Regimen Monograph

A - Regimen Name

ABEMFLVS Regimen

Abemaciclib-Fulvestrant

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 treatment of hormone-receptor-positive, HER2-negative advanced breast cancer in patients whose disease had progressed while receiving endocrine therapy.
Supplementary Public Funding	**fulvestrant** ODB - General Benefit (fulvestrant) (ODB Formulary)

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B - Drug Regimen

Cycle 1:

abemaciclib	150 mg	PO	BID
(This drug is not currently publicly funded for this regimen and intent)			
fulvestrant	500 mg	IM	Days 1 and 15

Cycle 2+:

abemaciclib	150 mg	PO	BID
(This drug is not currently publicly funded for this regimen and intent)			
fulvestrant	500 mg	IM	Day 1

Note: Pre- or perimenopausal women, and men should also be treated with gonadotropin releasing hormone (GnRH) agonists according to local clinical practice.

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C - Cycle Frequency

Abemaciclib: Continuous treatment

Fulvestrant: REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

- 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

Abemaciclib Dose Levels

Dose Level	Abemaciclib Dose (mg BID)
0	150
-1	100
-2	50
-3	Discontinue

Dose Modifications:

Toxicity	Grade	Abemaciclib Action	Fulvestrant Action
Hematologic*	Grade 3	Hold until ≤ grade 2; resume at same dose.	Not applicable
	Grade 4 or recurrent grade 3	Hold until ≤ grade 2; resume at 1 dose level ↓.	
Diarrhea**	Grade 2	If no resolution to ≤ grade 1 within 24 hours, hold until resolution; resume at same dose.	No adjustment required
	Grade 2 that persists/recurs after resumption at the same dose (despite maximal supportive measures)	Hold until ≤ grade 1; resume at 1 dose level ↓.	
	≥ Grade 3 or requires hospitalization		
Interstitial lung disease (ILD)/	Persistent or recurrent grade 2 toxicity that does	Hold until recovery to baseline or ≤ grade 1;	Not applicable

Pneumonitis	not resolve to baseline or grade 1 within 7 days (despite maximal supportive measures)	resume at 1 dose level ↓.	
	Grade 3 or 4	Discontinue	
Hepatotoxicity	Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN) WITHOUT increase in total bilirubin above 2 x ULN	No dose modification is required.	Hold until recovery then restart
	Persistent or recurrent grade 2, or grade 3 (ALT, AST >5 to 20 times ULN), WITHOUT increase in total bilirubin >2 times ULN	Hold until recovery to baseline or grade 1; resume at 1 dose level ↓.	Discontinue
	AST and/or ALT >3 times ULN with total bilirubin >2 times ULN (in the absence of cholestasis)	Discontinue	Discontinue
	Grade 4 (ALT, AST >20 times ULN)	Discontinue	Discontinue
Venous thromboembolism	Grade 3 or 4	Hold; restart when patient is stable and if clinically appropriate	Not applicable
Hypersensitivity	≥ Grade 3	Hold until recovery to baseline or ≤ grade 1; resume at 1 dose level ↓, OR consider discontinuing.	Consider discontinuing
All other non-hematologic toxicities	Persistent or recurrent grade 2 toxicity that does not resolve to baseline or grade 1 within 7 days (despite maximal supportive measures)	Hold until recovery to baseline or ≤ grade 1; resume at 1 dose level ↓.	No adjustment required
	Grade 3 or 4		

*If blood cell growth factors are required, hold abemaciclib for at least 48 hours after the last growth factor dose and until toxicity resolves to ≤ grade 2; resume at the next lower dose (unless already reduced due to the toxicity that required the growth factor). Growth factor use is as per current local guidelines.

**At the first sign of loose stools, begin management with antidiarrheal agents (i.e. loperamide) and increase oral fluid intake.

Hepatic Impairment

Hepatic Impairment	Abemaciclib Dose	Fulvestrant Dose
Mild or moderate impairment (Child-Pugh class A or B)	No dosage adjustment required.	Use with caution. No dose adjustment required.
Severe impairment (Child-Pugh class C)	Reduce the abemaciclib frequency to once daily.	Not studied. Use not recommended.

Renal Impairment

Renal Impairment	Abemaciclib Dose	Fulvestrant Dose
Mild or Moderate (CrCl ≥ 30 mL/min)	No dosage adjustment required.	No dose adjustment required.
Severe (CrCl < 30 mL/min); ESRD	Has not been studied	No data; use with caution.

Dosage in the Elderly

No dosage adjustment is required. Patients ≥65 years of age on abemaciclib reported more hematologic adverse events, hypokalemia (including grade 3), hypocalcemia, grade ≥3 infections, decreased appetite, and increased blood creatinine with abemaciclib compared to younger patients in a subgroup analysis from clinical studies.

Dosage based on Ethnicity

No dose adjustment based on race is required. Higher incidences of increased ALT and AST and neutropenia have been reported in East Asian patients on abemaciclib compared to Caucasian patients in clinical trials.

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F - Adverse Effects

Refer to abemaciclib, 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
• Diarrhea (may be severe)	• Infection (may be severe) • Myelosuppression (may be severe) • Fatigue • Nausea, vomiting (generally mild)	• Creatinine increased • Musculoskeletal pain • Headache • Cough, dyspnea • Mucositis • Flu-like symptoms • Anorexia, weight loss • Injection site reaction (may be severe) • ↑ LFTs (may be severe) • Rash, pruritus, dry skin • Alopecia • Peripheral edema • Constipation • Dizziness	• Cardiotoxicity • Arterial / Venous thromboembolism • Osteoporosis • Hypersensitivity • Nephrotoxicity • Pneumonitis • Estrogen deprivation symptoms

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G - Interactions

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

- Avoid co-administration of abemaciclib with strong CYP3A inhibitors. Use caution when abemaciclib is co-administered with moderate or weak CYP3A inhibitors.
    - If co-administration with a strong or moderate CYP3A inhibitor is unavoidable, reduce

abemaciclib dose to 50 mg twice daily.

- When combined with ketoconazole, abemaciclib dose should be reduced to 50 mg once daily.
- When combined with clarithromycin, diltiazem or verapamil, abemaciclib dose should be reduced to 100 mg twice daily.

- If co-administration with a weak CYP3A inhibitor is unavoidable, reduce abemaciclib dose to 100 mg twice daily.
- If the CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

- Avoid co-administration of abemaciclib with strong CYP3A inducers. Consider alternative agents with less CYP3A induction. Use with caution when co-administered with moderate or weak CYP3A inducers.
- Fulvestrant may interfere with estradiol immunoassay measurements (falsely elevated estradiol levels) due to its structural similarity with estradiol.

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H - Drug Administration and Special Precautions

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

Administration

Abemaciclib

- Abemaciclib tablets should be swallowed whole (do not to chew, crush, or split tablets before swallowing). Tablets should not be ingested if they are not intact.
- Abemaciclib doses may be taken with or without food and should be administered at approximately the same times every day.
- Avoid fruit or juice from grapefruit, Seville oranges or starfruit.
- Abemaciclib tablets contain lactose. Use with caution in patients with lactose intolerance.
- If a dose is missed or vomited, the next dose should be taken at the scheduled time. The patient should not take 2 doses at the same time to make up for the missed dose.
- Store at room temperature (15°C to 30°C).

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

Contraindications

- Patients who are hypersensitive to abemaciclib, fulvestrant, or to any of their components
- Fulvestrant is also contraindicated in pregnant and breastfeeding women

Other Warnings/Precautions

- There are no data regarding abemaciclib safety or efficacy in patients with prior exposure to other CDK 4/6 inhibitors.
- Use fulvestrant with caution in patients with bleeding disorders or on anticoagulants
- There is a potential osteoporosis risk due to fulvestrant's mechanism of action.

Pregnancy/Lactation

- This treatment is **contraindicated** in pregnancy. Adequate contraception should be used by both partners during treatment, and for at least **2 years** after the last fulvestrant dose.
- Breastfeeding is **contraindicated** with this treatment and not recommended for at least **3 weeks** after the last dose of abemaciclib.
- Fertility Effects:
    - Abemaciclib: Probable; may impair fertility in males
    - Fulvestrant: Probable

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; Baseline, every two weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.
- Renal function tests*; Baseline and as clinically indicated
- Liver function tests; Baseline, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.
- Clinical toxicity assessment for signs and symptoms of thromboembolism, injection site reactions, hypersensitivity, infections, estrogen deprivation symptoms, musculoskeletal, gastrointestinal, respiratory, dermatological effects and fatigue; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

  *Abemaciclib may increase serum creatinine, without affecting glomerular function, by inhibiting renal tubular secretion transporters. Consider alternative markers that are not based on creatinine (e.g. BUN) for determining renal function.

Suggested Clinical Monitoring

- Electrolytes, including calcium; Baseline and as clinically indicated

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J - Administrative Information

Outpatient prescription; drug administration at hospital or physician's office

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K - References

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

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

Sledge GW, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol. 2017;35:2875-84.

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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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