Regimen Monograph

A - Regimen Name

GILT Regimen

gilteritinib

Disease Site

Hematologic
Leukemia - Acute Myeloid (AML)

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 adult patients who have relapsed or refractory acute myeloid leukemia† (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation*, who have good performance status (ECOG ≤2) .

Refer to EAP criteria for dose escalations to achieve complete remission and for maintenance treatment after hematopoietic stem cell transplant.

† relapsed / refractory to a prior chemotherapy regimen used for AML.
* FLT3 mutation with either a FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836 is confirmed by an approved test taken after relapse on a chemotherapy regimen.

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Supplementary Public Funding	**gilteritinib** Exceptional Access Program (gilteritinib - Relapsed or Refractory FLT3-mutated acute myeloid leukemia) (EAP Website)

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B - Drug Regimen

gilteritinib	120* mg	PO	Daily

* Dose escalation up to 200 mg daily in the absence of clinical response may be considered

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity*

*A delay in clinical response can occur; gilteritinib treatment is recommended to continue for a minimum of 6 months (i.e., in the absence of disease progression or unacceptable toxicity).

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low – No routine prophylaxis; PRN recommended

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

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

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A validated test is required to confirm the FLT3 mutation prior to initiation of treatment.

Correct hypokalemia or hypomagnesemia prior to gilteritinib administration.

Patients proceeding to hematopoietic stem cell transplantation (HSCT) should stop gilteritinib one week before the HSCT conditioning regimen.

- Gilteritinib treatment may be restarted ≥ 30days after the transplantation if engraftment is successful and patient is in CRc* and has no grade ≥ 2 acute graft versus host disease or uncontrolled complications of transplantation.

*composite complete remission (CRc) is defined as the remission rate of all CR, CRp (achieved CR except for incomplete platelet recovery (<100 x 10^9/L)), and CRi (achieved CR except for incomplete hematological recovery with residual neutropenia (< 1 x 10^9/L) +/- complete platelet recovery).

Dosage with toxicity

Dose Levels

Dose Level	Gilteritinib Dose (mg/day)
0	120
-1	80

Toxicity	Grade	Action
Symptoms of Differentiation Syndrome	Any	If suspected, administer corticosteroids* for a minimum of 3 days and initiate hemodynamic monitoring until symptom resolution. Taper corticosteroids after resolution of symptoms. Hold if severe signs and/or symptoms persist for > 48 hours after corticosteroid initiation. With resolution to ≤ grade 2, restart at the same dose level .
Symptoms of Posterior Reversible Encephalopathy	Any	Discontinue

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Syndrome (PRES)		
QTc interval	>500 msec	Hold until QTc interval is within 30 msec of baseline or ≤480 msec. Restart at 1 dose level ↓.
	Increased by >30 msec on ECG on day 8 of cycle 1	Confirm with a repeat ECG on day 9. If confirmed, consider ↓ by 1 dose level .
Pancreatitis	Any	Hold until resolved. Restart at 1 dose level ↓.
Other toxicity (considered related to treatment)	≥ Grade 3	Hold until resolved to grade 1. Restart at 1 dose level ↓.

*dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid)

Hepatic Impairment

Mild or moderate hepatic impairment had no clinically meaningful effects on gilteritinib pharmacokinetics.

Hepatic Impairment	Gilteritinib Starting Dose
Mild (Child Pugh A)	No dose adjustment required.
Moderate (Child Pugh B)	
Severe (Child Pugh C)	No data available

Renal Impairment

Mild or moderate renal impairment had no clinically meaningful effects on gilteritinib pharmacokinetics.

It is not known if gilteritinib is removed by dialysis.

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CrCl (mL/min)	Gilteritinib Dose
≥ 30	No adjustment required
< 30	Limited data available

Dosage in the Elderly

No dose adjustment required; no overall differences in efficacy or safety were observed in patients ≥ 65 years of age compared to younger patients.

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F - Adverse Effects

Refer to gilteritinib 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
• ↑ LFTs • Diarrhea • Nausea, vomiting • Constipation • Cough, dyspnea • Febrile neutropenia • Fatigue • Headache • Eye disorders	• Peripheral edema • Dizziness • Anorexia • Hypotension • Abdominal pain • Musculoskeletal pain (may be severe) • Rash • Mucositis • Dysgeusia	• Cardiotoxicity • Prolonged QT interval • Anaphylaxis • Acute kidney injury • Peripheral neuropathy • Pancreatitis • RPLS / PRES • Differentiation syndrome

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G - Interactions

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Refer to gilteritinib drug monograph(s) for additional details

- Avoid concomitant use of with strong CYP3A4 and strong P-glycoprotein inducers as they may decrease gilteritinib concentration and/or efficacy.
- Consider alternative therapies to strong CYP3A4 and strong P-glycoprotein inhibitors as they may increase gilteritinib concentration and/or toxicity. If concomitant use cannot be avoided, monitor closely for gilteritinib-related toxicity.
- Avoid concomitant use with $5HT_{2B}$ receptor or sigma nonspecific receptor substrates unless use is considered essential as substrate concentration and/or efficacy may be decreased.

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H - Drug Administration and Special Precautions

Administration

- Administer tablets orally with or without food, about the same time each day.
- Do not break or crush tablets.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during gilteritinib treatment.
- If a dose is missed, administer the missed dose as soon as possible on the same day if there is ≥12 hours until the next scheduled dose (do not administer 2 doses within 12 hours). Return to the normal dosing schedule the following day.
- If vomiting occurs after dosing, patients should not take another dose but should return to the normal schedule the following day.
- Store at room temperature 15ºC to 30ºC.
- Keep container tightly closed, and protect from light, moisture and humidity.

Contraindications

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

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Other Warnings/ Precautions

- Use with caution in patients with acute promyelocytic leukemia (APL) or AML related to previous chemotherapy or radiation as they were excluded from clinical trials.
- Dizziness and syncope have been reported in patients taking gilteritinib; caution is required when driving or operating machinery.

Pregnancy/Lactation

- Gilteritinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose in women and at least **4 months** after the last dose in men.
- Breastfeeding is not recommended during treatment and for at least **2 months** after the last dose.
- Fertility Effects: Gilteritinib may impair fertility in male patients of reproductive potential.

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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, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of treatment
- Blood chemistry (including creatine kinase, creatinine, electrolytes); Baseline, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of treatment
- ECG ; Baseline, on days 8 and 15 of cycle 1 and prior to the start of the next 2 months of treatment and then as clinically indicated

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- Clinical toxicity assessment for differentiation syndrome, infection, pancreatitis, hypersensitivity reactions and cardiovascular, gastrointestinal, neurologic and ophthalmic effects; As clinically indicated

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Gilteritinib Drug Monograph, Ontario Health (Cancer Care Ontario).

Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med 2019;381(18):1728-1740. doi: 10.1056/NEJMoa1902688.

March 2022 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

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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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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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