Regimen Monograph

A - Regimen Name

APAL Regimen

apalutamide

Disease Site

Genitourinary
Prostate

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

- For the treatment of metastatic castration sensitive prostate cancer (mCSPC)† in patients with good performance status, and who have not experienced disease progression with another androgen receptor axis targeted therapy (ARAT) for castration sensitive prostate cancer.
- For the treatment of patients with high risk non-metastatic castration-resistant prostate cancer† (nmCRPC), who have ECOG performance status ≤2*.

†Refer to EAP for full funding criteria and exclusions.
*Not funded in patients who have received prior chemotherapy for the treatment of prostate cancer, unless it was in the adjuvant or neoadjuvant setting.

Supplementary Public Funding	**apalutamide** Exceptional Access Program (apalutamide - For the treatment of non-metastatic castration resistant prostate cancer (nmCRPC), based on criteria) (EAP Website)
	apalutamide Exceptional Access Program (apalutamide - For the treatment of metastatic castration sensitive prostate cancer (mCSPC), based on criteria) (EAP Website)

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B - Drug Regimen

apalutamide	240 mg	PO	Daily

Patients should also receive a gonadotropin-releasing hormone (GnRH) analog unless they have had a bilateral orchiectomy.

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Not applicable

Other Supportive Care:

- Patients should be assessed for the risk of fracture and fall and treated to prevent clinical fractures according to guidelines, with consideration given to use of bone-targeted agents.
- Patients with a cardiac or stroke history should be assessed before starting treatment. Manage patients optimally for risk factors such as hypertension, diabetes, or dyslipidemia.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Dose Level	Apalutamide Dose (mg/day)
0	240
-1	180
-2	120
-3	Discontinue

Toxicity	Action
Intolerable or ≥ Grade 3	Hold until recovery to ≤ grade 1 or baseline, resume at the same dose or at ↓ 1-2 dose level(s), if indicated. Recurrence ≥ grade 3: Hold until recovery to ≤ grade 1 or baseline, then ↓ 1 dose level.
Seizure	Discontinue.
Stevens-Johnson syndrome, Toxic epidermal necrolysis, or DRESS	Discontinue.
Interstitial lung disease	Hold and investigate. Discontinue if confirmed.

Hepatic Impairment

Hepatic Impairment at baseline	Action
Mild or moderate (Child-Pugh A or B)	No adjustment required
Severe or ESRD (Child-Pugh C)	No data

Renal Impairment

Renal Impairment	Action
Mild to moderate (CrCL ≥ 30 mL/min)	No adjustment required
Severe (CrCL ≤ 29 mL/min)	No data

Dosage in the Elderly

No dose adjustment is necessary for elderly patients. Patients ≥ 75 years treated with apalutamide experienced higher incidence of grade 3 or 4 adverse events and lower tolerance. Monitor elderly patients more closely for toxicity and adjust dose when needed.

Dosage based on Ethnicity:

No dose adjustments are necessary. There is no clinically relevant difference in exposure between White (Caucasian or Hispanic or Latino), Black (of African heritage or African American), Asian (non-Japanese), or Japanese patients. In clinical studies, the incidence of rash was more than 2-fold higher in the Japanese population compared with the entire study population.

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F - Adverse Effects

Refer to apalutamide drug monograph(s) for additional details of adverse effects.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Fatigue • Hypertension (may be severe)	• Rash/pruritus (may be severe) • Diarrhea • Nausea • Anorexia, weight loss • Arthralgia • Fall • Androgen deprivation symptoms • Fracture • Edema	• Seizure • Arterial thromboembolism • Cardiotoxicity • QT interval prolonged • Hypothyroidism • Stevens-Johnson syndrome • Toxic epidermal necrolysis • DRESS • Interstitial lung disease

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G - Interactions

Refer to apalutamide drug monograph(s) for additional details.

- Consider dose adjustment for apalutamide based on tolerability with co-administration of strong CYP2C8 or CYP3A4 inhibitors.
- Avoid co-administration with CYP3A4, CYP2C19 and CYP2C9 substrates. Substitute for these medications when possible or evaluate for loss of activity if medication is continued.
- Exercise caution with co-administration with P-gp, BCRP, OATP1B1 and UGT substrates. Evaluate for loss of activity if medication is continued (especially thyroxine).

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H - Drug Administration and Special Precautions

Refer to apalutamide drug monograph(s) for additional details.

Administration

- Tablets should be swallowed whole with a glass of water.
- Tablets can be taken with or without food.
- Take the dose at around the same time each day.
- A missed dose 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.
- For patients who have difficulty swallowing **60 mg tablets**, the dose may be mixed in applesauce. Refer to product monograph for the most up-to-date instructions.
    - Mix whole tablets in 120 mL of applesauce by stirring. Do not crush the tablets.
    - Wait 15 minutes, then stir the applesauce.
    - Wait another 15 minutes, then stir the applesauce until the tablets are well mixed with no chunks remaining.
    - Using a spoon, swallow the mixture right away.
    - Rinse the mixture container with 60 mL of water and drink this immediately.
    - Repeat the rinsing with another 60 mL of water, then drink this to ensure the entire dose is taken.
    - The mixture should be taken within 1 hour of preparation.
- For patients who have difficulty swallowing **240 mg tablets**, the dose may be dispersed in non-fizzy water, then mixed with non-fizzy beverages or soft foods. Refer to product monograph for the most up-to-date instructions.
    - Place whole 240 mg tablet in a cup. Do not crush or split the tablet.
    - Add about 10 mL of non-fizzy water. Wait 2 minutes for the tablet to disperse, then stir the mixture.
    - Add 30 mL of the following non-fizzy beverages or soft foods: orange juice, green tea, applesauce, or drinkable yogurt), then stir the mixture.
    - The mixture should be swallowed immediately.
    - Rinse the cup with enough water, then drink it immediately, to make sure the whole dose is taken.
- For **nasogastric (NG) tube** administration (8 French or greater), the **240 mg tablet** may be dispersed in 10 mL of non-carbonated water (in at least a 20 mL syringe). Wait 10 minutes and shake vigorously to disperse the tablet; then administer immediately through the NG tube. Flush the NG tube with non-carbonated water until no dispersed tablet is remaining in the syringe or the NG tube.

- Store tablets at 15°C to 30°C, in the original package to protect from light and moisture.
- If tablets are provided in a bottle, do not remove the silica gel desiccant from the bottle.

Contraindications

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Other Warnings/Precautions

- Exercise caution in patients with:
    - Cardiac disorders. 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 or clinically significant ventricular arrhythmias were excluded from clinically trials.
    - Seizures. Patients with a history of seizures or predisposing factors for seizures were excluded from clinical studies; patients on medications known to lower seizure threshold were prohibited while receiving apalutamide.
    - AT prolongation, risk factors for Torsade de pointes, or on medications known to prolong QTc.
    - nmCRPC at low risk of developing metastases. Apalutamide has not been studied in these patients and the benefit and risk profile is unknown.

Pregnancy & Lactation

- Apalutamide is **contraindicated** in patients who are or may become pregnant. It may cause harm to a developing fetus or lead to loss of pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Apalutamide is **only indicated in patients with prostate cancer**. There are no data on the presence of apalutamide or its metabolites in human milk.
- Fertility effects: Probable

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- TSH; Baseline and as clinically indicated
- ECG; Baseline and as clinically indicated; more frequent in patients at risk of QTc increase or taking medications known to prolong QT interval
- INR; If warfarin cannot be discontinued; baseline and during apalutamide treatment
- PSA and radiographic disease progression; Baseline and as clinically indicated
- Clinical toxicity assessment for androgen deprivation symptoms, hypertension, fatigue, infection, seizure, cardiac, stroke, gastrointestinal, respiratory or dermatologic effects, and risk of fracture and falls; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Blood glucose; As clinically indicated
- Cholesterol and triglycerides; As clinically indicated

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K - References

Apalutamide drug monograph, Ontario Health (Cancer Care Ontario).

Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med 2018;378:1408-18.

PEBC Advice Documents or Guidelines

- An Endorsement of the 2021 Guideline on the Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

January 2025 Updated Dose modifications and Fertility effects sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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