Regimen Monograph

A - Regimen Name

FLVSPALB Regimen

Fulvestrant-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, OR • As second-line or subsequent therapy after progression on any number of endocrine monotherapies (except progression during prior fulvestrant therapy) (Refer to EAP funding criteria details.)
Supplementary Public Funding	**fulvestrant** ODB - General Benefit (fulvestrant) (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)

back to top

B - Drug Regimen

Cycle 1:

palbociclib	125 mg	PO	Days 1 to 21
fulvestrant	500 mg	IM	Days 1 and 15

Cycle 2+:

palbociclib	125 mg	PO	Days 1 to 21
fulvestrant	500 mg	IM	Day 1

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

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

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.

Dosage with toxicity

Dose Level	Palbociclib Dose (mg/day) for 3 out of 4 weeks	Fulvestrant Dose (after loading dose in cycle 1)
0	125	500 mg IM q 4 weeks
-1	100	500 mg IM q 4 weeks
-2	75	500 mg IM q 4 weeks
-3	If further dose reduction required, discontinue.	500 mg IM q 4 weeks

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 ≥ 38.5^{o}C 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.

Fulvestrant:

Toxicity	Fulvestrant Dose
Hypersensitivity	Consider discontinuing if severe.
Mild hepatotoxicity	Hold until recovery and then restart.
Moderate to severe hepatotoxicity	Discontinue.

Hepatic Impairment

Fulvestrant is metabolized primarily in the liver. There are no efficacy and safety data in patients with breast cancer and hepatic impairment. Decreased clearance (by 2.2 fold) and changes in exposure (↑ 70%) were observed in women with moderate hepatic impairment compared to patients with normal hepatic function.

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

Hepatic Impairment	Palbociclib Dose	Fulvestrant Dose
Mild - Moderate (Child-Pugh class A and B)	No dosage adjustment needed.	Use with caution. No dosage adjustment needed.
Severe (Child-Pugh class C)	75 mg once daily (days 1 to 21; q28 days). Monitor for toxicity.	Not studied. Use not recommended.

Renal Impairment

Creatinine Clearance (ml/min)	Palbociclib Dose	Fulvestrant Dose
≥ 30	No adjustment required.	No dosage adjustment required.
15 - < 30		Use with caution; no data.
< 15	No data available.	

Dosage in the Elderly

No dose adjustment needed for either palbociclib or fulvestrant.

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.

back to top

F - Adverse Effects

Refer to palbociclib, fulvestrant 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
• Myelosuppression +/- infection, bleeding (may be severe)	• Fatigue • Nausea, vomiting • Mucositis	• Headache • Diarrhea • Joint disorders, musculoskeletal pain • Constipation • Alopecia • ↑ LFTs (may be severe) • Injection site reaction (may be severe) • Rash, dry skin • Anorexia • Cough, dyspnea • Insomnia • Dizziness	• Arterial thromboembolism • Venous thromboembolism • Hypersensitivity • Pneumonitis • Osteoporosis • Estrogen deprivation symptoms

back to top

G - Interactions

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

- 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.
- Fulvestrant may interfere with estradiol immunoassay measurements (falsely elevated

estradiol levels) due to its structural similarity with estradiol.

back to top

H - Drug Administration and Special Precautions

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

Administration: Fulvestrant

- Each dose consists of 2 pre-filled syringes (250 mg/5mL). Administer each pre-filled syringe as SLOW intramuscular injection (1-2 minutes per injection) into EACH buttock.
- Caution should be taken due to proximity of the sciatic nerve and large blood vessels.
- Administer according to local guidelines at the Cancer Centre or physician's office.
- Store refrigerated at 2 to 8°C in original package.

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 who are hypersensitive to palbociclib, fulvestrant or any of their components.
- Fulvestrant is contrainidecat in pregnant or breastfeeding women.

Warnings/Precautions

- Due to the route of administration, use with caution in patients with bleeding disorders or on anticoagulants.
- There is a potential osteoporosis risk due to fulvestrant's mechanism of action.
- As fatigue and dizziness have been reported with palbociclib and fulvestrant, 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 **contraindicated** in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **2 years** after the last dose.
- Breastfeeding is **contraindicated** with this treatment.
- Fertility effects: Probable

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 before each cycle, on day 15 of the first 2 cycles, one week after Grade 3 neutropenia, and as clinically indicated. If Grade ≤ 2 neutropenia 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
- Clinical toxicity assessment for injection site reactions, hypersensitivity, estrogen deprivation symptoms, infection, bleeding, thromboembolism, pneumonitis, rash, mucositis, fatigue, headache, GI and musculoskeletal effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Administrative Information

Palbociclib: Outpatient prescription for home administration

Fulvestrant: Outpatient prescription; drug administration at Cancer Centre or physician's office

back to top

K - References

Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17(4):425-39.

Fulvestrant and palbociclib drug monographs, Ontario Health (Cancer Care Ontario).

Harbeck N, Iyer S, Turner N, et al. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial. Ann Oncol 2016;27(6):1047-54.

February 2021 Updated rationale, dose modifications, adverse effects, interactions, drug administration, special precautions and monitoring sections

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