Regimen Monograph

A - Regimen Name

EVEREXEM Regimen

Everolimus-Exemestane

Disease Site	Breast
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	Treatment of postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer in combination with exemestane, after recurrence or progression following treatment with letrozole or anastrozole. Funded in patients for whom exemestane is considered appropriate and who have ECOG ≤ 2.
Supplementary Public Funding	**everolimus** Exceptional Access Program (everolimus - In combination with exemestane, for the treatment of hormone-receptor positive, HER2 negative advanced breast cancer, in postmenopausal women with ECOG performance status less than or equal to 2 after recurrence or progression following a non-steroidal aromatase inhibitor (NSAI)) (EAP Website)

exemestane
ODB - General Benefit (exemestane) (ODB Formulary)

back to top

B - Drug Regimen

everolimus*	10 mg	PO	Daily

(5 mg may be considered for certain patients)

(Outpatient prescription in 2.5 mg, 5 mg or 10 mg tablets)

exemestane	25 mg	PO	Daily

(Outpatient prescription in 25 mg tablets)

*Note: see section E for dose modifications for toxicity and organ dysfunction.

back to top

C - Cycle Frequency

CONTINUOUS TREATMENT

Unless disease progression or unacceptable toxicity occurs

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:
For more information about bone health via dietary and lifestyle measures, see pamphlet on Bone Health in Post Menopausal Women.

Everolimus:

- Manage stomatitis with non-irritant oral rinses. Antifungal agents should not be used unless an

oral fungal infection has been diagnosed. Consider a corticosteroid mouthwash during the first 8 weeks of treatment to reduce the risk and severity of stomatitis.
- Consider the use of PJP prophylaxis when concomitant use of corticosteroids or other immunosuppressants are required.

Also refer to CCO Antiemetic Recommendations.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Patients in whom drug-drug interactions are likely (and who cannot discontinue the concomitant medication) may require dose modification (refer to Interactions section for details). Optimal glycemic/lipidemic control must be ensured prior to starting therapy.

Dosage with toxicity

Everolimus:

Dose levels: 10 mg daily, 5 mg daily, 5 mg alternate days

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	No dosage adjustment required.	Hold until ≤ grade 1. Restart treatment at the same dose.	Hold until ≤ grade 1. Restart treatment at a lower dose.	Hold until ≤ grade 1. Restart treatment at a lower dose.
Neutropenia	No dosage adjustment required.	No dosage adjustment required.	Hold until ≤ grade 2. Restart treatment at the same dose.	Hold until ≤ grade 2. Restart treatment at a lower dose.
Febrile neutropenia	n/a	n/a	Hold until recovery of ANC to ≥ 1.25 x 10^9/L and afebrile. Restart treatment at a lower dose.	Discontinue and treat patient appropriately.

	Non-infectious pneumonitis	If asymptomatic, maintain same dose. Monitor and treat patient appropriately.	Consider hold until ≤ grade 1. Rule out infection and then consider corticosteroids. Restart with 1 dose level ↓ . Discontinue if no recovery within 4 weeks.	Hold until ≤ grade 1. Rule out infection and then consider corticosteroids. Restart with 1 dose level ↓. Discontinue if grade 3 recurs.	Discontinue, investigate and treat patient appropriately.
	Stomatitis	As above and manage with non-alcoholic mouthwash several times daily.	Hold until ≤ grade 1 and restart at same dose. If recurs, hold until ≤ grade 1 and restart with 1 dose level ↓. Manage with topical analgesic mouth treatments with or without topical corticosteroids.	Hold until ≤ grade 1 and restart with 1 dose level ↓. Manage with topical analgesic mouth treatments with or without topical corticosteroids.	As above.
	Metabolic events (e.g. hyperglycemia, hyperlipidemia)*	Maintain same dose. Monitor and start appropriate therapy.	Maintain same dose. Monitor and start appropriate therapy.	Hold until ≤ grade 1 and restart with 1 dose level ↓. Monitor and start appropriate therapy.	As above.
	Other related non-hematologic toxicities	If tolerable, maintain same dose and treat appropriately.	Maintain same dose if tolerable. If intolerable, hold until ≤ grade 1 and restart at same dose. If recurs, hold until ≤ grade 1 and restart with	Hold until ≤ grade 1 and restart with 1 dose level ↓. Consider discontinuing if recurs.	As above.

		1 dose level ↓.		
* consider urgent therapy if hypertriglyceridemia due to risk of pancreatitis				

Exemestane:

Toxicity	Exemestane Dose
Myelosuppression	No adjustment required
Severe cutaneous reactions or acute generalized exanthematus pustulosis (AGEP)	Discontinue permanently

Hepatic Impairment

Hepatic impairment (baseline and during treatment)	Everolimus dose	Exemestane dose
Mild (Child-Pugh class A)	7.5mg once daily. ↓ to 5mg daily if not well tolerated	No dose adjustment required.
Moderate (Child-Pugh class B)	5mg daily. ↓ to 2.5 mg daily if not well tolerated	No dose adjustment required.
Severe (Child-Pugh class C)	Use only when benefits outweigh risks, at 2.5 mg daily	No dose adjustment required.

Renal Impairment

No dose adjustment required for exemestane and everolimus.

Dosage in the Elderly

No dose adjustment required; monitor patients carefully. In the advanced breast cancer study, higher incidences of adverse events leading to treatment discontinuation and deaths due to any cause (within 28 days of last dose) were observed in elderly patients.

back to top

F - Adverse Effects

Refer to everolimus, exemestane drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
	• Mucositis • Fatigue • Diarrhea • Rash (may be severe) • Nausea, vomiting • Increased LFTs (may be severe) • Anorexia • Fluid retention (may be severe) • Cough, dyspnea	• Headache • Musculoskeletal pain (may be severe) • Hyperglycemia • Pneumonitis (may be severe) • Insomnia • Dysgeusia • Myelosuppression +/- infection, bleeding (may be severe) • Estrogen deprivation symptoms (e.g. hot flashes, osteoporosis) • Hypertension (may be severe) • Dizziness	• Hypersensitivity, angioedema • Renal failure • Venous / arterial thromboembolism • Cardiotoxicity • Hyperlipidemia • GI obstruction • Pure red cell aplasia • Delayed wound healing • Secondary malignancy • Rhabdomyolysis

back to top

G - Interactions

Refer to everolimus, exemestane drug monograph(s) for additional details

- Do not use with strong CYP3A4 and PGP inhibitors (e.g. azole antifungals, clarithromycin, Grapefruit juice) as they may increase everolimus toxicity
- Avoid moderate CYP3A4 and PGP inhibitors (e.g. erythromycin, diltiazem, aprepitant). If must co-administer, reduce everolimus dose 50%. Monitor for toxicity.
- Avoid strong CYP3A4 or PGP inducers (e.g. rifampin, St. John's wort, corticosteroids) as these may decrease treatment efficacy. If must co-administer, monitor patient response and adjust dose, if required.
- Caution and monitor with statins, anticoagulants and antiplatelets as these may increase the risk of rhabdomyolysis and bleeding, respectively.
- Caution and monitor with ACE inhibitors as these may increase the risk of angioedema.
- Avoid concomittant use of estrogenic agents as these may antagonize exemestane.
- Caution and monitor with NSAIDs as these may increase the risk of gastric ulcer.
- Caution and monitor PT/INR when switching patients on warfarin from tamoxifen to exemestane.

back to top

H - Drug Administration and Special Precautions

Refer to everolimus, exemestane drug monograph(s) for additional details

Administration: everolimus

- Give everolimus consistently with food or without food, at the same time each day.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- Swallow whole with a glass of water; do not crush or chew.
- Note: Everolimus oral tablets and the DISPERZ™ tablets (for oral suspension) are non-interchangeable. Only everolimus oral tablets are indicated for use in metastatic breast cancer.
- If a dose is missed, it may be taken up to 6 hours after the time it is normally taken. Otherwise, skip this and take the next dose on the following day at its usual scheduled time.
- Store in original package at room temperature; protect from light.

Administration: exemestane

- Swallow whole tablet with a glass of water after a meal (to enhance absorption)
- Store tablets at room temperature.

Contraindications/ precautions:

- Contraindicated in patients with known hypersensitivity to exemestane or everolimus and in pre-menopausal women
- Avoid co-administration with estrogen-containing agents as this could interfere with pharmacological action
- Exercise caution in patients with pre-existing severe osteoporosis, hepatic impairment,

cardiovascular disease
- Caution and monitor patients receiving warfarin and switching from tamoxifen to exemestane (see Interactions)

Pregnancy & lactation

- This regimen should not be used in women of child-bearing potential

back to top

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

- CBC; baseline and as clinically indicated
- Cholesterol and lipids evaluation; baseline and periodic
- Fasting blood glucose; baseline and periodic (more frequent with concomitant use of drugs that can cause hyperglycemia)
- Liver function tests; baseline and periodic
- Renal function tests, electrolytes (including Ca, Mg and PO_4), urinalysis; baseline and periodic
- Clinical assessment of estrogen withdrawal symptoms, fatigue, cardiovascular, musculoskeletal, thromboembolism, rhabdomyolysis, hypersensitivity, mucositis and other GI effects, fluid retention, pulmonary toxicity, infection, rash, bleeding; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Pulmonary function tests in patients with significant lung disease; baseline and as clinically indicated
- Bone mineral density; baseline and as clinically indicated

back to top

J - Administrative Information

Outpatient prescription for home administration

back to top

K - References

Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor positive advanced breast cancer. N Engl J Med 2012;366(6):520-9.

Everolimus and exemestane drug monographs, Cancer Care Ontario.

May 2020 Changed exemestane public funding to ODB General Benefit

back to top

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.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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.

While care has been taken in the preparation of the information contained in the Formulary, 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.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top