contents of Container
ERLEADA is available in opaque, high-density polyethylene bottles with child-resistant polypropylene closure and induction seal liner. Each bottle contains 120 tablets and a desiccant.

Instructions for Use and Handling and Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

HOW SUPPLIED
Erleada film-coated (FC) tablets
Box, 1 bottle @ 120 tablets
Reg. No.: DKI2110901817A1

DATE OF FIRST AUTHORISATION
31 December 2019

HARUS DENGAN RESEP DOKTER

Manufactured by:
Janssen Ortho LLC, Gurabo, Puerto Rico, USA

Primary packaged by:
Janssen Ortho LLC, Gurabo, Puerto Rico, USA
Janssen Cilag SpA, Latina, Italy

Secondary packaged by:
Janssen Ortho LLC, Gurabo, Puerto Rico, USA
Janssen Cilag SpA, Latina, Italy
Janssen Pharmaceutica NV, La Louvière, Belgium

Released by:
Janssen Cilag SpA, Latina, Italy

Registered by:
PT Integrated Healthcare Indonesia, Jakarta – Indonesia
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or (021) 2935-3935

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INFORMASI PRODUK UNTUK PASIEN
ERLEADA® (apalutamide) 60mg tablet

Baca semua informasi produk ini secara seksama sebelum Anda mulai menggunakan obat ini.
- Simpan informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker.

Apa yang ada dalam informasi produk ini

1. Apakah ERLEADA dan digunakan untuk apa

ERLEADA mengandung zat aktif apalutamide. Termasuk dalam kelompok obat yang disebut "*androgen receptor inhibitor*".
ERLEADA digunakan untuk mengobati:
- kanker prostat yang telah menyebar ke bagian lain dari tubuh dan masih merespon pengobatan yang menurunkan testosterone dalam kombinasi dengan terapi deprivasi androgen (ADT).
- kanker prostat resisten kastrasi yang belum mengalami metastasis pada pria dewasa yang berisiko tinggi mengalami metastasis yang belum menyebar ke bagian lain dari tubuh dan tidak lagi merespon pengobatan medis atau bedah yang menurunkan testosteron.

2. Apa saja yang perlu Anda ketahui sebelum menggunakan ERLEADA

Jangan menggunakan ERLEADA:
- jika Anda sedang atau mungkin hamil. ERLEADA dapat membahayakan janin Anda
- jika Anda memiliki riwayat alergi terhadap bahan aktif atau bahan tambahan yang terkandung dalam ERLEADA

Sebelum Anda menggunakan ERLEADA, bicarakan dengan tenaga kesehatan Anda jika Anda:
- memiliki riwayat penyakit jantung, tekanan darah tinggi, diabetes, memiliki gangguan lemak atau kolesterol abnormal dalam darah Anda (dislipidemia)
- memiliki riwayat kejang, penyakit tulang, resiko jatuh, stroke, penyakit jantung, cedera otak, atau tumor otak (non-kanker atau kanker).
- pernah mengalami ruam parah di seluruh tubuh biasanya disertai dengan demam dan pembengkakan kelenjar getah bening, dan efek pada sel darah dan organ (reaksi obat dengan eosinofilia dan gejala sistemik atau DRESS) atau ruam kulit parah atau kulit mengelupas, melepuh dan/atau sariawan (sindrom Stevens Johnson/nekrolisis epidermal toksik)
- memiliki pasangan yang sedang hamil atau mungkin hamil. Pria yang aktif secara seksual dengan wanita yang sedang hamil harus menggunakan kondom selama pengobatan dan 3 bulan setelah pengobatan dengan ERLEADA. Jika pasangan Anda mungkin hamil, kondom dan bentuk lain dari pengendalian kelahiran yang sangat efektif harus digunakan selama pengobatan dan selama 3 bulan setelah pengobatan. Bicarakan dengan dokter Anda jika Anda memiliki pertanyaan tentang pengendalian kelahiran.
- menggunakan obat-obatan yang mencegah pembekuan darah (contoh: warfarin, acenocoumarol).
- memiliki penyakit jantung dan pembuluh darah, termasuk gangguan pada irama jantung (aritmia).

Erleada mungkin dapat menurunkan kesuburan pria.

Wanita, bayi, dan anak-anak
ERLEADA tidak digunakan pada wanita dan anak-anak.

Obat-obatan lain dan ERLEADA
Beritahu dokter Anda tentang semua obat yang Anda gunakan, termasuk obat resep dan obat bebas, vitamin, dan suplemen herbal, termasuk diantaranya obat-obatan yang:

- menurunkan kadar lemak darah (contoh: gemfibrozil)
- mengatasi infeksi bakteri (contoh: moxifloxacin, clarithromycin)
- mengatasi infeksi jamur (contoh: itraconazole, ketoconazole)
- digunakan pada infeksi HIV (contoh: ritonavir, efavirenz, darunavir)
- mengatasi kecemasan (contoh: midazolam, diazepam)
- mengatasi epilepsi (contoh: fenitoin, asam valproat)
- mengatasi refluks gastroesophageal / GERD / kondisi dimana terlalu banyak asam pada lambung (contoh: omeprazole)
- mencegah pembekuan darah (contoh: warfarin, clopidogrel, dabigatran etexilate)
- mengatasi alergi dan rhinitis (contoh: fexofenadine)
- menurunkan kadar kolesterol (contoh: golongan statin seperti rosuvastatin, simvastatin)
- mengatasi penyakit jantung atau menurunkan tekanan darah (contoh: digoxin, felodipine)
- mengatasi gangguan irama jantung (contoh: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutulide)
- mengatasi penyakit tiroid (contoh: levothyroxine)
- mengatasi gout / asam urat (contoh: colchicine)
- menurunkan kadar gula darah (contoh: repaglinide)
- digunakan pada kanker (contoh: lapatinib, methotrexate)
- mengatasi ketergantungan opioid atau nyeri (contoh: methadone)
- mengatasi gangguan kejiwaan serius (contoh: haloperidol)

Anda tidak boleh memulai atau menghentikan obat apa pun sebelum Anda bicara dengan dokter yang meresepkan ERLEADA.

Mengemudi dan mengoperasikan mesin
Sehubungan dengan penggunaan ERLEADA saat mengemudi dan mengoperasikan mesin, Erleada mempunyai efek samping serius termasuk kejang. Beritahu dokter apabila Anda mempunyai risiko tinggi untuk kejang.

3. Bagaimana cara menggunakan ERLEADA

Bagaimana obat diberikan

- Minum ERLEADA persis seperti yang diberitahukan oleh dokter Anda.
- Minum dosis ERLEADA yang diberikan untuk Anda satu kali sehari.
- Minum ERLEADA dengan atau tanpa makanan.
- Telan tablet ERLEADA secara utuh.
  Jika Anda memiliki masalah menelan seluruh tablet:
  1. Aduk tablet utuh ERLEADA di dalam 4 ons (120 mL) saus apel. Jangan hancurkan tablet.
  2. Aduk setelah 15 menit.
  3. Aduk kembali setelah 30 menit sampai tablet tercampur dengan baik dan tidak ada lagi bagian-bagian tablet yang tersisa.
  4. Menggunakan sendok, telan campuran tersebut secepatnya.
  5. Bilas tempat campuran yang sudah kosong dengan 2 ons air. Minum air campuran dan ulangi bilas dengan 2 ons air sekali lagi untuk memastikan obat sudah ditelan seluruhnya. Minum campuran dalam waktu satu jam dari pembuatan. Jangan simpan ERLEADA yang sudah dicampur dengan saus apel.
- Dokter Anda dapat mengubah dosis Anda jika diperlukan.
- Jangan berhenti menggunakan ERLEADA sesuai dengan dosis yang telah ditentukan tanpa berbicara dengan dokter Anda terlebih dahulu.
- Dokter Anda dapat melakukan tes darah untuk memeriksa kemungkinan efek samping yang terjadi.

Jika Anda lupa menggunakan ERLEADA

Jika Anda melewatkan dosis ERLEADA, ambillah dosis normal Anda sesegera mungkin pada hari yang sama. Kembalilah ke jadwal normal Anda pada hari berikutnya. Anda tidak harus mengambil tablet tambahan untuk mengganti dosis yang terlewatkan.

Jika Anda menggunakan ERLEADA lebih dari yang seharusnya
Jika Anda secara tidak sengaja mengambil lebih dari dosis biasa, hubungi dokter Anda.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter Anda.

4. Apa Efek samping yang mungkin terjadi selama menggunakan ERLEADA

Seperti semua obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

ERLEADA dapat menyebabkan efek samping yang serius termasuk:
- Resiko jatuh dan patah tulang. Pengobatan ERLEADA dapat menyebabkan tulang dan otot melemah dan dapat meningkatkan risiko Anda jatuh dan patah tulang. Jatuh dan patah tulang telah terjadi pada pasien selama pengobatan dengan ERLEADA. Jatuh tidak disebabkan oleh hilangnya kesadaran (pingsan) atau kejang. Penyedia layanan kesehatan Anda akan memantau risiko Anda jatuh dan patah tulang selama perawatan dengan ERLEADA.
- Penyakit jantung, strok atau strok ringan. Penyumbatan pembuluh darah di jantung atau di bagian otak yang dapat menyebabkan kematian telah terjadi pada beberapa pasien selama pengobatan dengan ERLEADA. Penyedia layanan kesehatan Anda akan memantau Anda untuk tanda dan gejala masalah jantung atau otak selama pengobatan Anda dengan ERLEADA. Hubungi penyedia layanan kesehatan Anda atau kunjungi ruang gawat darurat terdekat segera jika Anda merasa sakit atau tidak nyaman pada dada saat istirahat atau saat beraktivitas atau sesak napas, atau jika Anda mengalami kelemahan atau kelumpuhan otot di bagian tubuh Anda, atau kesulitan bicara selama pengobatan Anda dengan ERLEADA.
- Kejang. Pasien yang menggunakan ERLEADA jarang mengalami kejang. Beritahu dokter Anda segera jika Anda kehilangan kesadaran atau kejang. Dokter Anda akan menghentikan ERLEADA jika Anda mengalami kejang selama perawatan.
- Efek samping pada kulit yang parah (SCAR). Pasien yang menggunakan ERLEADA dapat mengalami SCAR, termasuk reaksi obat dengan eosinofilia dan gejala sistemik (DRESS) atau sindrom Stevens Johnson/nekrolisis epidermal toksik (SJS/TEN) walaupun jarang, yang dapat mengancam jiwa atau dapat menyebabkan kematian. DRESS dapat muncul sebagai ruam parah di seluruh tubuh biasanya disertai dengan demam dan pembengkakan kelenjar getah bening, dan efek pada sel darah dan organ selama pengobatan. SJS/TEN dapat muncul sebagai ruam parah dengan lepuh dan kulit mengelupas di seluruh tubuh termasuk luka pada mulut, tenggorokan, hidung, mata, dan alat kelamin selama pengobatan. Demam dan gejala seperti flu dapat terjadi sebelum ruam kulit yang parah ini berkembang. Berhenti minum ERLEADA dan hubungi penyedia layanan kesehatan Anda atau segera cari bantuan medis jika Anda mengalami ruam parah atau gejala kulit lainnya selama pengobatan.
- Penyakit Paru Interstisial. Pasien yang menggunakan ERLEADA dapat mengalami peradangan non-infeksi di paru-paru yang dapat menyebabkan kerusakan permanen dan dapat mengancam nyawa atau bahkan kematian. Segera berhenti konsumsi ERLEADA dan hubungi penyedia layanan kesehatan Anda atau segera dapatkan bantuan medis jika Anda mengalami batuk dan sesak napas, terkadang disertai demam, yang bukan disebabkan oleh aktivitas fisik.

Efek samping yang sangat umum (mungkin terjadi pada lebih dari 1 diantara 10 orang):
- merasa sangat lelah
- nyeri sendi
- ruam kulit
- tekanan darah tinggi
- rasa hangat/panas yang dapat disertai kemerahan pada kulit (*hot flashes/hot flushes*)
- diare
- patah tulang
- jatuh
- penurunan berat badan
- nafsu makan menurun

Efek samping yang umum (mungkin terjadi pada 1 diantara 10 orang):
- kejang otot
- gatal
- perubahan indra perasa (*Dysgeusia*)
- tes darah menunjukkan kenaikan kadar kolesterol
- tes darah menunjukkan kenaikan kadar lemak darah / trigliserida
- penyakit jantung (penyakit jantung iskemik)
- penurunan fungsi tiroid yang menyebabkan kelelahan
- strok atau strok ringan yang disebabkan oleh aliran darah yang rendah ke bagian otak

Efek samping yang tidak umum (dapat dialami hingga 1 dari 100 orang):
- Perasaan tidak nyaman, adanya rasa ingin untuk menggerakkan kaki yang tak tertahankan, dan terkadang lengan, dan bagian tubuh lainnya

Efek samping lain (yang frekuensi nya tidak diketahui berdasarkan data):
- ketidaknormalan hasil EKG / rekam jantung
- peradangan di dalam paru-paru yang dapat menyebabkan kerusakan permanen (penyakit paru interstitial)
- ruam parah disertai dengan kulit melepuh dan mengelupas di seluruh tubuh termasuk luka pada mulut, tenggorokan, hidung, mata, dan alat kelamin. Demam dan gejala seperti flu dapat terjadi sebelum ruam kulit yang parah ini berkembang. Kondisi ini dapat mengancam jiwa dengan ruam, lepuh, atau pengelupasan kulit yang mempengaruhi sebagian besar tubuh (*Stevens Johnson syndrom*/nekrolisis epidermal toksik)
- ruam parah di seluruh tubuh, biasanya disertai dengan demam dan pembengkakan kelenjar getah bening, dan efek pada sel darah dan organ (reaksi obat dengan eosinofilia dan gejala sistemik atau DRESS)

Efek samping di atas tidak mencakup semua efek samping yang berkaitan dengan ERLEADA. Beritahu dokter Anda jika Anda memiliki efek samping yang mengganggu Anda atau yang menetap.

5. Bagaimana cara menyimpan ERLEADA

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
Simpan pada suhu di bawah 30°C.
Batas kedaluarsa setelah kemasan dibuka: 6 minggu.

6. Isi kemasan dan informasi lainnya

Zat aktif ERLEADA adalah apalutamide
Bahan tambahan lainnya adalah colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl methylcellulose-acetate succinate, magnesium stearate, microcrystalline cellulose, dan microcrystalline cellulose (silicified). The film-coating contains iron oxide black, iron oxide yellow, polyethylene glycol, polyvinyl alkohol, talk, dan titanium dioxide.

Seperti apa ERLEADA dan isi didalamnya.

ERLEADA tablet 60 mg berwarna agak kekuningan hingga hijau keabu-abuan, tablet berbentuk lonjong dengan tulisan “AR 60” di satu sisi.

No. Registrasi: DKI2110901817A1

HARUS DENGAN RESEP DOKTER

Dibuat oleh
Janssen Ortho LLC, Gurabo, Puerto Rico, USA

Dikemas primer oleh:
Janssen Ortho LLC, Gurabo, Puerto Rico, USA
Janssen Cilag SpA, Latina, Italy

Dikemas sekunder oleh:
Janssen Ortho LLC, Gurabo, Puerto Rico, USA
Janssen Cilag SpA, Latina, Italy
Janssen Pharmaceutica NV, La Louvière, Belgium

Dirilis oleh:
Janssen Cilag SpA, Latina, Italy

Didaftarkan oleh:
PT Integrated Healthcare Indonesia, Jakarta - Indonesia

Untuk pelaporan efek samping dan keluhan kualitas produk, dapat menghubungi drugsafety@jacid.jnj.com atau telp. (021) 2935-3935.

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