PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

Apalutamide Prostate Cancer

PROTOCOL REF: MPHAAPECR
(Version No. 1.0)

Approved for use in:

In combination with androgen deprivation therapy (ADT) for the treatment of **non-metastatic hormone-resistant (castration-resistant) prostate cancer** in patients who are at high risk of developing metastatic disease (High risk is defined as a blood prostate specific antigen (PSA) level that has doubled in 10 months or less on continuous ADT.)

In combination with androgen deprivation therapy (ADT) for the treatment of patients with **newly diagnosed metastatic hormone-sensitive prostate cancer** who are ineligible for chemotherapy with docetaxel.

**** Blueteq registration required****

Dosage:

Drug	Dosage	Route	Frequency
Apalutamide	240mg	Oral	Daily

Continuous until disease progression or unacceptable toxicity.

Administration:

- The tablets should be swallowed whole with water, and can be taken with or without food.

- **Caution should be used in administration to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold.**

Supportive treatments:

No routine supportive treatments recommended.

Dosing in renal and hepatic impairment:

Renal	eGFR ≥ 30 ml/min/1.73m^2	No dose adjustment needed
	eGFR < 30 ml/min/1.73m^2	Not studied. No dose adjustment anticipated but **use with caution**.

Hepatic

Mild hepatic impairment (Child-Pugh Class A) to moderate (Child-Pugh Class B) – No dose adjustment needed.

Severe (Child-Pugh Class C) hepatic impairment - Not studied in this patient group. Not recommended as apalutamide is primarily hepatically eliminated.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)

	Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)
	INR: International Normalised Ratio. Child-Pugh Class A = 5-6 points Child-Pugh Class B = 7-9 points Child-Pugh Class C = 10 or more points **Please note**: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.			

Interactions:

Please refer to the SmPC for the full list of drug interactions

Potential for other medicinal products to affect Apalutamide exposures	*CYP2C8 inhibitors and inducers* • Strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8 are to be avoided or used with caution. *CYP3A4 inhibitors and inducers* • No dose adjustment is necessary when apalutamide co-administered with inhibitors or inducers of CYP3A4. • The concomitant use of strong CYP3A4 inducers with apalutamide is not recommended.
Potential to affect exposures to other medicinal products	Apalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19, and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). The transport protein P-gp may also be induced. Groups of medicinal products that can be affected include, but are not limited to: • Analgesics (fentanyl, tramadol) • Antibiotics (clarithromycin, doxycycline) • Anticoagulants (warfarin)

	• Antiepileptics (carbamazepine, clonazepam, phenytoin, primidone, valproic acid) • Antipsychotics (haloperidol) • Betablockers (bisoprolol, propanolol) • Calcium channel blockers (diltiazem, felodipine, nicardipine, nifedipine, verapamil) • Cardiac glycosides (digoxin) • Corticosteroids (dexamethasone, prednisolone) • HIV antivirals (indinavir, ritonavir) • Hypnotics (diazepam, midazolam, zolpidem) • Statins metabolized by CYP3A4 (simvastatin) • Thyroid agents (levothyroxine) Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If apalutamide is co-administered with an anticoagulant metabolised by CYP2C9 additional International Normalised Ratio (INR) monitoring should be conducted.

Main toxicities:

Apalutamide	
Endocrine	Hypothyroidism
Cardiovascular	Ischaemic heart disease, Patients should be monitored for signs and symptoms of ischaemic heart disease and management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidaemia should be optimised as per standard of care. Hot flushes, hypertension.
Nervous system disorders	Seizure, the mechanism by which apalutamide may lower the seizure threshold is not known. 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.

Skin and subcutaneous tissue disorders	Dry skin, pruritus
Musculoskeletal disorders	Fractures and falls Muscle spasm, arthralgia
Gastrointestinal	Diarrhoea

Please refer to the SmPC or the full list of toxiciti

Investigations and treatment plan:

	Pre	C1	C2	C3	C4	Ongoing
Informed Consent	X					
Clinical Assessment	X	X	X	X		First three cycles and then every 12 weeks
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X		X	X	X	Every cycle
U&E & LFTs	X		X	X	X	Every Cycle
PSA	X	X	X	X	X	Every cycle
CT scan	X					If clinically indicated
Serum creatinine	X		X	X	X	Every cycle
Blood pressure measurement	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle
Height recorded	X					

Dose Modifications and Toxicity Management:

Non-haematological toxicity:

Patients who experience treatment related seizure should discontinue treatment.

For patients experiencing grade>3 toxicities they should hold treatment and resume once toxicity reduces to Grade 1 or returns to baseline. If toxicity recurs at grade 3 or higher the dose should be reduced to the next dose level.

Dose Level	Total daily dose
0	**240mg**
-1	**180mg**
-2	**120mg**

Haematological toxicity:

Blood Pressure Guidance:

- Pre-existing hypertension should be controlled (usually via the GP) before treatment with apalutamide starts.
- Baseline blood pressure should be < 150/100mmHg.
- Monitoring of BP and management until stabilised, may require GP involvement.

Blood pressure measurements	
Systolic 140-150 mmHg or Diastolic <90 mmHg:	Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary
Systolic 150-160mmHg or Diastolic 90-100mmgh:	-Continue treatment at same dose. -Repeat BP at GP, treatment needed if remained elevated or higher. -Continue with vigilant BP monitoring until BP <140/90mmHg.
Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart):	Continue treatment at same dose -Instigate BP treatment, to be reviewed at GP within 5 days. -Continue with vigilant BP monitoring until BP <140/90mmHg
Severe hypertension (>180mmHg systolic or >110mmHg diastolic)	Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment at reduced dose may be resumed once hypertension is appropriately controlled.

References:

Clinical Study Protocol: SPARTAN;(Selective Prostate AR Targeting with ARN-509) A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer.

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Kim N Chi, N Argawal. Apalutamide for metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine*; July 2019; Vol 381; page13-24.

M Smith et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *New England Journal of Medicine*; April 2018; Vol 378; pages 1408-1418.

NICE final appraisal document 8th September 2021: https://www.nice.org.uk/guidance/gid-ta10423/documents/final-appraisal-determination-document

Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

Circulation/Dissemination

Date added into Q-Pulse	6th December 2021
Date document posted on the Intranet	

Version History

Date	Version	Author name and designation	Summary of main changes
December 2021	1.0	**Rachel Pritchard** **Urology SRG Pharmacist**	New Regimen Protocol