Regimen Monograph

A - Regimen Name

ENZL Regimen

Enzalutamide

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.

This **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). 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.

Rationale and Uses

- For the treatment of patients with metastatic castration sensitive† prostate cancer (mCSPC), who have good performance status, and have not had 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 an ECOG performance status ≤ 2, and have not received prior chemotherapy for prostate cancer, except in the adjuvant or neoadjuvant setting.

- For the treatment of patients with metastatic castration-resistant† prostate cancer (mCRPC), who:

  - have received and had disease progression on docetaxel,
    OR
    are using enzalutamide pre-docetaxel for mCRPC and have not previously experienced disease progression on enzalutamide, another second generation androgen receptor inhibitor, or abiraterone sequenced immediately before enzalutamide,
    AND
    who have an ECOG performance status ≤ 2.

† Refer to EAP for full details of funding criteria and exclusions.

Supplementary Public Funding

enzalutamide
Exceptional Access Program (enzalutamide - For the treatment of metastatic castrate-resistant prostate cancer (mCRPC), with specific clinical criteria) (EAP Website)

enzalutamide
Exceptional Access Program (enzalutamide - For the treatment of high risk non-metastatic castration-resistant prostate cancer (nmCRPC), with specific clinical criteria) (EAP Website)

enzalutamide
Exceptional Access Program (enzalutamide - For the treatment metastatic castration sensitive prostate cancer (mCSPC), with specific clinical criteria) (EAP Website)

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B - Drug Regimen

enzalutamide	160 mg	PO	Daily

Patients who have not had a bilateral orchiectomy should receive/remain on GnRH agonists during enzalutamide treatment. Patients were allowed, but not required, to take glucocorticoids in the phase III clinical trial (Scher et al).

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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

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E - Dose Modifications

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

Prior to starting enzalutamide treatment:

- Patients with cardiac history should be assessed for active cardiac disease.
- Management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia should be optimized.
- Patients should be assessed for the risk of fracture and fall and managed according to guidelines with consideration given to the use of bone-targeted agents.

Dosage with toxicity

Dose Level	Enzalutamide Dose (mg/day)
0	160
-1	120
-2	80
-3	Discontinue

Toxicity	Grade	Action
Hypersensitivity reactions	Any	Hold and promptly seek medical care.
	≥ grade 3	Discontinue.
PRES	Any	Discontinue.
Seizure		
Ischemic heart disease	≥ grade 3	Discontinue.
Treatment emergent hypertension	Any	Monitor blood pressure and treat appropriately.
All other toxicities	Intolerable or ≥ grade 3	Hold until ≤ grade 2. Resume at the same dose OR ↓ dose level. Consider discontinuing if grade 4.

Hepatic Impairment

Hepatic Impairment	Enzalutamide Dose (mg/day)
Mild or moderate (Child-Pugh Class A or B)	No adjustment required
Severe (Child-Pugh C)	Increased drug half-life was observed; clinical significance unknown. No dosage adjustment required.

Renal Impairment

Creatinine Clearance (mL/min)	Enzalutamide Dose (mg/day)

≥ 30	No adjustment required
< 30	Has not been studied. Exercise caution.

Dosage in the Elderly

No dose adjustment required. No overall differences in safety or efficacy were found in patients ≥ 65 years compared to younger patients; however, an increased frequency of dose interruption/reduction and discontinuation was observed.

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F - Adverse Effects

Refer to enzalutamide 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 • Musculoskeletal pain	• Diarrhea • Edema • Androgen deprivation symptoms • Hypertension (may be severe) • Dizziness • Nausea • Fall/fracture • Anorexia, weight loss	• Prolonged QT interval • Ischemic heart disease • Myelosuppression +/- infection • Seizures, PRES • Cognitive disturbance/hallucinations • GI bleed • Hypersensitivity • Secondary malignancy

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G - Interactions

Refer to enzalutamide drug monograph(s) for additional details

- Enzalutamide is an inducer and inhibitor of several CYP isoenzymes and susceptible to many drug interactions.
- Since the half-life of enzalutamide is 5.8 days, the effects on enzymes may persist for ≥ 1 month after stopping the drug.
- Avoid strong CYP2C8 inhibitors (e.g., gemfibrozil, montelukast) as they may increase enzalutamide toxicity; if concomitant use with strong CYP2C8 inhibitor cannot be avoided, reduce enzalutamide dose to 80mg daily.
- Avoid strong inducers of CYP3A4 (e.g., rifampin) as they may reduce the efficacy of enzalutamide.
- Avoid concomitant use with CYP3A4, CYP2C9 and CYP2C19 substrates with narrow therapeutic range as substrate exposure may be affected. Consider dose adjustment of substrate if concomitant use cannot be avoided. Monitor INR closely with concurrent warfarin use.
- Avoid concomitant use with UGT1A1, UGT1A4, or CYP2B6 substrates as enzalutamide may reduce their efficacy. Consider dose adjustment of substrate if concomitant use cannot be avoided.

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H - Drug Administration and Special Precautions

Refer to enzalutamide drug monograph(s) for additional details

Administration:

- Swallow capsules whole with a glass of water, with or without food.
- Do not chew, dissolve, or open the capsules.
- Take the dose at around the same time each day.
- If a dose is missed for the day, give it as soon as it is remembered on the same day. If it is forgotten for the whole day, skip this dose and give the next usual dose. Do not double the dose to make up for the missed one.
- Store at room temperature (15 to 30°C.

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Exercise caution in these patient populations:
  - Significant cardiovascular disease. Patients with significant cardiovascular disease (i.e. recent MI, unstable angina, LVEF < 45%, bradycardia or uncontrolled hypertension) were excluded from clinical trials.
  - History of QT prolongation, risk factors for Torsades de Pointes, or on medications known for QT prolongation
  - History of seizures or have risk factors for seizures (i.e. brain injury with loss of consciousness, recent TIA, CVA, brain metastases, or on medications that lower the seizure threshold). These patients were excluded from clinical trials. Avoid dosing above 160mg as this was observed to have a greater risk of seizures.
  - Enzalutamide may cause neuropsychiatric events such as cognitive or memory impairment, seizures, hallucinations, etc. Patients should take caution and avoid tasks in which mental impairment or loss of consciousness may harm themselves or others.
  - Severe hepatic impairment (Child-Pugh C) at baseline. These patients were excluded from clinical trials.
- Patients with hereditary fructose intolerance should not take enzalutamide as it contains sorbitol.

Pregnancy/Lactation:

- Enzalutamide is not indicated in women and is **contraindicated** in pregnancy or in women who may become pregnant. Two effective forms of contraception (one of which must include condoms) should be used during treatment and for **3 months** after the last dose.
- Breastfeeding is **contraindicated**.
- Fertility Effects: Yes

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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

- Blood pressure; Baseline and as clinically indicated
- ECG and electrolytes; Baseline and as clinically indicated, in patients at risk of QT prolongation
- Ischemic heart disease; Baseline and as clinically indicated
- Disease progression radiographically in addition to serum PSA; As clinically indicated, in patients with nmCRPC
- INR monitoring for patients on warfarin; Baseline and as clinically indicated
- Clinical toxicity assessment for ischemic heart disease, androgen withdrawal, gastrointestinal effects, hypersensitivity, fatigue, seizures and other neuropsychiatric effects, musculoskeletal effects including falls/fractures and edema; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019 Nov 10;37(32):2974-2986.

Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014 Jul 31;371(5):424-33.

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

Hussain M, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N

Engl J Med. 2018 Jun 28;378(26):2465-2474.

Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187-97.

PEBC Advice Documents or Guidelines

- Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer
- An Endorsement of the 2021 Guideline on the Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

April 2022 Updated Dose Modifications, Adverse Effects, Interactions, Drug Administration and Special Precautions and Recommended Clinical Monitoring sections

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M - Disclaimer

Regimen Abstracts

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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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