Regimen Monograph

A - Regimen Name

EXEMPALB Regimen

Exemestane - Palbociclib

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	For the treatment of estrogen-receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer: • As first-line therapy for unresectable locally advanced or metastatic disease, OR • As second-line therapy after progression on a chemotherapy for unresectable locally advanced or metastatic disease (Refer to EAP funding criteria details.)
Supplementary Public Funding	**exemestane** ODB - General Benefit (exemestane) (ODB Formulary) **palbociclib** Exceptional Access Program (palbociclib - For the treatment of patients with

estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER 2)-negative, unresectable locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant, according to clinical criteria) (EAP Website)

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B - Drug Regimen

exemestane	25 mg	PO	Daily
palbociclib	125 mg	PO	Days 1 to 21

Note: Pre- or perimenopausal women should also be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to local clinical practice.

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C - Cycle Frequency

Exemestane: CONTINUOUS TREATMENT

Palbociclib: **REPEAT EVERY 28 DAYS (3 weeks on, 1 week off)**

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Also refer to CCO Antiemetic Recommendations.

Other Supportive Care:

- Assess patient's risk factors for osteoporosis and consider calcium and vitamin D supplements and bisphosphonates where appropriate. Refer patients to the Bone Health During Cancer Treatment pamphlet for more information.

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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	Exemestane Dose (mg/day) continuous	Palbociclib Dose (mg/day) for 3 out of 4 weeks
0	25	125
-1	25	100
-2	25	75
-3	25	If further dose reduction required, discontinue.

Exemestane:

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

Palbociclib:

Toxicity	Grade	Palbociclib Dose
Hematologic	3	Day 1: Hold and repeat CBC within 1 week. When recovered to Grade ≤ 2, re-start next cycle at same dose. Day 15 of 1st 2 cycles: Continue current dose to complete the cycle. Repeat CBC day 22. If Grade 4 on Day 22, see Grade 4 recommendation below. Consider dose reduction if > 1 week recovery or recurrent Grade 3 neutropenia in subsequent cycles.

	3 with fever ≥ 38.5ºC and/or infection	Hold until recovery to Grade ≤ 2. Restart at the next lower dose.
	4	Hold until recovery to Grade ≤ 2. Restart at the next lower dose.
Symptoms of interstitial lung disease (ILD)/pneumonitis (treatment–related)	Any	Hold dose and investigate; discontinue if severe ILD confirmed.
Other non-hematologic	3 or 4 (if persisting despite medical treatment)	Hold until recovery to Grade ≤ 1 or Grade ≤ 2 (if not considered a safety risk). Restart at the next lower dose.

Hepatic Impairment

Although AUC of exemestane is tripled in the presence of liver impairment (Child-Pugh C), adverse effects are not increased.

Mean fraction of unbound palbociclib in plasma increased with worsening hepatic function.

Hepatic Impairment	Exemestane Dose	Palbociclib Dose
Mild - Moderate (Child-Pugh class A and B)	No dosage adjustment needed.	No dosage adjustment needed.
Severe (Child-Pugh class C)	No dosage adjustment needed.	75 mg once daily (days 1 to 21; q28 days). Monitor for toxicity.

Renal Impairment

Although AUC of exemestane is tripled in the presence of severe renal impairment (CrCl < 30 mL/min), adverse effects are not increased.

Creatinine Clearance (mL/min)	Exemestane Dose	Palbociclib Dose
≥ 15	No dosage adjustment needed.	No dosage adjustment needed.
< 15	No dosage adjustment needed.	No data.

Dosage in the Elderly

No overall differences in efficacy were observed between patients aged 65 and older compared to younger patients. No dosage adjustment is required for either exemestane or palbociclib.

Dosage based on Gender:

Gender and body weight had no significant effect on palbociclib exposure.

Dosage based on Ethnicity:

No dose modification of palbociclib is required based on pharmacokinetic, safety and efficacy data across Asian and non-Asian populations.

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F - Adverse Effects

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

The following table is based on the LETRPALB regimen.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression +/- infection, bleeding (may be severe)	• Fatigue • Nausea, vomiting • Headache, musculoskeletal pain • Alopecia	• Cough, dyspnea • Estrogen deprivation symptoms • Constipation • Rash	• Arterial thromboembolism • Venous thromboembolism • Arrhythmia • Cardiotoxicity • Hypersensitivity

	• Diarrhea	• Anorexia • Stomatitis • Insomnia • Dizziness • Osteoporosis, fracture • Abdominal pain • Edema • ↑ LFTs • Dysgeusia	• Eye disorders • Pneumonitis

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G - Interactions

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

- Avoid concomittant use of estrogen-containing or estrogenic agents due to decreased effect of exemestane.
- Avoid strong CYP3A inhibitors due to increased risk of palbociclib toxicity.
- Avoid strong CYP3A inducers and, if possible, moderate CYP3A inducers due to decreased palbociclib concentration/efficacy.
- Administer palbociclib **capsules** with food to reduce variable drug exposure and minimize drug interactions with drugs that alter gastric pH. This does not apply to palbociclib tablets.
- Consider reducing the dose of CYP3A substrates with narrow therapeutic indices (e.g. cyclosporine) as palbociclib may increase substrate concentration.
- Monitor PT/INR of patients on warfarin switching from tamoxifen to exemestane due to possible INR level changes.

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H - Drug Administration and Special Precautions

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

Administration: Exemestane

- Tablets should be swallowed whole with a glass of water after a meal (to enhance absorption).
- Store tablets at room temperature (15-30°C).

Administration: Palbociclib

- Palbociclib **capsules** should be administered **with food;** palbociclib **tablets** may be given **with or without food.**
- Capsules or tablets should be swallowed whole and not chewed, crushed, opened, or split prior to administration.
- If a patient vomits or misses a dose, an extra dose should not be taken to make up for the vomited or missed dose. The next dose should be taken at the usual time.
- Grapefruit, pomegranate, starfruit, Seville oranges, their juices or products should be avoided during palbociclib treatment.
- **Capsules** should be stored at 20 to 25^{o}C, with excursions permitted between 15 to 30^{o}C. **Tablets** should be stored at 15 to 30^{o}C in original packaging to protect from moisture.

Contraindications

- Patients with known hypersensitivity to exemestane, palbociclib or any of its components

Warnings/Precautions

- Patients with pre-existing severe osteoporosis, a history of osteoporotic fracture or significant cardiac disorders were excluded from clinical trials in early breast cancer.
- Exemestane may increase risk of gastric ulcers especially in patients on NSAIDs or with a prior history.
- As fatigue and dizziness have been reported with palbociclib, patients should exercise caution when driving or operating machinery.
- Palbociclib **capsules** contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Pregnancy/Lactation

- This treatment is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** (general recommendation) after the last dose.
- Breastfeeding is not recommended with this treatment.
- 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

- CBC; Baseline and before each cycle, on day 15 of the first 2 cycles, one week after Grade 3 neutropenia, and as clinically indicated. If neutropenia Grade 2 or less in the first 6 cycles, may monitor every 3rd cycle thereafter.
- Liver function tests; Baseline and as clinically indicated
- Renal function tests; Baseline and as clinically indicated
- Bone mineral density; Baseline and as clinically indicated
- Cholesterol and lipids evaluation; baseline and as clinically indicated
- Clinical assessment of infection, bleeding, thromboembolism, pneumonitis, rash, headache, mucositis, estrogen deprivation symptoms, fatigue, cardiovascular, musculoskeletal, hypersensitivity, skin, GI effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- INR for patients on warfarin (when switching from tamoxifen to exemestane); As clinically indicated

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Exemestane and palbociclib drug monographs. Ontario Health (Cancer Care Ontario).

Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25-35.

LETRPALB regimen monograph. Ontario Health (Cancer Care Ontario).

February 2021 Expanded to full regimen monograph

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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.

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