Apalutamide (Prostate)

Indication
Treatment of high-risk hormone-relapsed non-metastatic prostate cancer in combination with androgen deprivation therapy.

(NICE TA740)

Treatment of hormone-sensitive metastatic prostate cancer in combination with androgen deprivation therapy.

(NICE TA741)

ICD-10 codes
C61

Regimen details

Drug	Dose	Route
Apalutamide	240mg OD	Oral

Cycle frequency
Continuous

Number of cycles
Continued until disease progression or unacceptable toxicity

Administration
Apalutamide is available as 60mg tablets.

Tablets should be swallowed whole with water, either with or without food.

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 a missed dose.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential (no routine antiemetics are required).

Additional supportive medication
Nil

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&E (including creatinine)	14 days
LFTs	14 days
PSA	14 days
Thyroid function	14 days
ECG	14 days

Consider a falls and fracture risk assessment before commencing Apalutamide

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Monthly, increasing to 2-monthly as appropriate
U&E (including creatinine)	Monthly, increasing to 2-monthly as appropriate
LFTs	Monthly, increasing to 2-monthly as appropriate
PSA	Monthly, increasing to 2-monthly as appropriate
Thyroid function	As indicated
ECG	As indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Creatinine clearance (CrCl)	≥30ml/min
Bilirubin	≤1.5 x ULN
AST/ALT	<5 x ULN
Neutrophils	≥1 x 10^9/L

Dose modifications

Dose level	Dose
Full dose	240mg
Dose level -1	180mg
Dose level -2	120mg

- **Haematological toxicity**

Withhold apalutamide if neutrophils < 1 x 10^9/L

- **Renal impairment**

No dose adjustment is required for patients with mild or moderate renal impairment (CrCl ≥30ml/min)

Apalutamide should be used with caution in patients with severe renal impairment (CrCl<30ml/min). Patients should be monitored for adverse reactions and started at a dose reduction. Discuss with consultant.

- **Hepatic impairment**

No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A and B).
Apalutamide is not recommended in severe hepatic impairment as it has not been studied in this population.

Child Pugh Classification:

Score	1	2	3
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
PT (s prolonged)	<4	4-6	>6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

The individual scores are summed and then grouped as:

- <7 = A
- 7-9 = B
- >9 = C

- **Other toxicities**

If ≥ Grade 3 toxicity or intolerable adverse reaction, apalutamide should be held until symptoms improve to ≤ Grade 1 (or original grade) then restarted at either the same dose or a dose reduction, if appropriate, as outlined above. Discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Seizures
QT prolongation
Ischaemic heart disease

- **Frequently occurring side effects**

Hypertension
Diarrhoea
Rash, pruritis
Arthralgia
Fatigue

- **Other side effects**

Hypothyroidism
Hot flushes

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants – avoid. If unavoidable, additional INR monitoring should be conducted due to CYP2C9 induction by apalutamide.
Strong CYP2C8 inhibitors e.g. gemfibrozil, clopidogrel – potential for increased apalutamide exposure. No starting dose reduction indicated but reduce dose to tolerability as indicated.
Strong CYP3A4 inhibitors e.g. intraconazole, ketoconazole, ritonavir, clarithromycin - potential for increased apalutamide exposure. No starting dose reduction indicated but reduce dose to tolerability as indicated.
CYP2B6 substrates e.g. efavirenz – monitor for loss of efficacy or adverse reaction from substrate as apalutamide and its metabolite N-desmethyl apalutamide are strong inducers and moderate inhibitors of CYP2B6

CYP3A4 substrates e.g. darunavir, felodipine, midazolam, simvastatin – reduced exposure to substrate, consider alternative or monitor efficacy.
CYPA2C19 substrates e.g. diazepam, omeprazole - reduced exposure to substrate, consider alternative or monitor efficacy.
CYP2C9 substrates e.g. phenytoin - reduced exposure to substrate, consider alternative or monitor efficacy.
UGT substrates e.g. levothyroxine, valproic acid – reduced exposure to substrate, monitor for loss of efficacy and dose adjust substrate as indicated
P-gp substrates e.g. fexofenadine, colchicine, dabigatran, digoxin - reduced exposure to substrate, monitor for loss of efficacy and dose adjust substrate as indicated
BCRP/OATP1B1 substrates e.g. methotrexate, rosuvastatin, repaglinide - reduced exposure to substrate, monitor for loss of efficacy and dose adjust substrate as indicated
Medicinal products which prolong the QT interval: avoid concomitant use if possible, carefully evaluate risk if to be used in combination.
Medicinal products which reduce the seizure threshold: increased risk of seizure, use with caution.

Additional comments

Patients with clinically significant cardiovascular disease in the past 6 months were excluded from clinical studies; therefore the safety of apalutamide in these patients has not been established. If apalutamide is prescribed for patients with clinically significant cardiovascular disease they should be monitored for risk factors such as hypercholesterolaemia and hypertriglyceridaemia and managed as per treatment guidelines.

Apalutamide is not recommended in patients with a history of seizures or other pre-disposing factors e.g. underlying brain injury, stroke within the previous year or brain metastases.

References

- National Institute for Health and Care Excellence (NICE TA740) accessed 11th November 2021 via www.nice.org.uk
- National Institute for Health and Care Excellence (NICE TA741) accessed 11th November 2021 via www.nice.org.uk
- Summary of Product Characteristics – Apalutamide (Janssen-Cilag) accessed 11th November 2021 via www.medicines.org.uk
- Chi, K. *et al.* Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13-24
- Smith, M.R. *et al.* Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408-1418

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