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# ERLYAND<sup>®</sup>

## apalutamide

### DATA SHEET

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#### 1. PRODUCT NAME

ERLYAND apalutamide 60 mg film-coated tablet bottle

#### 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:

- metastatic castration-sensitive prostate cancer (mCSPC) or
- non-metastatic, castration-resistant prostate cancer (nmCRPC) (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  $\geq$  Grade 3 toxicity or an intolerable adverse effect, hold dosing until symptoms improve to  $\leq$  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  $\leq$  29 mL/min/1.73m<sup>2</sup>), 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 ERLYAND 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.

In two randomised studies, SPARTAN and TITAN, five patients (0.4%) treated with ERLYAND and two patients (0.2%) treated with placebo experienced a seizure. In these studies, patients with a history of seizure or predisposing factors for seizure were excluded. 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) and ischaemic cerebrovascular disorders***

Ischaemic heart disease and ischaemic cerebrovascular disorders, including events leading to death, occurred in patients treated with ERLYAND. Patients with a cardiac history should be assessed for active cardiac disease before starting treatment with ERLYAND. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidaemia. 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.

In a randomised study SPARTAN, ischaemic heart disease occurred in 4% of patients treated with ERLYAND and 3% of patients treated with placebo. In a randomised study TITAN, ischaemic heart disease occurred in 4% of patients treated with ERLYAND and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLYAND and 2 patients (0.2%) treated with placebo died from ischaemic heart disease.

In the SPARTAN study, with a median exposure of 32.9 months for ERLYAND and 11.5 months for placebo, ischaemic cerebrovascular disorders occurred in 4% of patients treated with ERLYAND and 1% of patients treated with placebo (see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). In the TITAN study, ischaemic cerebrovascular disorders occurred in a similar proportion of patients in the ERLYAND (1.5%) and placebo (1.5%) groups. Across the SPARTAN and TITAN studies, 2 patients (0.2%) treated with ERLYAND and no patients treated with placebo died from an ischaemic cerebrovascular disorder.

Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischaemic attack within six months of randomization were excluded from the SPARTAN and TITAN studies.

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 ( $\Delta$ QTcF) 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 1327 patients who received ERLYAND in clinical studies 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over. In patients aged  $\geq 75$  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**).

## 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<sub>2</sub>-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**

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. 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<sub>max</sub>.

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.

### ***Gonadotropin-releasing hormone (GnRH) analogue***

In metastatic castration-sensitive prostate cancer (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.

## **Effects on Laboratory Tests**

See **section 4.8 Undesirable effects**.

## **4.6 Fertility, pregnancy and lactation**

### **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 foetal 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 foetus. 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 embryofoetal development studies have not been conducted with ERLYAND.

### **Breast-feeding**

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.

### **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  $\geq 25$  mg/kg/day in rats (0.5 times the human exposure based on AUC) and  $\geq 2.5$  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  $\geq 25$  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.

## **4.7 Effect on ability to drive and use machinery**

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 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.

In studies of patients with mCSPC or nmCRPC who were using a GnRH analog, or were previously treated with orchiectomy, ERLYAND was administered at a dose of 240 mg daily.

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 commonly ( $\geq 1/100$  to  $< 1/10$ ) occurring in the ERLYAND arm in clinical studies that occurred with a  $\geq 2\%$  absolute increase in frequency compared to placebo or were events of special interest. Table 2 shows laboratory abnormalities that occurred in  $\geq 15\%$  of patients, and more frequently (>5%) in the ERLYAND arm compared to placebo.

**Table 1: Adverse events in the clinical studies that commonly occurred in ERLYAND-treated patients, and with at least a 2% absolute increase in frequency compared to placebo.**

System/Organ Class Adverse event	ERLYAND N=1327		Placebo N=925	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
<b>General disorders and administration site conditions</b>				
Fatigue <sup>1,2</sup>	26.2	1.1	18.7	0.8
<b>Vascular disorders</b>				
Hypertension	22.4	12.1	17.6	10.3
Hot flush	17.7	0	13.0	0
<b>Cardiac disorders</b>				
Ischemic Heart Disease <sup>7</sup>	4.0	1.7	2.1	1.1
<b>Skin and subcutaneous tissue disorders</b>				
Skin rash <sup>3</sup>	25.9	5.7	7.7	0.5
Pruritus <sup>2</sup>	8.1	0.2	3.2	0.1
<b>Gastrointestinal disorders</b>				
Diarrhoea	16.3	0.7	10.1	0.3
Nausea	18	0	16	0
<b>Nervous system disorders</b>				
Dysgeusia	5.6	0	1	0
Ischaemic cerebrovascular disorders <sup>9</sup>	3.0	1.2	1.3	0.4
Seizure	0.4	0.1	0.2	0
<b>Injury, poisoning and procedural complications</b>				
Fall <sup>2</sup>	13.1	1.5	8.0	0.8
Fracture <sup>4</sup>	10.5	2.3	5.7	0.9
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia <sup>2</sup>	17.1	0.2	12.0	0.5
Muscle spasm	3.8	0	1.8	0
<b>Investigations</b>				
Weight decreased <sup>2</sup>	12.7	1.0	5.6	0.6
<b>Endocrine disorders</b>				
Hypothyroidism <sup>8</sup>	7.8	0	1.5	0
<b>Metabolism and nutrition disorders</b>				
Decreased appetite <sup>5</sup>	12	0.1	9	0

Peripheral oedema <sup>6</sup>	11	0	9	0
Hypercholesterolemia	5.7	0.2	1.1	0
Hypertriglyceridemia	3.7	0.8	1.1	0.3

<sup>1</sup> Includes fatigue and asthenia

<sup>2</sup> Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

<sup>3</sup> 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, dermatitis and rash vesicular

<sup>4</sup> 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

<sup>5</sup> Includes appetite disorder, decreased appetite, early satiety, and hypophagia

<sup>6</sup> Includes peripheral oedema, generalised oedema, oedema, oedema genital, penile oedema, peripheral swelling, scrotal oedema, lymphoedema, swelling, and localised oedema

<sup>7</sup> 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

<sup>8</sup> Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroxine decreased, autoimmune thyroiditis, thyroxine free decreased, tri-iodothyronine decreased

<sup>9</sup> 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 ischemia. Addition of adverse reaction was based on data of the final analysis for the SPARTAN study with a median exposure of 32.9 months for ERLYAND and 11.5 months for 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,**

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

<sup>1</sup> Does not reflect fasting values



## Description of selected adverse events

### ***Falls and Fractures***

In SPARTAN, a randomised study of patients with nmCRPC, 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. In TITAN, a randomised study of patients with mCSPC, nonpathological fractures occurred in 6% of patients treated with ERLYAND and in 5% of patients treated with placebo. 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***

In the combined data of two randomised, placebo-controlled studies, 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 30% of subjects in the apalutamide arm and in 3% of subjects in the placebo arm. In subjects not previously receiving thyroid replacement therapy, hypothyroidism occurred in 7% of subjects treated with apalutamide and in 2% 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%). Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted. See **sections 4.4 Special warnings and precautions for use and 4.5 Effect of ERLYAND on drug metabolising enzymes**.

### ***Skin Rash***

In the combined data of two randomised, placebo-controlled clinical studies, skin rash associated with ERLYAND was most commonly described as macular or maculo-papular. Adverse events of skin rash were reported for 26% of subjects treated with ERLYAND versus 8% of subjects treated with placebo. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLYAND treatment (6%) versus placebo (0.5%). There were no reported events of toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS).

The onset of skin rash occurred at a median of 83 days of ERLYAND treatment and resolved in 78% of patients, within a median of 78 days from onset (range: 2 to 709 days). Rash was commonly managed with oral antihistamines, topical corticosteroids and 19% of subjects received systemic corticosteroids. Rash led to dose interruption in 28%, dose reduction in 14% and treatment discontinuation in 7% of cases. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLYAND.

## Post marketing data

Adverse events identified during post-marketing experience with frequency category estimated from spontaneous reporting rates. The frequencies are provided according to the following convention:

Very common  $\geq 1/10$

Common  $\geq 1/100$  and  $< 1/10$

Uncommon  $\geq 1/1,000$  and  $< 1/100$

Rare  $\geq 1/10,000$  and  $< 1/1,000$

Very rare  $< 1/10,000$

Not known Cannot be estimated from the available data

System Organ Class: **Respiratory, thoracic and mediastinal disorders**

Interstitial lung disease<sup>a</sup> Not known

<sup>a</sup> The adverse reaction was not identified from clinical trials

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

## 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 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<sub>A</sub>-gated chloride channel***

GABA<sub>A</sub> 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<sup>+</sup> channel with an IC<sub>50</sub> below steady-state C<sub>max</sub> 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 ( $\Delta$ QTcF) 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

The efficacy of ERLYAND was established in two randomised placebo-controlled multicentre Phase 3 clinical studies of subjects with mCSPC (TITAN) or nmCRPC (SPARTAN). All subjects in these studies received concomitant GnRH analogue or had prior bilateral orchiectomy.

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

TITAN (56021927PCR3002) was a randomised, double-blind, placebo-controlled, multinational, multicentre clinical trial in which 1052 subjects with mCSPC were randomised (1:1) to receive either ERLYAND 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 analogue 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 of subjects had high-volume disease and 37% had low-volume disease. Sixteen percent 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 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 ERLYAND), 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 ERLYAND (54%).

The major efficacy outcome measures of the study were overall survival (OS) and radiographic progression-free survival (rPFS). Efficacy results of TITAN are summarized in Table 3 and Figures 1 and 2.

**Table 3: Summary of Efficacy Results – Intent-to-treat mCSPC Population (TITAN)**

Endpoint	ERLYAND N=525	Placebo N=527
<b>Overall Survival</b>		
Deaths (%)	83 (16%)	117 (22%)
Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI) <sup>a</sup>	0.671 (0.507, 0.890)	
p-value <sup>b</sup>	0.0053	
<b>Radiographic Progression-free Survival</b>		
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) <sup>a</sup>	0.484 (0.391, 0.600)	
p-value <sup>b</sup>	<0.0001	

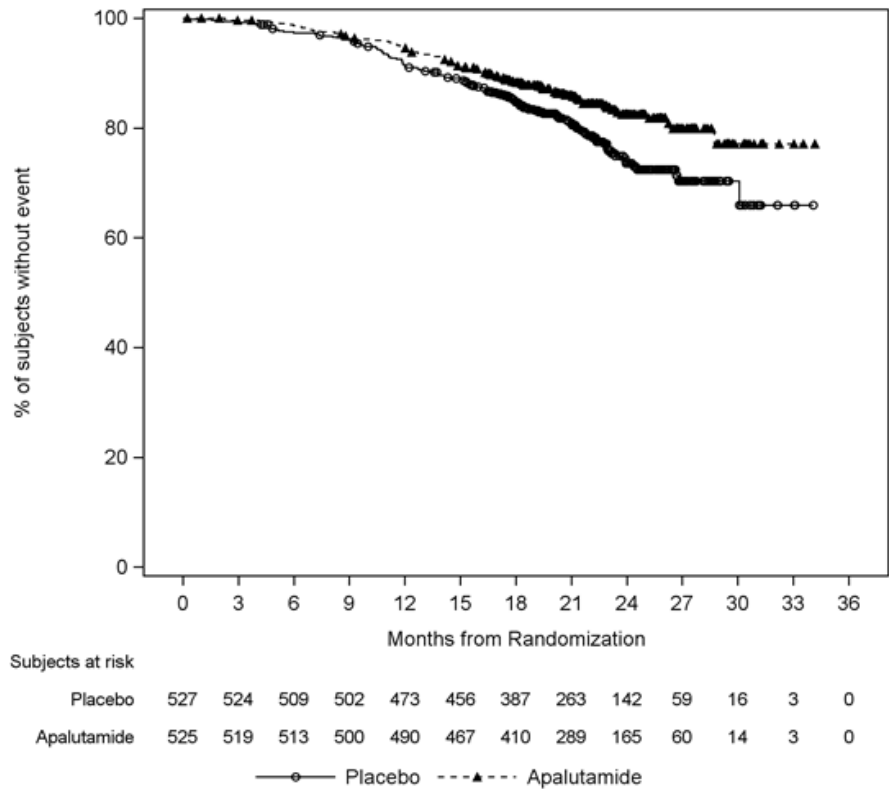
<sup>a</sup> Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favour active treatment.

<sup>b</sup> p-value is from the log-rank test stratified by Gleason score at diagnosis ( $\leq 7$  vs.  $>7$ ), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).

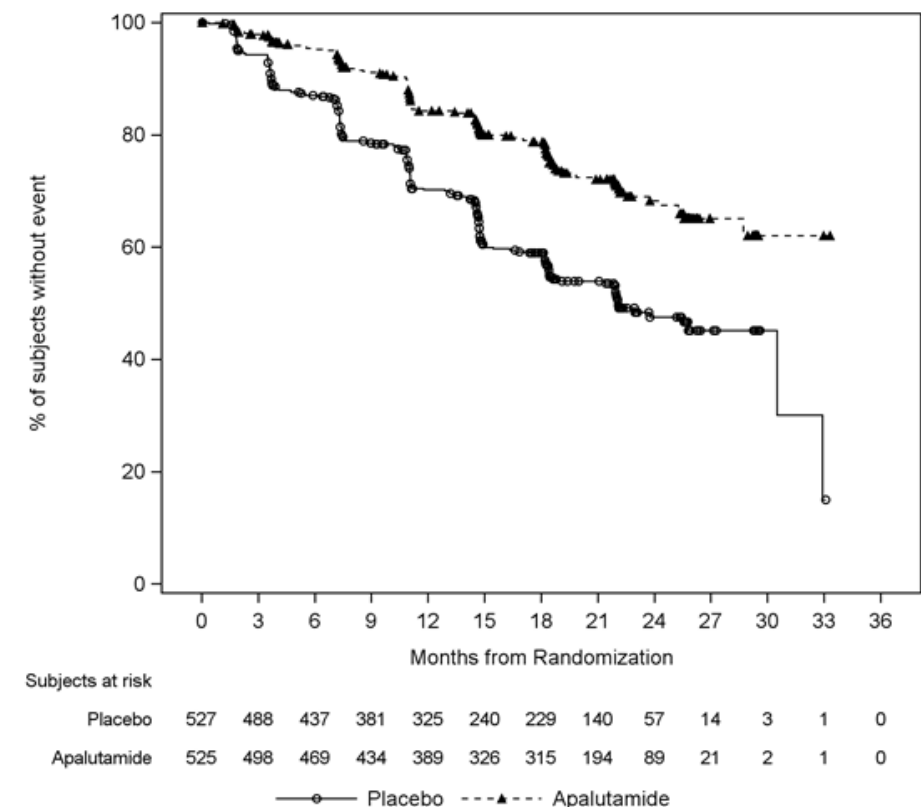
NE=Not Estimable

A statistically significant improvement in OS and rPFS was demonstrated in subjects randomised to receive ERLYAND compared with subjects randomised to receive placebo. Consistent improvement was observed across patient subgroups including high- or low-volume disease, prior docetaxel use (yes or no), age ( $< 65$ ,  $\geq 65$ , or  $\geq 75$  years old), baseline PSA above median (yes or no), and number of bone lesions ( $\leq 10$  or  $>10$ ).

**Figure 1: Kaplan-Meier Plot of 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)**



Treatment with ERLYAND 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.

Functional outcomes, as measured by the FACT-P, showed no difference between the ERLYAND and placebo arms. There was no significant FACT-P total score change from baseline within the ERLYAND treatment arm (cycle 25, LS Means 0.50) and no differences compared to placebo ( $p=0.24$ ).

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

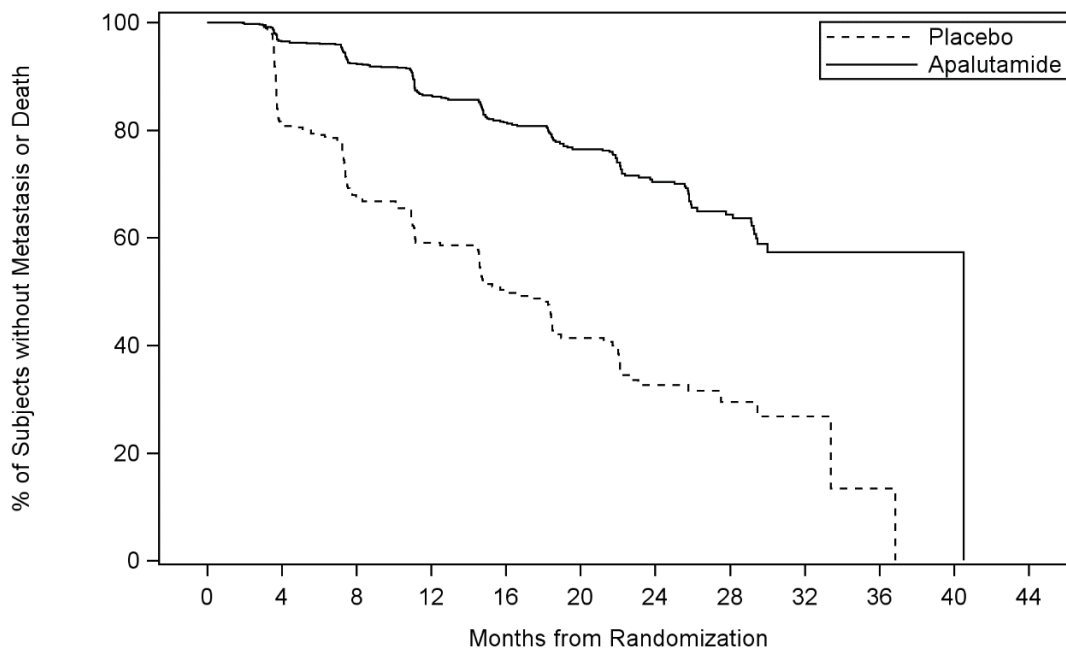
SPARTAN (Study ARN 509-003) was a multicentre, double-blind, randomised, placebo-controlled clinical trial in which 1207 subjects with nm-CRPC were randomised 2:1 to receive either ERLYAND orally at a dose of 240 mg once daily ( $n=806$ ) or placebo once daily ( $n=401$ ). All patients received a concomitant gonadotropin-releasing hormone (GnRH) analogue, or had a bilateral orchiectomy. Patients were required to have a PSADT  $\leq 10$  months and confirmation of non-metastatic disease by blinded independent central review (BICR). Patients with pelvic lymph nodes  $<2$  cm in short axis (N1) located below the iliac bifurcation could enter the SPARTAN study. Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT;  $>6$  months vs  $\leq 6$  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 ERLYAND compared with patients randomised to receive placebo. Consistent results were observed across patient subgroups including PSADT ( $\leq 6$  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 3 and Table 4.

**Figure 3: Kaplan-Meier Metastasis-Free Survival (MFS) Curve in SPARTAN Study (ARN 509-003)**



Subjects at risk		0	4	8	12	16	20	24	28	32	36	40
Placebo		401	291	220	153	91	58	34	13	5	1	0
Apalutamide		806	713	652	514	398	282	180	96	36	16	3

**Table 4: Summary of Efficacy Analysis SPARTAN Study (ARN-509-003)**

Endpoint	ERLYAND	Placebo	HR (95% CI) p value <sup>1</sup>
	(n=806) Median (months)	(n=401) Median (months)	
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

<sup>1</sup> 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 <sup>14</sup>C-AUC following a single oral administration of <sup>14</sup>C-labeled apalutamide 240 mg.

## Elimination

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<sup>2</sup>, 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<sup>2</sup>) or severe hepatic impairment (Child-Pugh Class C) on apalutamide pharmacokinetics is unknown.

## 5.3 Preclinical safety data

### Carcinogenicity

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

### 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.

## 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

60 mg tablets have a shelf-life of 3 years. 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. Store in the original container, 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

No special requirements.

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: medinfo@janau.jnj.com

## 9. DATE OF FIRST APPROVAL

17 October 2019

## 10. DATE OF REVISION OF THE TEXT

03 December 2020

### Summary table of changes

Section changes	Summary of new information
4.1	1. Addition of new indication in castrate sensitive and metastatic. Editorial change to the existing approved indication wording
4.5	2. Introduction of new text "Gonadotropin-releasing hormone (GnRH) analogue"
5.1	3. Updated Clinical Trials section to include the TITAN castrate sensitive metastatic prostate cancer study results