Apalutamide Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Apalutamide is indicated for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.	C61	00574a	CDS 01/08/2021

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Apalutamide is administered as a single oral daily dose until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Apalutamide	240mg daily	PO with or without food at the same time each day. Capsule should be swallowed whole with water.	Continuous
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.			
Medical castration with gonadotropin releasing hormone analogue (GnRHa) should be continued during treatment in patients not surgically castrated.			

ELIGIBILITY:

- Indication as above
- ECOG 0 or 1
- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features with high risk for development of metastases, defined as prostate-specific antigen doubling time (PSADT) ≤10 months.
- Castration-resistant prostate cancer demonstrated during continuous ADT, defined as 3 PSA rises, at least 1 week apart, with the last PSA greater than >2ng/mL.
- Surgically or medically castrated, with testosterone levels of <50ng/dL.
- Adequate haematologic, hepatic, and renal function

EXCLUSIONS:

- Hypersensitivity to apalutamide or any of the excipients
- Presence of confirmed distant metastases, including central nervous system and vertebral or meningeal involvement
- Prior treatment with second generation anti-androgens
- Prior treatment with CYP17 inhibitors

- Prior chemotherapy for prostate cancer except if administered in the adjuvant/neoadjuvant setting
- History of seizure or condition that may pre-dispose to seizure
- Clinically significant cardiovascular disease
- Gastrointestinal disorder affecting absorption

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC
- Renal and liver profile
- Thyroid function
- ECG in patients at risk of QT prolongation
- INR for patients on warfarin.

Regular tests:

- FBC
- Renal and liver profile
- ECG as clinically indicated
- Weekly INR tests if patient is on warfarin until stable warfarin dose established
- Thyroid function as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Table 1: Dose modification of apalutamide

Dose Level	Recommended Dose Modification
0	240mg
-1	180mg
-2	120mg

Table 2: Dose modification of apalutamide in renal and hepatic impairment

Renal Impairment	Hepatic 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. If treatment is started, patients should be monitored for the adverse reactions and dose reduced.	No dose adjustment is necessary for patients with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively). Apalutamide is not recommended in patients with severe hepatic impairment as there are no data in this patient population and apalutamide is primarily hepatically eliminated

Table 3: Dose modification of apalutamide for adverse events

Adverse reactions	Recommended dose modification
Intolerable or ≥ Grade 3	Withhold until symptoms improve to ≤ Grade 1 or original grade, then treatment may be resumed at the same dose or a reduced dose (180mg or 120mg), if warranted
Seizures	Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (Refer to local policy). PREMEDICATIONS: Not specified.
OTHER SUPPORTIVE CARE:

Apalutamide has no or negligible influence on the ability to drive and use machines. However, seizures have been reported in patients taking apalutamide. Patients should be advised of this risk in regards to driving or operating machines.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Apalutamide is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Seizure**: Apalutamide 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 apalutamide, treatment should be discontinued permanently. The risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold. Seizure occurred in 0.2% of patients receiving apalutamide in clinical studies. These studies excluded patients with a history of seizure or predisposing factors for seizure. There is no clinical experience in re-administering apalutamide to patients who experienced a seizure.
- **Falls and fractures**: Falls and fractures occurred in patients receiving apalutamide. Patients should be evaluated for fractures and fall risk before starting apalutamide and should continue to be monitored and managed for fractures according to established treatment guidelines and use of bone-targeted agents should be considered.

- **Concomitant use with other medicinal products:** Apalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. A review of concomitant medicinal products should therefore be conducted when apalutamide treatment is initiated. Concomitant use of apalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations. Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If apalutamide is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.
- **Recent cardiovascular disease:** Patients with clinically significant cardiovascular disease in the past 6 months including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g. pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias were excluded from the clinical studies. Therefore, the safety of apalutamide in these patients has not been established. If apalutamide is prescribed, patients with clinically significant cardiovascular disease should be monitored for risk factors such as hypercholesterolaemia, hypertriglyceridaemia, or other cardio-metabolic disorders. Patients should be treated, if appropriate, after initiating apalutamide 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, physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating apalutamide.
- **Hypothyroidism:** Hypothyroidism was reported for 8.1% of patients treated with apalutamide and 2.0% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. There were no grade 3 or 4 adverse events. Hypothyroidism occurred in 28% of patients already receiving thyroid replacement therapy in the apalutamide arm and in 5.9% of patients in the placebo arm. In patients not receiving thyroid replacement therapy, hypothyroidism occurred in 5.7% of patients treated with apalutamide and in 0.8% of patients treated with placebo. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted
- **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, and rash vesicular. Adverse reactions of skin rash were reported for 24% of patients treated with apalutamide. Grade 3 skin rashes (defined as covering > 30% body surface area [BSA]) were reported with apalutamide treatment in 5.2% of patients.

DRUG INTERACTIONS:

- Apalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Apalutamide SmPC EMA. Accessed Jan 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/erleada-epar-product-information_en.pdf
2. Saad F. Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2018 Oct;19(10):1404-1416. https://doi.org/10.1016/S1470-2045(18)30456-X. Including supplementary appendix and protocol.
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	08/01/2020		Prof. Maccon Keane
2	06/01/2021	Reviewed	Prof. Maccon Keane
3	01/08/2021	Reimbursement status updated	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.