▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

ERLYAND®

APALUTAMIDE

AUSTRALIAN PRODUCT INFORMATION

1. NAME OF THE MEDICINE

Apalutamide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ERLYAND 60 mg tablets contain 60 mg of apalutamide.

For a full list of excipients, see **section 6.1** List of excipients.

3. PHARMACEUTICAL FORM

ERLYAND is supplied as slightly yellowish green to greyish green, oblong-shaped, film-coated tablets, debossed with “AR 60” on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ERLYAND (apalutamide) is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (see **section 5.1 Clinical trials**).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose in adults

The recommended dose of ERLYAND is 240 mg (four 60 mg tablets) administered orally once daily.

Patients should concurrently receive a gonadotropin-releasing hormone (GnRH) analogue, unless they have had a bilateral orchiectomy.

Method of administration

ERLYAND should be administered orally once daily, with or without food. The tablets should be swallowed whole.

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.

Dosage adjustment

Adverse effects

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse 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.

Hepatic insufficiency

No dosage adjustment is necessary for patients with baseline mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

No data are available in patients with severe hepatic impairment (Child-Pugh class C), see **section 5.2 Special populations**.

Renal insufficiency

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

No data are available in patients with severe renal impairment or end-stage renal disease (eGFR £ 29 mL/min/1.73m^2), see **section 5.2 Special populations**.

Use in the elderly

No dosage adjustment is necessary based on patient age (see **sections 4.4 Special warnings and precautions for use** and **5.2 Special populations**).

Paediatric use

The safety and efficacy of ELYAND in patients aged less than 18 years have not been established (see **section 4.4 Special warnings and precautions for use**).

4.3 CONTRAINDICATIONS

ERLYAND is contraindicated in women who are or may become pregnant, see **section 4.6 Use in pregnancy**.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Falls and Fractures

Evaluate patients for fracture and fall risk and manage according to established treatment guidelines, including consideration of bone-targeted agents.

ERLYAND adds to the increased risk of osteopenia and osteoporosis associated with prolonged ADT therapy, which may contribute to the increased risk of fall and injury. Falls and fall-related injuries (including non-pathological fractures) occurred in patients receiving ERLYAND in the registrational study, and one patient died due to a skull fracture after a fall. Fall and fall-related injuries occurred more commonly in patients over 75 years of age. See **section 4.8 Description of selected adverse events**.

Seizure

Permanently discontinue ERLYAND in patients who develop a seizure during treatment. Advise patients of the risk of developing a seizure while receiving ERLYAND and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. It is

unknown whether anti-epileptic medications will prevent seizures with ERLYAND. There is no clinical experience in re-administering ERLYAND to patients who experienced a seizure.

Seizure occurred in 2 patients (0.2%) receiving ERLYAND in the registrational study, in which subjects with a history of seizure or predisposing factors for seizure were excluded from participating. See **sections 4.8 Description of selected adverse events** and **4.7 Effects on ability to drive and use machines**.

Hypothyroidism

Initiation or adjustment of thyroid replacement therapy may be required. As levothyroxine exposure may be reduced when it is co-administered with apalutamide, evaluate for loss of levothyroxine efficacy and need for dose adjustment (see **section 4.5 Effects of ERLYAND on other medicines**).

Hypothyroidism occurred in patients receiving ERLYAND in the registrational study, based on elevation of thyroid-stimulating hormone (TSH). Hypothyroidism occurred more commonly in patients who were already receiving thyroid replacement therapy, and in patients > 75 years of age (see **section 4.8 Description of selected adverse events).**

Cardiac effects

Ischaemic heart disease (IHD)

Patients with a cardiac history should be assessed for active cardiac disease before starting treatment with ERLYAND. The safety of ERLYAND has not been characterised in patients with recent (within 6 months) significant cardiovascular disease (including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial/venous thromboembolic events, clinically significant ventricular arrhythmias and uncontrolled hypertension), as these patients were excluded from the registrational trial.

Adverse events indicative of ischaemic heart disease and cardiac failure were reported more frequently in patients treated with ERLYAND in the registrational study, including 3 fatal myocardial infarctions (see section **4.8 Description of selected adverse events)**.

QT interval prolongation

In patients with a history of QT prolongation, who are taking concomitant medications that may prolong the QT interval, or who have other risk factors for torsades de pointes, consider electrocardiogram (ECG) and electrolyte monitoring.

In a dedicated QT study in patients with CRPC taking ERLYAND 240 mg once daily plus ADT, based on the longest QTcF change at any time for each patient at steady-state, the mean maximum QTcF change from baseline (ΔQTcF) was 20.2 msec (upper 90% CI bound 23.7 msec). Pharmacokinetic and pharmacodynamic analysis showed a concentration-dependent increase in QTcF with apalutamide and N-desmethyl apalutamide. See **section 5.1 Pharmacodynamic effects**.

Use in hepatic impairment

See **section 4.2 Dose and Method of Administration *Dosage adjustment in Hepatic insufficiency***

Use in renal impairment

See **section 4.2 Dose and Method of Administration *Dosage adjustment in Renal insufficiency***

Use in the elderly

Of the 803 patients who received ERLYAND in the SPARTAN study, 87% were ≥65 years, 49% were ≥75 years and 26% were ≥80 years of age. In patients aged ≥75 years, the incidence of severe (grade 3 or higher) adverse events was 52% in the ERLYAND arm and 38% in the placebo arm. Falls, fall-related injuries and hypothyroidism occurred more frequently in patients older than 75 years, and all patients who died from adverse reactions were over 75 years of age.

No overall differences in effectiveness between older patients and younger patients were observed.

See **section 4.2 Dose and Method of Administration *Dosage adjustment Use in the elderly.***

Paediatric use

The safety and efficacy of ERLYAND in patients aged less than 18 years have not been established. No data are available (see **section 4.2 Dose and Method of Administration**).

Effects on laboratory tests

See **section 4.8 Adverse effects**.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicines on ERLYAND

CYP2C8 inhibitors

Apalutamide C_{max} decreased by 21% while AUC increased by 68% following co-administration of ERLYAND as a 240 mg single dose with gemfibrozil (a strong CYP2C8 inhibitor). Gemfibrozil is predicted to increase the steady-state apalutamide C_{max} by 32% and AUC by 44%. For the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide), the predicted steady-state C_{max} increased by 19% and AUC by 23%.

No initial dose adjustment is necessary however, reduce the ERLYAND dose based on tolerability [see **section 4.2 Adverse effects**]. Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of apalutamide.

CYP3A4 inhibitors

Apalutamide C_{max} decreased by 22% while AUC was similar following co-administration of ERLYAND as a 240 mg single dose with itraconazole (a strong CYP3A4 inhibitor). Ketoconazole (a strong CYP3A4 inhibitor) is predicted to increase the steady-state apalutamide C_{max} by 38% and AUC by 51%. For the active moieties, the predicted steady-state C_{max} increased by 23% and AUC by 28%.

No initial dose adjustment is necessary however, reduce the ERLYAND dose based on tolerability (see **section 4.2 Adverse effects**). Mild or moderate inhibitors of CYP3A4 are not expected to affect the exposure of apalutamide.

CYP3A4/CYP2C8 inducers

Rifampin (a strong CYP3A4 and moderate CYP2C8 inducer) is predicted to decrease the steady-state apalutamide C_{max} by 25% and AUC by 34%. For the active moieties, the predicted steady-state C_{max} decreased by 15% and AUC by 19%.

Acid lowering agents

Apalutamide is not ionisable under relevant physiological pH conditions, therefore acid lowering agents (e.g. proton pump inhibitors, H_2-receptor antagonists, antacids) 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.

Effects of ERLYAND on other medicines

Effect of ERLYAND on drug metabolising enzymes

CYP 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.

In humans, ERLYAND is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. Co-administration of ERLYAND with single oral doses of sensitive CYP substrates resulted in a 92% decrease in the AUC of midazolam (a CYP3A4 substrate), 85% decrease in the AUC of omeprazole (a CYP2C19 substrate), and 46% decrease in the AUC of S-warfarin (a CYP2C9 substrate). ERLYAND did not cause clinically meaningful changes in exposure to pioglitazone (a CYP2C8 substrate).

Concomitant use of ERLYAND with medications that are primarily metabolised 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 Normalised Ratio (INR) during ERLYAND treatment.

UGT

Apalutamide may induce UDP-glucuronosyl transferase (UGT).

Concomitant administration of ERLYAND 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 ERLYAND and evaluate for loss of efficacy (see **Section 4.4 Hypothyroidism**).

Effect of apalutamide on drug transporters

P-gp, BCRP and OATP1B1

Apaluatmide 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. Co-administration of ERLYAND with single oral doses of transporter substrates resulted in a 30% decrease in the AUC of fexofenadine (a P-gp substrate) and 41% decrease in the AUC of rosuvastatin (a BCRP/OATP1B1 substrate) but had no impact on C_{max}.

Concomitant use of ERLYAND 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 ERLYAND and evaluate for loss of efficacy if medication is continued.

OCT2, OAT1, OAT3 and MATEs
In vitro, apalutamide and N-desmethyl apalutamide inhibit organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3) and multidrug and toxin extrusions (MATEs), and do not inhibit organic anion transporter 1. Apalutamide is not predicted to cause clinically significant changes in exposure to OAT3 substrates.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Based on animal studies, apalutamide may impair fertility in males of reproductive potential.

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 (0.5 times the human exposure based on AUC) and ≥ 2.5 mg/kg/day in dogs (0.5 times the human exposure based on AUC).

In a fertility study 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 (0.5 times the human exposure based on AUC). Effects on male rats were reversible after 8 weeks from the last apalutamide administration.

Use in pregnancy

Category D

ERLYAND is contraindicated in women who are or may become pregnant. Based on its mechanism of action, ERLYAND may cause fetal harm when administered during pregnancy. There are no data available with the use of ERLYAND during pregnancy in humans.

ERLYAND 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 ERLYAND.

Animal embryofetal development studies have not been conducted with ERLYAND.

Use in lactation

ERLYAND is not indicated for use in females. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of ERLYAND on the ability to drive or use machines have been performed. Patients with a history of seizures or other predisposing factors should be advised of the risk of driving or operating machines (see **section 4.4 Special warnings and precautions for use - Seizure).**

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Because clinical trials are conducted under widely varying conditions, adverse event 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 practice.

SPARTAN was a randomised (2:1), double-blind, placebo-controlled, multi-centre clinical study, that enrolled patients who had non-metastatic, castration-resistant prostate cancer (NM-CRPC). In this study, patients received either ERLYAND at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analogue or had a bilateral orchiectomy. The median duration of exposure was 16.9 months (range: 0.1 to 42 months) in patients who received ERLYAND and 11.2 months (range: 0.1 to 37 months) in patients who received placebo.

Overall, 8 patients (1%) who were treated with ERLYAND died from adverse events. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral haemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse event of cardiopulmonary arrest (n=1). ERLYAND was discontinued due to adverse events in 11% of patients, most commonly from rash (3%). Adverse events leading to dose interruption or reduction of ERLYAND occurred in 33% of patients; the most common (>1%) were rash, diarrhoea, fatigue, nausea, vomiting, hypertension, and haematuria. Serious adverse events occurred in 25% of ERLYAND - treated patients and 23% in patients receiving placebo. The most common serious adverse events (>2%) were fracture (3%) in the ERLYAND arm and urinary retention (4%) in the placebo arm.

Table 1 shows adverse events occurring in ≥10% on the ERLYAND arm in SPARTAN that occurred with a 2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLYAND arm compared to placebo.

Table 1: Adverse events in the SPARTAN study that occurred in ≥10% of ERLYAND-treated patients, and with at least a 2% absolute increase in frequency compared to placebo.

	ERLYAND N=803		**Placebo N=398**	
Median duration of follow up	***19 months***		***13 months***	
System/Organ Class	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Adverse event	**%**	**%**	**%**	**%**
General disorders and administration site conditions				
Fatigue[1,2]	39	1	28	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush[2]	14	0	9	0
Skin and subcutaneous tissue disorders				
Skin rash[3]	24	5	6	0.3
Gastrointestinal disorders				
Diarrhoea	20	1	15	0.5
Nausea	18	0	16	0
Injury, poisoning and procedural complications				
Fall[2]	16	2	9	0.8
Fracture[4]	12	3	7	0.8
Musculoskeletal and connective tissue disorders				
Arthralgia[2]	16	0	8	0
Investigations				
Weight decreased[2]	16	1	6	0.3
Metabolism and nutrition disorders				
Decreased appetite[5]	12	0.1	9	0
Peripheral oedema[6]	11	0	9	0

[1] Includes fatigue and asthenia
[2] Grade 4 definitions do not exist for these reactions
[3] Includes 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
[4] 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
[5] Includes appetite disorder, decreased appetite, early satiety, and hypophagia
[6] Includes peripheral oedema, generalised oedema, oedema, oedema genital, penile oedema, peripheral swelling, scrotal oedema, lymphoedema, swelling, and localised oedema

Additional clinically significant adverse events occurring in at least 2% of patients treated with ERLYAND included:

- Hypothyroidism – 8.1% versus 2.0% on placebo (includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine decreased, autoimmune thyroiditis, thyroxine free decreased, tri-iodothyronine decreased).
- Dysgeusia – 7.1% versus 1.5% on placebo.
- Pruritus - 6.2% versus 2.0% on placebo.
- Ischaemic heart disease – 3.7% versus 2.0% on placebo (includes angina pectoris, coronary artery disease, myocardial infarction, myocardial ischaemia, angina unstable, arteriosclerosis coronary artery, acute coronary syndrome, acute myocardial infarction, coronary artery occlusion, silent myocardial infarction).
- Depression – 3.9% versus 2.0% on placebo (includes depression, major depression and suicidal ideation).
- Heart failure – 2.2% versus 1.0% on placebo.

Table 2: Laboratory abnormalities occurring in ≥15% of ERLYAND-treated patients and at a higher incidence than placebo (between arm difference >5% all grades) in SPARTAN,

	ERLYAND N=803		Placebo N=398	
Laboratory Abnormality	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Haematology				
Anaemia	70	0.4	64	0.5
Leukopenia	47	0.3	29	0
Lymphopenia	41	2	21	2
Chemistry				
Hypercholesterolaemia[1]	76	0.1	46	0
Hyperglycaemia[1]	70	2	59	1
Hypertriglyceridemia[1]	67	2	49	0.8
Hyperkalaemia	32	2	22	0.5

[1] Does not reflect fasting values

Description of selected adverse events

Falls and Fractures

In the SPARTAN study, falls were reported for 16% of subjects treated with ERLYAND versus 9% of subjects treated with placebo, and were not associated with loss of consciousness or seizure. Non-pathological fracture was reported for 12% of subjects treated with ERLYAND and 7% of subjects treated with placebo. In half of these cases in both arms, a fall had occurred in the proceeding 7 days. Severity was grade 3-4 in 3% of patients treated with ERLYAND and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLYAND. Routine bone density assessment and treatment of osteoporosis with bone targeted agents were not performed in the SPARTAN study. See **section 4.4 Special warnings and precautions for use.**

Seizure

In the SPARTAN study, two patients (0.2%) treated with ERLYAND experienced a seizure versus none in the placebo arm. Seizure occurred from 354 to 475 days after initiation of ERLYAND. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded from the study. See **section 4.4 Special warnings and precautions for use**.

Hypothyroidism

Hypothyroidism was reported for 8% of subjects treated with ERLYAND and 2% of subjects treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. The median onset was Day 113. There were no grade 3 or 4 adverse events.

In patients who were already receiving thyroid replacement therapy, hypothyroidism occurred in 28% of subjects in the apalutamide arm and in 6% of subjects in the placebo arm. In subjects not previously receiving thyroid replacement therapy, hypothyroidism occurred in 6% of subjects treated with apalutamide and in 1% of subjects treated with placebo.

Thyroid replacement therapy was initiated in 7% of patients treated with ERLYAND. In patients who discontinued ERLYAND and had a reported event of hypothyroidism (n=14), the event resolved in 5 patients (36%). In patients who discontinued ERLYAND and had increased laboratory values for TSH (>5.5 mIU/L) (n=45), TSH levels returned to normal in 27 patients (60%). See **sections 4.4 Special warnings and precautions for use and 4.5 Effect of ERLYAND on drug metabolising enzymes**).

Skin Rash

In the SPARTAN study, skin rash associated with ERLYAND was most commonly described as macular or maculo-papular. Adverse events of skin rash were reported for 24% of subjects treated with ERLYAND versus 5.5% of subjects treated with placebo. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLYAND treatment (5.2%) versus placebo (0.3%).

The onset of skin rash occurred at a median of 82 days of ERLYAND treatment and resolved in 81% of patients, within a median of 60 days from onset (range: 2 to 709 days). Four (4%) of patients treated with ERLYAND received systemic corticosteroids for treatment of skin rash. Rash recurred in approximately half of patients who were re-challenged with ERLYAND. Rash led to dose interruption in 28%, dose reduction in 12% and treatment discontinuation in 9% of cases.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Treatment

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLYAND, undertake general supportive measures until clinical toxicity has been diminished or resolved. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

Pharmacodynamic effects

Effect on $GABA_A$-gated chloride channel

$GABA_A$ inhibition is an off-target activity of both apalutamide and N-desmethyl apalutamide. This is considered the mechanism for the seizures/convulsions observed at high doses in toxicology studies in animals.

Effect on QT/QTc interval and cardiac electrophysiology

Apalutamide and N-desmethyl apalutamide inhibit the hERG K+ channel with an IC_{50} below steady-state C_{max} at the recommended dose. In a dedicated QT study in men with CRPC administered apalutamide 240 mg once daily plus ADT, based on the longest QTcF change at any time for each patient at steady-state, the mean maximum QTcF change from baseline (ΔQTcF) was 20.2 msec (upper 90% CI bound 23.7 msec). Pharmacokinetic and pharmacodynamic analysis showed a concentration-dependent increase in QTcF with apalutamide and N-desmethyl apalutamide. See **section 4.4 Special warnings and precautions for use.**

Clinical trials

SPARTAN (Study ARN 509-003) was a multicentre, double-blind, randomised, placebo-controlled clinical trial in which 1207 subjects with NM-CRPC were randomised 2:1 to receive either ERLYAND orally at a dose of 240 mg once daily (n=806) or placebo once daily (n=401). All patients received a concomitant gonadotropin-releasing hormone (GnRH) analogue, or had a bilateral orchiectomy. Patients were required to have a PSADT ≤ 10 months and confirmation of non-metastatic disease by blinded independent central review (BICR). Patients were stratified by

Prostate Specific Antigen (PSA) Doubling Time (PSADT; >6 months vs ≤ 6 months), the use of bone-sparing agents, and presence of locoregional disease. Systemic corticosteroids were not allowed at study entry. PSA results were blinded and were not used for treatment discontinuation. Subjects randomised to either arm discontinued treatment for disease progression confirmed by BICR, initiation of new treatment, unacceptable toxicity or withdrawal. Upon BICR-confirmed development of distant metastatic disease, subjects were offered abiraterone acetate 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. In the SPARTAN study, metastases were detected by technetium-99m bone scan, CT or MRI of the chest, abdomen and pelvis. Seventy-three percent (73%) of subjects had received prior treatment with a first-generation anti-androgen; 69% of subjects had received bicalutamide and 10% of subjects had received flutamide. All subjects enrolled had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) performance status score of 0 or 1 at study entry. Among the patients who discontinued study treatment (N = 279 for placebo and N = 314 for ERLYAND), a greater proportion (80%) of patients treated with placebo received subsequent therapy compared to patients treated with ERLYAND (56%). Locoregional-only progression occurred in 2% of patients overall.

The primary efficacy outcome was metastasis-free survival (MFS), defined as the time from randomisation to the time of first evidence of BICR-confirmed distant metastasis (defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation) or death due to any cause, whichever occurred first. Additional efficacy endpoints were time to metastasis (TTM), progression-free survival (PFS) which also includes locoregional progression, time to symptomatic progression, and overall survival (OS).

A statistically significant improvement in MFS was demonstrated in patients randomised to receive ERLEADA compared with patients randomised to receive placebo. Consistent results were observed across patient subgroups including PSADT (≤ 6 months or > 6 months), use of a prior bone-sparing agent (yes or no), and locoregional disease (N0 or N1). The major efficacy outcome was supported by statistically significant improvements in TTM, PFS, and time to symptomatic progression. Overall survival (OS) data were not mature at the time of final MFS analysis (24% of the required number of events). The primary efficacy results and the above supporting results from SPARTAN are summarised in Figure 2 and Table 3.

Figure 2: Kaplan-Meier Metastasis-Free Survival (MFS) Curve in Study ARN 509-003

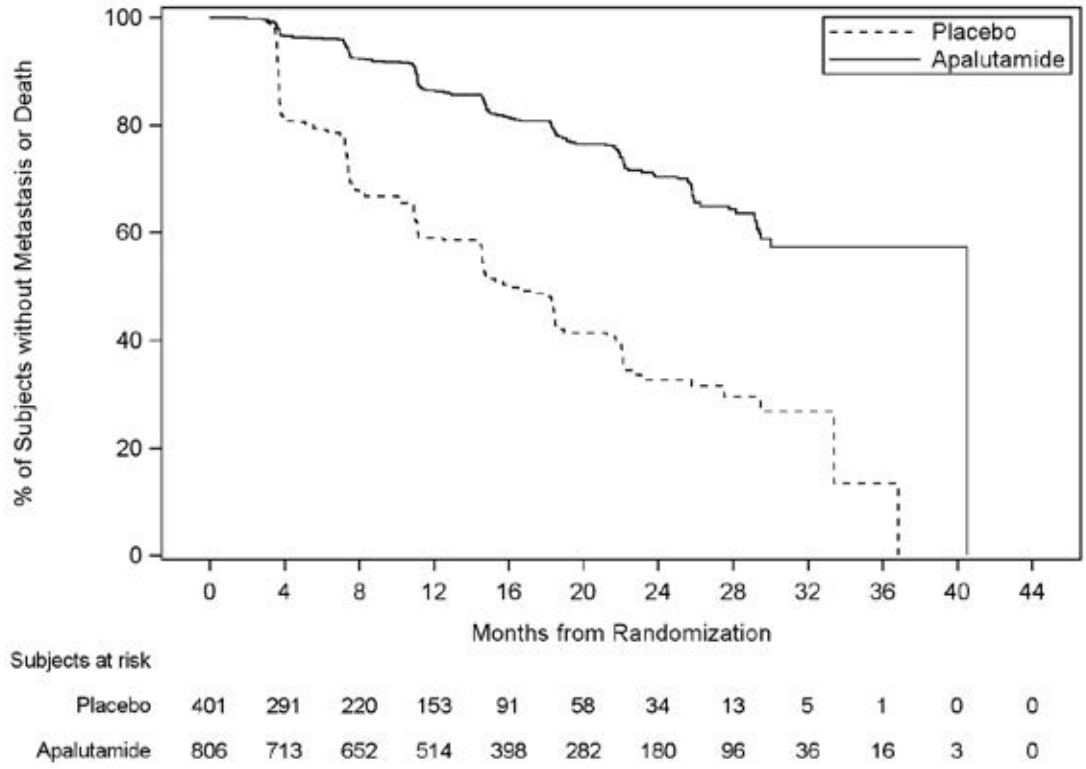


Table 3: Summary of Efficacy Analysis (Study ARN-509-003)

Endpoint	ERLYAND (n=806) Median (months)	Placebo (n=401) Median (months)	HR (95% CI) p value[1]
Metastasis Free Survival (MFS)	40.5	16.2	0.28 (0.23-0.35) < 0.0001
Time to Metastasis (TTM)	40.5	16.6	0.27 (0.22-0.34) < 0.0001
Progression-free Survival (PFS)	40.5	14.7	0.29 (0.24-0.36) < 0.0001

NR = Not reached
[1] p value from stratified log-rank test

5.2 PHARMACOKINETIC PROPERTIES

Apalutamide pharmacokinetic parameters are presented as the mean (coefficient of variation; CV%) unless otherwise specified. Following repeat once-daily dosing, apalutamide exposure (C_{max} and AUC) increased in a dose-proportional manner across the dose range of 30 mg to 480 mg (0.125 to 2 times the recommended dosage). Following administration of the recommended dosage, apalutamide steady state was achieved after 4 weeks and the mean accumulation ratio was approximately 5-fold. At steady-state, apalutamide C_{max} was 6 µg/mL (28%) and AUC was 100 µg.h/mL (32%). 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 major active metabolite (N-desmethyl apalutamide) C_{max} and was 5.9 µg/mL (18%) and AUC was 124 µg.h/mL (19%). N-desmethyl apalutamide is characterised by a flat concentration-time profile at steady-state with a mean peak-to-trough ratio of 1.27. The 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 contributes to the clinical activity of apalutamide.

Absorption

Mean absolute oral bioavailability is approximately 100%. Median time to achieve peak plasma concentration (t_{max}) was 2 hours (range: 1 to 5 hours).

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.

Distribution

The mean apparent volume of distribution at steady-state of apalutamide is about 276 L (greater than the volume of total body water, indicative of extensive extravascular distribution).

Apalutamide is 96% (and N-desmethyl apalutamide is 95%) bound to plasma proteins, with no concentration dependency. Studies in rodents and dogs indicate that apalutamide and N-desmethyl apalutamide can cross the blood brain barrier.

Metabolism

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 by carboxylesterase to form an inactive carboxylic acid metabolite. 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.

Apalutamide (45%), N-desmethyl apalutamide (44%), and an inactive carboxylic acid metabolite (3%) represented most of the total ^{14}C-AUC following a single oral administration of ^{14}C-labeled apalutamide 240 mg.

Excretion

Up to 70 days following a single oral administration of radiolabeled apalutamide, 65% of the dose 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 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

No clinically significant differences in the pharmacokinetics of apalutamide or N-desmethyl apalutamide were observed based on age (18-94 years), race (Black, non-Japanese Asian, Japanese), mild to moderate renal impairment (eGFR 30-89 mL/min/1.73m^2, estimated by the modification of diet in renal disease [MDRD] equation) or mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment.

The effect of severe renal impairment or end stage renal disease (eGFR ≤29 mL/min/1.73m^2) or severe hepatic impairment (Child-Pugh Class C) on apalutamide pharmacokinetics is unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Apalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* rat micronucleus assay or the *in vivo* rat Comet assay.

Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of apalutamide.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Colloidal anhydrous silica
Croscarmellose sodium
Hypromellose acetate succinate
Magnesium stearate
Microcrystalline cellulose
Silicified microcrystalline cellulose

Film-coat

Opadry® II 85F210036 Green

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep out of the sight and reach of children. Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

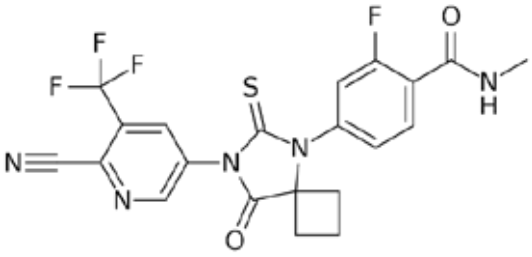
ERLYAND is available in opaque, high-density polyethylene bottles with child-resistant polypropylene closure and induction seal liner. Each bottle contains 120 tablets and a desiccant.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

956104-40-8

The drug substance has a dissociation constant pKa of 9.7 (acidic carboxamide moiety) and is practically insoluble in aqueous media over a wide range of pH values and practically insoluble to very soluble in organic solvents. The Log P at 20°C between 1-octanol and an aqueous buffered solution (pH 7.0) is 2.89. The Log D at 20°C between 1-octanol and aqueous buffered solutions (pH 1.0, 4.0 and 7.0) is 2.86, 2.80 and 2.89 respectively. Molecular formula: $C_{21}H_{15}F_4N_5O_2S$. Molecular weight: 477.43.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine

8. SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

NZ Office: Auckland New Zealand

9. DATE OF FIRST APPROVAL (ARTG ENTRY)

05 July 2018