1. NAME OF THE MEDICINAL PRODUCT

ERLEADA® (apalutamide) 60mg Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 60 mg of apalutamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Slightly yellowish to greyish green, oblong-shaped, film-coated tablets (17 mm long x 9 mm wide), debossed with "AR 60" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ERLEADA® is indicated:

- in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (see section 5.1).
- in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) (see section 5.1).

4.2 Posology and method of administration

Treatment with apalutamide should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer.

Posology

The recommended dose is 240 mg (four 60 mg tablets) as an oral single daily dose.

Medical castration with gonadotropin releasing hormone analogue (GnRHa) should be continued during treatment in patients not surgically castrated.

If a dose is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra tablets should not be taken to make up the missed dose.

If a ≥ Grade 3 toxicity or an intolerable adverse reaction is experienced by the patient, dosing should be held rather than permanently discontinuing treatment until symptoms improve to ≤ Grade 1 or original grade, then should be resumed 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 (from 240 mg to 180 mg, and from 180 mg to 120 mg). A maximum of 2 dose level reductions (to 120 mg) is allowed. If further dose reductions are needed, apalutamide should be discontinued. Permanently discontinue apalutamide in patients who develop a seizure during treatment. For the most common adverse reactions, see section 4.8.

Special populations

Elderly
No dose adjustment is necessary for elderly patients (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with mild to moderate renal impairment.

Caution is required in patients with severe renal impairment as apalutamide has not been studied in this patient population (see section 5.2). If treatment is started, patients should be monitored for the adverse reactions listed in section 4.8 and dose reduce as per section 4.2 Posology and method of administration.

Hepatic impairment
No dose adjustment is necessary for patients with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively).

For patients with severe hepatic impairment (Child-Pugh Class C), the recommended dose is 120 mg (two 60 mg tablets) administered orally once daily (see section 5.2).

Paediatric population
There is no relevant use of apalutamide in the paediatric population.

Method of administration

Oral use.

The tablets should be swallowed whole to ensure that the full intended dose is taken. The tablets should not be crushed or split. The tablets can be taken with or without food.
Taking Erleada with non-fizzy beverage or soft food

For patients who cannot swallow tablets whole, Erleada can be dispersed in non-fizzy water and then mixed with one of the following non-fizzy beverages or soft foods; orange juice, green tea, applesauce, drinkable yogurt, or additional water as follows:

1. Place the entire prescribed dose of Erleada in a cup. Do not crush or split the tablets.
2. Add about 20 mL (4 teaspoons) of non-fizzy water to make sure that the tablets are completely in water.

3. Wait 2 minutes until the tablets are broken up and spread out, then stir the mixture.
4. Add in 30 mL (6 teaspoons or 2 tablespoons) of one of the following non-fizzy beverages or soft foods; orange juice, green tea, applesauce, drinkable yogurt, or additional water and stir the mixture.
5. Swallow the mixture immediately.
6. Rinse the cup with enough water to make sure the whole dose is taken and drink it immediately.
7. Do not save the medicinal product/food mixture for later use.

Administration by nasogastric feeding tube

Erleada can also be administered through a nasogastric feeding tube (NG tube) 8 French or greater as follows:

1. Place the entire prescribed dose of Erleada in the barrel of a syringe (use at least a 50 mL syringe) and draw up 20 mL of non-fizzy water into the syringe.
2. Wait 10 minutes and then shake vigorously to disperse the contents completely.
3. Administer immediately through the NG feeding tube.
4. Refill the syringe with non-fizzy water and administer. Repeat until no tablet residue is left in the syringe or feeding tube.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Women who are or may become pregnant (see section 4.6).

4.4 Special warnings and precautions for use

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 randomised studies (SPARTAN and TITAN), seizure occurred in 0.6% of patients receiving apalutamide and in 0.2% of patients treated with placebo. These studies excluded patients with a history of seizure or predisposing factors for seizure.

There is no clinical experience in re-administering ERLEADA® to patients who experienced a seizure.

Falls and fractures

Falls and fractures occurred in patients receiving apalutamide (see section 4.8). Patients should be evaluated for fracture and fall risk before starting ERLEADA® and should continue to be monitored

and managed according to established treatment guidelines and use of bone-targeted agents should be considered.

Ischaemic heart disease and ischaemic cerebrovascular disorders
Ischaemic heart disease and ischaemic cerebrovascular disorders, including events leading to death, occurred in patients treated with apalutamide (see section 4.8). The majority of patients had cardiac/cerebrovascular ischaemic disease risk factors. Patients should be monitored for signs and symptoms of ischaemic heart disease and ischaemic cerebrovascular disorders. Management of risk factors, such as hypertension, diabetes, or dyslipidaemia should be optimised as per standard of care.

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 (see section 4.5). 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 (see section 4.5) 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 of apalutamide 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 (see section 4.5).

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 ischaemic attacks), or clinically significant ventricular arrhythmias were excluded from the clinical studies. Therefore, the safety of apalutamide in these patients has not been established. If ERLEADA® is prescribed, patients with clinically significant cardiovascular disease should be monitored for risk factors such as hypercholesterolaemia, hypertriglyceridaemia, or other cardio-metabolic disorders (see section 4.8). Patients should be treated, if appropriate, after initiating ERLEADA® for these conditions according to established treatment guidelines.

Androgen deprivation therapy may prolong the QT interval
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 (see section 4.5), physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating ERLEADA®.

Severe Cutaneous Adverse Reactions (SCARs)
Postmarketing reports of SCARs including drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), which

can be life-threatening or fatal, have been observed in association with ERLEADA® treatment (see section 4.8).

Patients should be advised of signs and symptoms suggestive of DRESS or SJS/TEN. If these symptoms are observed, ERLEADA® should be withdrawn immediately and patients should seek immediate medical consultation.

ERLEADA® must not be restarted in patients who have experienced DRESS or SJS/TEN while taking ERLEADA® at any time and an alternative treatment should be considered.

Interstitial Lung Disease (ILD)
Cases of ILD have been observed in patients treated with apalutamide, including fatal cases. 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 appropriate treatment initiated as necessary (see section 4.8).

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per 240 mg dose (4 tablets), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The elimination of apalutamide and formation of its active metabolite, N-desmethyl apalutamide, is mediated by both CYP2C8 and CYP3A4 to a similar extent at steady-state. No clinically meaningful changes in their overall exposure is expected as a result of drug interaction with inhibitors or inducers of CYP2C8 or CYP3A4. Apalutamide is an inducer of enzymes and transporters and may lead to an increase in elimination of many commonly used medicinal products.

Potential for other medicinal products to affect apalutamide exposures

Medicinal products 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 C_{max} 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), C_{max} 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 (see section 4.2). Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of apalutamide.

Medicinal products 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 (see section 4.2). Mild or moderate inhibitors of CYP3A4 are not expected to affect the exposure of apalutamide.

Medicinal products 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.

Potential for apalutamide to affect exposures to other medicinal products

Apalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites.

Drug metabolising 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, apalutamide 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 apalutamide 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). Apalutamide did not cause clinically meaningful changes in exposure to the CYP2C8 substrate. Concomitant use of ERLEADA® with medicinal products that are primarily metabolised by CYP3A4 (e.g., darunavir, felodipine, midazolam, simvastatin), CYP2C19 (e.g., diazepam, omeprazole), or CYP2C9 (e.g., warfarin, phenytoin) can result in lower exposure to these medicinal products. Substitution for these medicinal products is recommended when possible or evaluation for loss of efficacy should

be performed if the medicinal product is continued. If given with warfarin, INR should be monitored 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 medicinal products that are substrates of UGT (e.g., levothyroxine, valproic acid) can result in lower exposure to these medicinal products. When substrates of UGT are co-administered with ERLEADA®, 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.

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 apalutamide 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 medicinal products that are substrates of P-gp (e.g., colchicine, dabigatran etexilate, digoxin), BCRP or OATP1B1 (e.g., lapatinib, methotrexate, rosuvastatin, repaglinide) can result in lower exposure of these medicinal products. When substrates of P-gp, BCRP or OATP1B1 are co-administered with ERLEADA®, 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.

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 Analogue
In mHSPC subjects receiving leuprolide acetate (a GnRH analogue), co-administration with apalutamide had no apparent effect on the steady-state exposure of leuprolide.

Laboratory test interference

Falsely elevated digoxin plasma level results with the chemiluminescent microparticle immunoassay (CMIA) have been identified in patients treated with apalutamide, independently of being treated with digoxin. Therefore, results of digoxin plasma levels obtained by CMIA should be interpreted with caution and confirmed by another type of assay before taking any action with digoxin doses.

<u>Medicinal products which prolong the QT interval</u>
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of ERLEADA® with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g., quinidine, disopyramide) or class III (e.g.,

amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics (e.g. haloperidol), etc. should be carefully evaluated (see section 4.4).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
It is not known whether apalutamide or its metabolites are present in semen. ERLEADA® may be harmful to a developing foetus. For patients having sex with female partners of reproductive potential, a condom should be used along with another highly effective contraceptive method during treatment and for 3 months after the last dose of ERLEADA®.

Pregnancy
ERLEADA® is contraindicated in women who are or may become pregnant (see section 4.3). Based on an animal reproductive study and its mechanism of action, ERLEADA® may cause foetal harm and loss of pregnancy when administered to a pregnant woman. There are no data available from the use of ERLEADA® in pregnant women.

Breast-feeding
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 decrease fertility in males of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

ERLEADA® has no or negligible influence on 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.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions are fatigue (26%), skin rash (26% of any grade and 6% Grade 3 or 4), hypertension (22%), hot flush (18%), arthralgia (17%), diarrhoea (16%), fall (13%), and weight decreased (13%). Other important adverse reactions include fractures (11%), decreased appetite (11%) and hypothyroidism (8%).

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies and/or in post-marketing experience are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10);

common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

System Organ Class	Adverse reaction and frequency
Blood and lymphatic system disorders	common: neutropenia
	not known: agranulocytosis
Endocrine disorders	common: hypothyroidism[a]
Metabolism and nutrition disorders	very common: decreased appetite
	common: hypercholesterolaemia, hypertriglyceridaemia
Nervous system disorders	common: dysgeusia, ischaemic cerebrovascular disorders[b]
	uncommon: seizure[c] (see section 4.4), restless legs syndrome
Cardiac disorders	common: ischaemic heart disease[d]
	not known: QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	very common: hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	Not known: interstitial lung disease[e]
Gastrointestinal disorders	very common: diarrhoea
Skin and subcutaneous tissue disorders	very common: skin rash[f]
	common: pruritus, alopecia
	uncommon: lichenoid eruption
	not known: drug reaction with eosinophilia and systemic symptoms (DRESS)[e] , Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)[e]
Musculoskeletal and connective tissue disorders	very common: fracture[g], arthralgia
	common: muscle spasm
General disorders and administration site conditions	very common: fatigue
Investigations	very common: weight decreased
Injury, poisoning and procedural complications	very common: fall

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

[b] Includes transient ischaemic attack, cerebrovascular accident, cerebrovascular disorder, ischaemic stroke, carotid arteriosclerosis, carotid artery stenosis, hemiparesis, lacunar infarction, lacunar stroke, thrombotic cerebral infarction, vascular encephalopathy, cerebellar infarction, cerebral infarction, and cerebral ischaemia

[c] Includes tongue biting

[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 ischaemia

[e] See section 4.4

[f] See "Skin rash" under "Description of selected adverse reactions"

[g] 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. See below.

Description of selected adverse reactions

Skin rash

Skin rash associated with apalutamide 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, dermatitis, and rash vesicular. Adverse reactions of skin rash were reported for 26% of patients treated with apalutamide. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with apalutamide treatment in 6% of patients.

The median days to onset of skin rash was 83 days. Seventy-eight percent of patients had resolution of rash with a median of 78 days to resolution. Medicinal products utilised included topical corticosteroids, oral anti-histamines, and 19% of patients received systemic corticosteroids. Among patients with skin rash, dose interruption occurred in 28% and dose reduction occurred in 14% (see section 4.2). Skin rash recurred in 59% of patients who had dose interruption. Skin rash led to apalutamide treatment discontinuation in 7% of patients who experienced skin rash.

Falls and fractures
In Study ARN-509-003, fracture was reported for 11.7% of patients treated with apalutamide and 6.5% of patients treated with placebo. Half of the patients experienced a fall within 7 days before the fracture event in both treatment groups. Falls were reported for 15.6% of patients treated with apalutamide *versus* 9.0% of patients treated with placebo (see section 4.4).

Ischaemic heart disease and ischaemic cerebrovascular disorders
In a randomised study (SPARTAN) of patients with nmCRPC, ischaemic heart disease occurred in 4% of patients treated with apalutamide and 3% of patients treated with placebo. In a randomised study (TITAN) in patients with mHSPC, ischaemic heart disease occurred in 4% of patients treated with apalutamide and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with apalutamide and 2 patients (0.2%) treated with placebo died from ischaemic heart disease (see section 4.4).

In the SPARTAN study, with a median exposure of 32.9 months for apalutamide and 11.5 months for placebo, ischaemic cerebrovascular disorders occurred in 4% of patients treated with apalutamide and 1% of patients treated with placebo (see above). In the TITAN study, ischaemic cerebrovascular disorders occurred in a similar proportion of patients in the apalutamide (1.5%) and placebo (1.5%) groups. Across the SPARTAN and TITAN studies, 2 patients (0.2%) treated with apalutamide and no patients treated with placebo died from an ischaemic cerebrovascular disorder (see section 4.4).

Hypothyroidism
Hypothyroidism was reported for 8% of patients treated with apalutamide and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. There were no grade 3 or 4 adverse events. Hypothyroidism occurred in 30% of patients already receiving thyroid replacement therapy in the apalutamide arm and in 3% of patients in the placebo arm. In patients not receiving thyroid replacement therapy, hypothyroidism occurred in 7% of patients treated with apalutamide and in 2% of patients treated with placebo. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted (see section 4.5).

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 via the national reporting system.

4.9 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 in section 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, anti-androgens, ATC code: L02BB05

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. Apalutamide treatment decreases tumour cell proliferation and increases apoptosis leading to potent antitumour activity. A major metabolite, N-desmethyl apalutamide, exhibited one-third the *in vitro* activity of apalutamide.

Prostate Specific Antigen (PSA) reduction

Apalutamide 240 mg daily in combination with ADT in patients with mHSPC (in TITAN study) reduced PSA to undetectable levels (<0.2 ng/mL) at any time in 68% of patients compared to 32% of patients taking ADT alone. Median time to undetectable PSA for patients receiving apalutamide in combination with ADT was 1.9 months. Apalutamide in combination with ADT led to a ≥ 50% PSA reduction from baseline at any time in 90% of patients compared to 55% of patients taking ADT alone.

Apalutamide 240 mg daily in combination with ADT in patients with nmCRPC (in SPARTAN study) reduced PSA to undetectable levels (<0.2 ng/mL) at any time in 38% of patients compared to no patients (0%) taking ADT alone. Median time to undetectable PSA for patients receiving apalutamide in combination with ADT was 2.8 months. Apalutamide in combination with ADT led to a ≥ 50% PSA reduction from baseline at any time in 90% of patients compared to 2.2% of patients taking ADT alone.

Cardiac electrophysiology
The effect of apalutamide 240 mg once daily on the QTc interval was assessed in an open-label, uncontrolled, multi-centre, single-arm dedicated QT study in 45 patients with CRPC. At steady-state, 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 efficacy and safety
The efficacy and safety of apalutamide has been established in two Phase 3 randomised, placebo-controlled studies, Study ARN-509-003 (nmCRPC) and 56021927PCR3002 (mHSPC).

TITAN: Metastatic Hormone-sensitive Prostate Cancer (mHSPC)

TITAN was a randomised, double-blind, placebo-controlled, multinational, multicentre clinical study in which 1052 patients with mHSPC were randomised (1:1) to receive either apalutamide

orally at a dose of 240 mg once daily (N = 525) or placebo once daily (N = 527). All patients were required to have at least one bone metastasis on Technetium ^{99m} bone scan. Patients were excluded if the site of metastases was limited to either the lymph nodes or viscera (e.g., liver or lung). All patients in the TITAN study received concomitant GnRH analogue or had prior bilateral orchiectomy. Around 11% of patients received prior treatment with docetaxel (maximum of 6 cycles, last dose ≤ 2 months prior to randomisation and maintained response prior to randomisation). The exclusion criteria included known brain metastases; prior treatment with other next generation anti-androgens (eg, enzalutamide), CYP17 inhibitors (eg, abiraterone acetate), immunotherapy (eg, sipuleucel-T), radiopharmaceutical agents or other treatments for prostate cancer; or history of seizure or condition that may predispose to seizure. Patients were stratified by Gleason score at diagnosis, prior docetaxel use, and region of the world. Patients with both high- and low-volume mHSPC were eligible for the study. High-volume disease was defined as either visceral metastases and at least 1 bone lesion or at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis. Low-volume disease was defined as the presence of bone lesion(s) not meeting the definition of high-volume.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 68 years (range 43-94) and 23% of patients were 75 years of age or older. The racial distribution was 68% Caucasian, 22% Asian, and 2% Black. Sixty-three percent (63%) of patients had high-volume disease and 37% had low-volume disease. Sixteen percent (16%) of patients had prior surgery, radiotherapy of the prostate or both. A majority of patients had a Gleason score of 7 or higher (92%). Sixty-eight percent (68%) of patients received prior treatment with a first-generation anti-androgen in the non-metastatic setting. Although criteria for castration resistance were not determined at baseline, 94% of patients demonstrated a decrease in prostate specific antigen (PSA) from initiation of androgen deprivation therapy (ADT) to first dose of apalutamide or placebo. All patients except one in the placebo group, had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry. Among the patients 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 patients treated with placebo received subsequent anti-cancer therapy compared to patients treated with Erleada® (54%).

The major efficacy outcome measures of the study were overall survival (OS) and radiographic progression-free survival (rPFS). Efficacy results of TITAN are summarised in Table 2 and Figures 1 and 2.

Table 2: Summary of efficacy results – Intent-to-treat mHSPC 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,e]	<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 favours 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.
[e] This p-value is nominal instead of being used for formal statistical testing.

NE=Not Estimable

A statistically significant improvement in OS and rPFS was demonstrated in patients randomised to receive Erleada® compared with patients randomised to receive placebo in the primary analysis. 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. The improvement in OS was demonstrated even though 39% of patients 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 patient subgroups including high- or low-volume disease, metastasis stage at diagnosis (M0 or M1), prior docetaxel use (yes or no), age (< 65, ≥ 65, or ≥ 75 years old), baseline PSA above median (yes or no), and number of bone lesions (≤ 10 or > 10).

Consistent improvement in OS was observed across patient subgroups including high- or low-volume disease, metastasis stage at diagnosis (M0 or M1), and Gleason score at diagnosis (≤ 7 vs. > 7).

Figure 1: Kaplan-Meier plot of updated overall survival (OS); Intent-to-treat mHSPC population (TITAN)

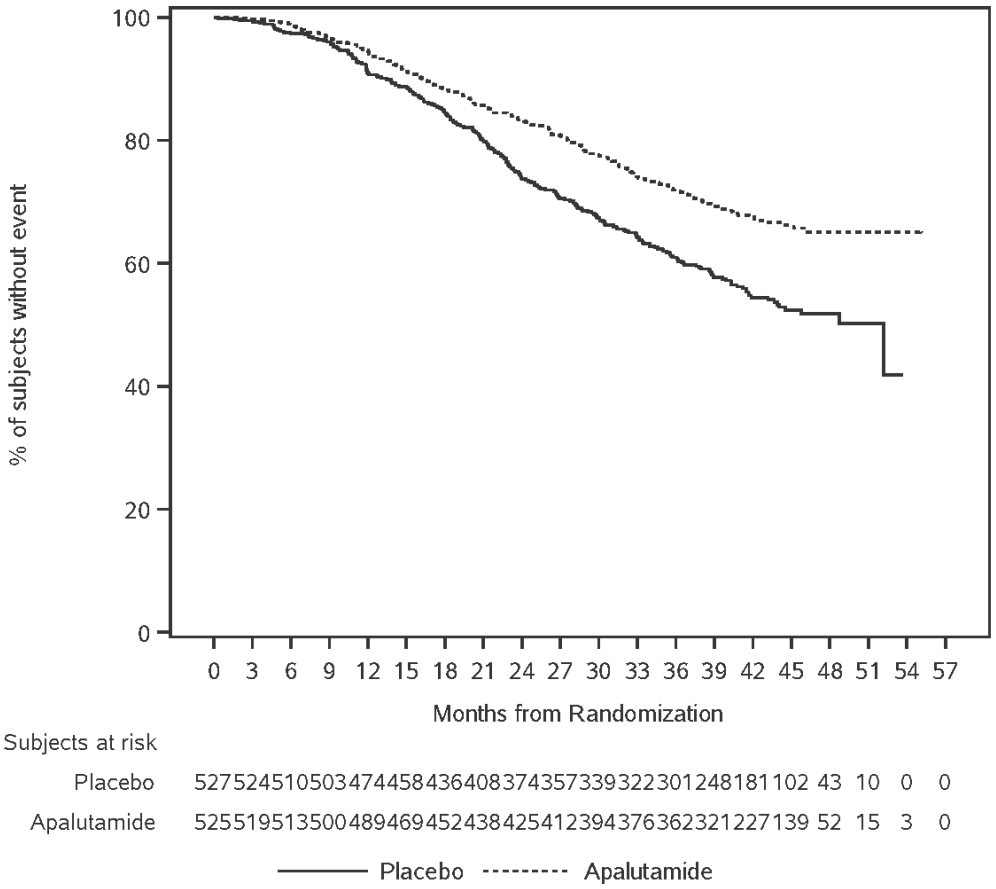
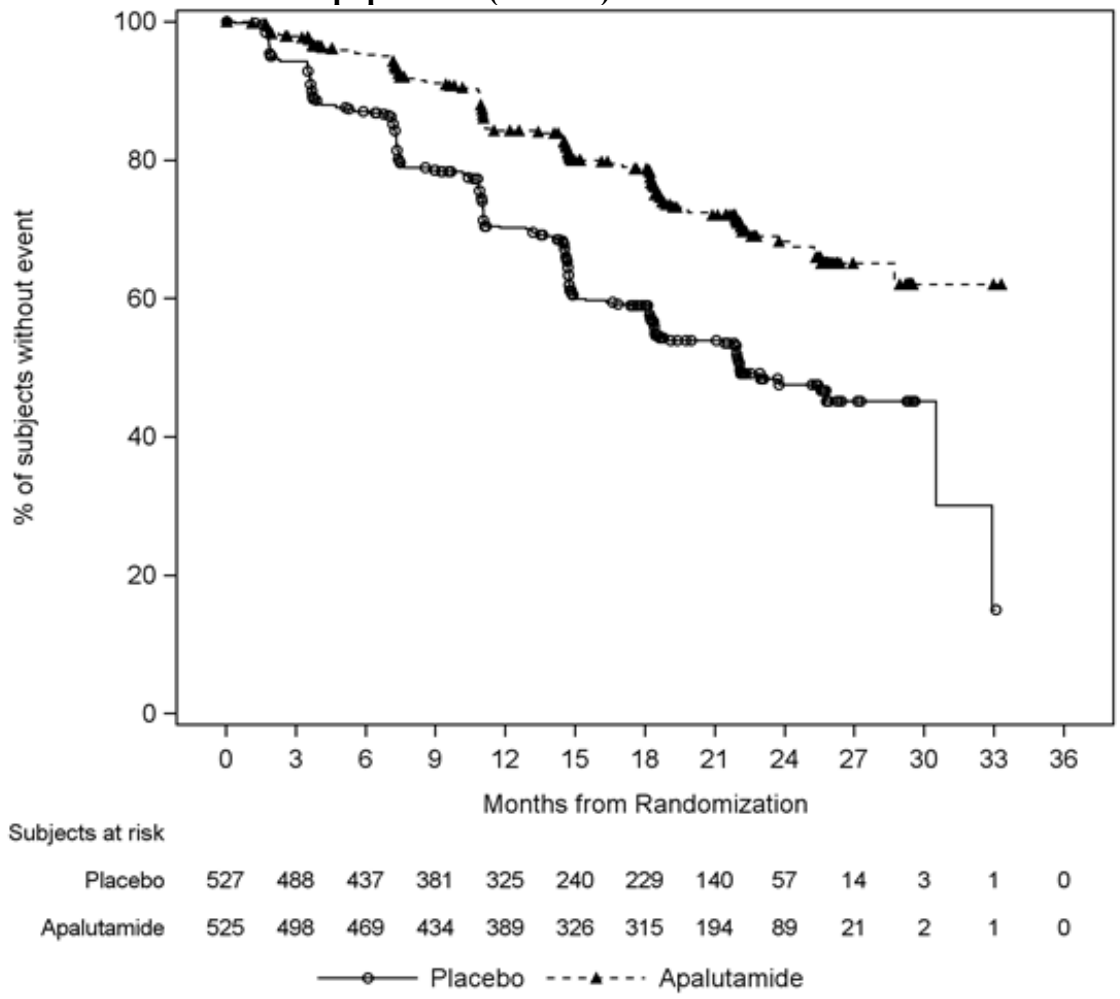


Figure 2: Kaplan-Meier plot of radiographic progression-free survival (rPFS); Intent-to-treat mHSPC population (TITAN)



Treatment with Erleada® statistically significantly delayed the initiation of cytotoxic chemotherapy (HR = 0.391, 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.

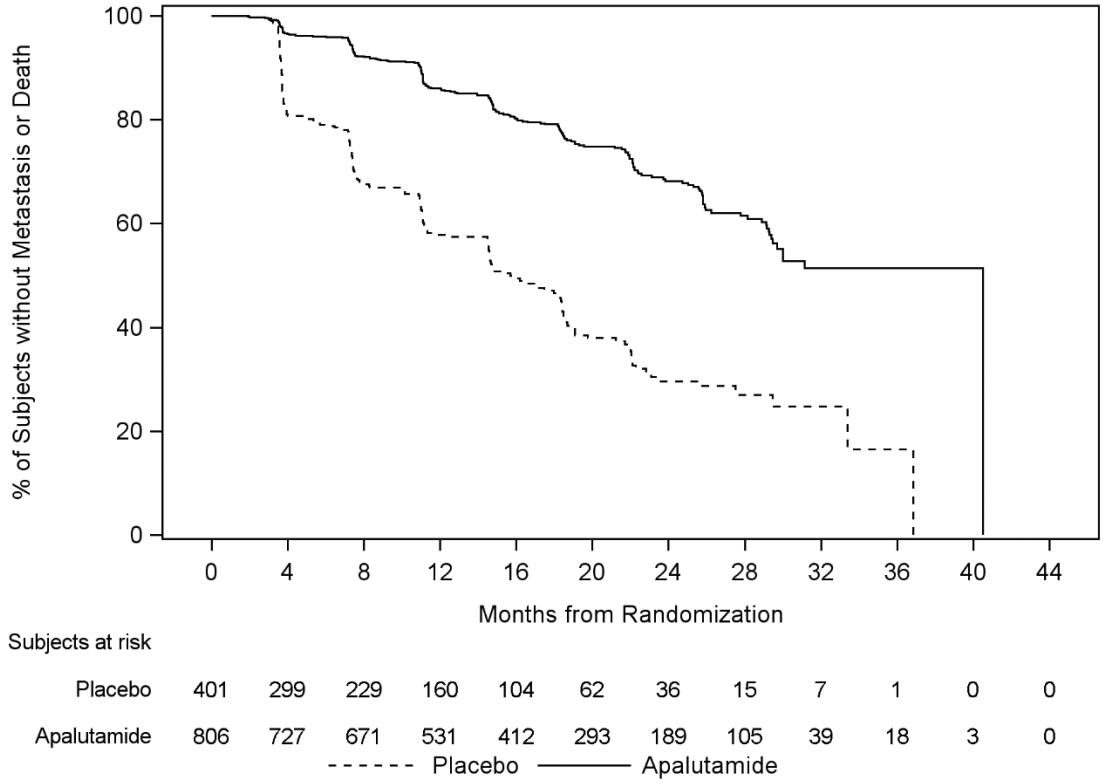
SPARTAN: Non-Metastatic Castration Resistant Prostate Cancer (nmCRPC)

A total of 1207 subjects with NM-CRPC were randomised 2:1 to receive either apalutamide orally at a dose of 240 mg once daily in combination with androgen deprivation therapy (ADT) (medical castration or prior surgical castration) or placebo with ADT in a multicentre, double-blind, clinical study (Study ARN-509-003). Subjects enrolled had a Prostate Specific Antigen (PSA) Doubling Time (PSADT) ≤ 10 months, considered to be at high risk of imminent metastatic disease and prostate cancer-specific death. All subjects who were not surgically castrated received ADT continuously throughout the study. PSA results were blinded and were not used for treatment discontinuation. Subjects randomised 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.

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. 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. 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) was the primary endpoint, defined as the time from randomisation 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 relative risk of distant metastasis or death by 70% compared to placebo (HR = 0.30; 95% CI: 0.24, 0.36; p < 0.0001). The median MFS for ERLEADA® was 41 months and was 16 months for placebo (see Figure 3). Consistent improvement in MFS with ERLEADA® was observed for all pre-specified subgroups, including age, race, region of the world, nodal status, prior number of hormonal therapies, baseline PSA, PSA doubling time, baseline ECOG status and use of bone-sparing agents.

Figure 3: Kaplan-Meier metastasis-free survival (MFS) curve in Study ARN-509-003

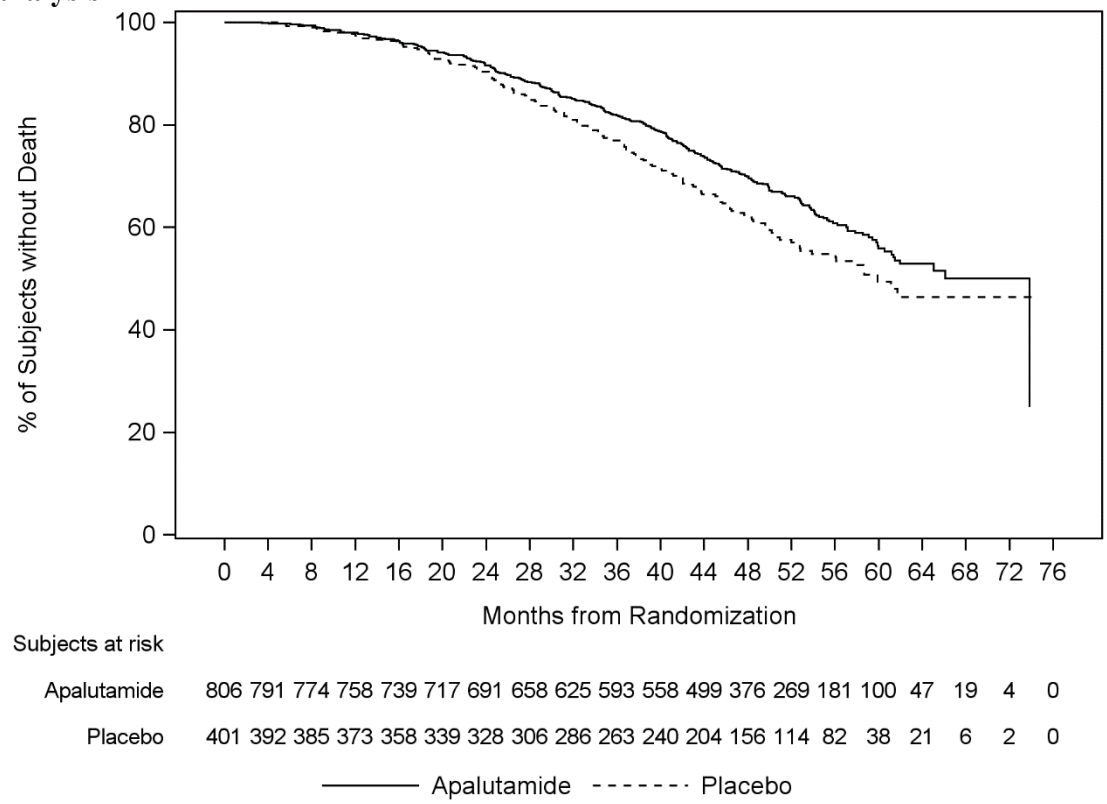


Taking account of all data, subjects treated with ERLEADA® and ADT showed significant improvement over those treated with ADT alone for the following secondary endpoints of time to metastasis (HR = 0.28; 95% CI: 0.23, 0.34; p < 0.0001), progression-free survival (PFS) (HR = 0.30; 95% CI: 0.25, 0.36; p < 0.0001); time to symptomatic progression (HR = 0.57; 95% CI: 0.44, 0.73; p < 0.0001); overall survival (OS) (HR = 0.78; 95% CI: 0.64, 0.96; p = 0.0161) and time to initiation of cytotoxic chemotherapy (HR = 0.63; 95% CI: 0.49, 0.81; p = 0.0002).

Time to symptomatic progression was defined as time from randomisation to development of a skeletal related event, pain/symptoms requiring initiation of a new systemic anti-cancer therapy, or loco-regional tumour progression requiring radiation/surgery. While the overall number of events was small, the difference between the two arms was sufficiently large to reach statistical significance. Treatment with ERLEADA® decreased the risk of symptomatic progression by 43% compared with placebo (HR = 0.567; 95% CI: 0.443, 0.725; p < 0.0001). The median time to symptomatic progression was not reached in either treatment group.

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) was crossed and statistical significance was achieved. This improvement was demonstrated even though 19% of patients in the placebo arm received ERLEADA® as subsequent therapy.

Figure 4: Kaplan-Meier overall survival (OS) curve in Study ARN-509-003 at 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.

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

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 favour of ERLEADA® observed in the analysis of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score and subscales.

5.2 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 characterised 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.

<u>Absorption</u>
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 section 4.2).

Apalutamide is not ionisable 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.

In vitro, apalutamide and its N-desmethyl metabolite are substrates for P-gp. 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.

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.

Biotransformation

Following single oral administration of ^{14}C-labelled 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 metabolised primarily by CYP2C8 and CYP3A4 to form N-desmethyl apalutamide. Apalutamide and N-desmethyl apalutamide are further metabolised 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 the level of contribution is expected to change at steady-state due to induction of CYP3A4 by apalutamide after repeat dose.

Elimination

Apalutamide, mainly in the form of metabolites, is eliminated primarily via urine. Following a single oral administration of radiolabelled 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 faeces (1.5% of dose as unchanged apalutamide and 2% as N-desmethyl apalutamide).

The apparent oral clearance (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 patients is about 3 days at steady-state.

In vitro data indicate that apalutamide and its N-desmethyl metabolite are not substrates for BCRP, OATP1B1 or OATP1B3.

Special populations

The effects of renal impairment, hepatic impairment, age, race, and other extrinsic factors on the pharmacokinetics of apalutamide are summarised below.

Renal impairment
A dedicated renal impairment study for apalutamide 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 apalutamide exposure was observed in subjects with pre-existing mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] between 30 to 89 mL/min/1.73 m^2; N=585) compared to subjects with baseline normal renal function (eGFR ≥ 90 mL/min/1.73 m^2; N=372). The potential effect of severe renal impairment or end stage renal disease (eGFR ≤29 mL/min/1.73 m^2) have not been established due to insufficient data.

Hepatic impairment
A dedicated hepatic impairment study compared the systemic exposure of apalutamide and N-desmethyl apalutamide in subjects with baseline mild hepatic impairment (N=8, Child-Pugh Class A, mean score = 5.3) or moderate hepatic impairment (N=8, Child-Pugh Class B, mean score = 7.6) *versus* healthy controls with normal hepatic function (N=8). Following a single oral 240 mg dose of apalutamide, the geometric mean ratio (GMR) for AUC and C_{max} for apalutamide in subjects with mild impairment was 95% and 102%, respectively, and the GMR for AUC and C_{max} of apalutamide in subjects with moderate impairment was 113% and 104%, respectively, compared to healthy control subjects.

Another dedicated hepatic impairment study compared the systemic exposure of apalutamide and N-desmethyl apalutamide in subjects with baseline severe hepatic impairment (N=10, Child-Pugh Class C, mean score = 10.9) *versus* healthy controls with normal hepatic function (N=8). Following a single oral dose of 120 mg or 240 mg of apalutamide for severe hepatic impairment or normal hepatic function, respectively, the dose-normalised geometric mean ratio (GMR) for AUC and C_{max} for unbound apalutamide in subjects with severe impairment was 206% and 156%, respectively (see section 4.2).

Ethnicity and race
Based on population pharmacokinetic analysis, there were no clinically relevant differences in apalutamide pharmacokinetics between White (Caucasian or Hispanic or Latino; N=761), Black (of African heritage or African American; N=71), Asian (non-Japanese; N=58) and Japanese (N=58).

Age
Population pharmacokinetic analyses showed that age (range: 18 to 94 years) does not have a clinically meaningful influence on the pharmacokinetics of apalutamide.

5.3 Preclinical safety data

Apalutamide was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests.
Apalutamide was not carcinogenic in a 6-month study in the male transgenic (Tg.rasH2) mouse at doses up to 30 mg/kg per day, which is 1.2 and 0.5 times for apalutamide and N-desmethyl apalutamide respectively, the clinical exposure (AUC) at the recommended clinical dose of 240 mg/day.

In a 2-year 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). Neoplastic findings were noted including 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.

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 and dogs, atrophy, aspermia/hypospermia, degeneration and/or hyperplasia or hypertrophy in the reproductive system were observed at doses corresponding to exposures approximately equal to 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 doses corresponding to exposures 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 preliminary embryofoetal developmental toxicity study in rats, apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-20). These doses resulted in systemic exposures approximately 2, 4 and 6 times, respectively, on an AUC basis, the exposure in humans at the dose of 240 mg/day. Findings included non-pregnant females at 100 mg/kg/day and embryofoetal lethality (resorptions) at doses ≥ 50 mg/kg/day, decreased foetal anogenital distance and a misshapen pituitary gland (more rounded shape) at ≥ 25 mg/kg/day. Skeletal variations (unossified phalanges, supernumerary short thoracolumbar rib(s) and/or abnormalities of the hyoid) were also noted at doses ≥ 25 mg/kg/day, without resulting in an effect on mean foetal weight.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Colloidal anhydrous silica
Croscarmellose sodium
Hypromellose acetate succinate
Magnesium stearate
Microcrystalline cellulose
Microcrystalline cellulose (silicified)

Film-coating
Iron oxide black (E172)
Iron oxide yellow (E172)

Macrogol
Polyvinyl alcohol (partially hydrolysed)
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package to protect from light and moisture. Do not remove desiccant from the bottle. Keep out of the sight and reach of children.

6.5 Nature and contents of container

ERLEADA® is available in white opaque high-density polyethylene (HDPE) bottle with a polypropylene (PP) child-resistant closure and induction seal liner. Each bottle contains 120 film-coated tablets and a total of 6 g of silica gel desiccant.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Janssen Ortho LLC
State Road 933, Km 0.1, Mamey Ward,
Gurabo, Puerto Rico 00778, United States.

8. PRODUCT REGISTRATION HOLDER

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Level 8, The Pinnacle,
Persiaran Lagoon, Bandar Sunway,
46150, Petaling Jaya, Selangor, Malaysia

9. DATE OF REVISION OF THE TEXT

19 May 2026 (Based on EU SmPC v26Mar2026)