Indication	Monotherapy for the treatment of relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation. Gilteritinib should not be given as maintenance therapy after a haematopoietic stem cell transplant (SCT), it can be given to patients who relapse post SCT if they have not had previous treatment with gilteritinib. NB the patient must not have received previous systemic therapy with other FLT3 inhibitors (with the exception of sorafenib or midostaurin or quizartinib used in first-line therapy or clinical trials in 1st line therapy).
Treatment Intent	Disease modification.
Frequency and number of cycles	Repeat every 28 days Continue until it is considered the patient has been cured, or until progressive disease, unacceptable toxicity or patient choice, whichever occurs first, or the patient receives a haematopoietic stem cell transplant. NB: Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response.

Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.
	• FBC, U&Es (including creatine phosphokinase) and LFTs before cycle 1 on day 15 of cycle 1 and before each cycle thereafter.
	• If neutrophils <1 and/or platelets <50 and considered to be related to treatment discuss with consultant.
	• Hypokalaemia or hypomagnesaemia should be corrected prior to treatment and throughout treatment if necessary.
	• **ECG** prior to treatment, on day 8 and 15 of cycle 1 and before cycles 2, 3 and 4.
	• BP prior to treatment and as clinically indicated.
	• **Hepatic Impairment:** No dose adjustment is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Use in severe (Child-Pugh class C) hepatic impairment is not recommended.
	• **Renal Impairment**: No dose adjustment is necessary in patients with mild, ~~or~~ moderate or severe renal impairment.
	• **Dose modification**
	  ○ Starting dose of gilteritinib is 120mg OD, in the absence of a response (patient did not achieve a CRc) after 4 weeks of treatment, the dose can be increased to 200 mg once daily, if tolerated or clinically warranted.
	  ○ See table 1 for dose modifications for adverse effects including, symptoms of differentiation syndrome, symptoms of posterior reversible encephalopathy syndrome, QTcF interval changes and pancreatitis.
	  ○ If a dose reduction is required, the daily dose should be reduced from 120mg to 80mg or from 200mg to 120mg.
	• **Common drug interactions: (for comprehensive list refer to BNF/SPC)**
	Concomitant use of gilteritinib with strong CYP3A4 inducers (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, St John's Wort) and strong P-gp inducers should be avoided.

	If concomitant use of gilteritinib with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, posaconazole, voriconazole, azithromycin) and strong P-gp and /or BCRP inhibitors (e.g. amiodarone) cannot be avoided patients should be closely monitored for toxicity. Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these medicinal products with gilteritinib unless use is considered essential for the care of the patient. • **Adverse reactions:** **Posterior Reversible Encephalopathy Syndrome** (PRES) has been reported with gilteritinib. In patients developing PRES, discontinuation of treatment is recommended. **Differentiation syndrome** Gilteritinib has been associated with differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy (dexamethasone 10mg iv BD) should be initiated along with hemodynamic monitoring until symptom resolution. Furosemide may be required to treat signs and symptoms of fluid overload. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, treatment should be interrupted until signs and symptoms are no longer severe. Corticosteroids can be tapered after resolution of symptoms and must be administered for a minimum of 3 days as symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. • **Prolonged QT interval:** QT prolongation can be observed in the first three months of treatment with gilteritinib. Caution is warranted in patients with relevant cardiac history. Gilteritinib should be interrupted in patients who have a QTcF >500 msec. The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on a careful consideration of benefits and risks. If gilteritinib is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment. • **Pancreatitis:** Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. Gilteritinib should be interrupted and can be resumed at a reduced dose (80mg or 120mg as per table 1) when the signs and symptoms of pancreatitis have resolved. • **Missed dose:** If a dose is missed, the dose should be administered as soon as possible on the same day, and patients should return to the normal schedule the following day. If vomiting occurs after dosing, patients should not take another dose. • **Driving and machinery:** Dizziness has been reported in some patients, this should be considered when driving or operating machinery. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	KMCC protocol HAEM-AML-034 V2 SPC accessed online 12.12.2024. CDF list V1.336 accessed online 12.12.2024

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Dose interruption, reduction and discontinuation recommendations in patients with relapsed or refractory AML

Criteria	**Gilteritinib dosing**
Symptoms of differentiation syndrome	• If differentiation syndrome is suspected, administer corticosteroids and initiate hemodynamic monitoring. • Interrupt gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids. • Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2[a] or lower.
Symptoms of posterior reversible encephalopathy syndrome	• Discontinue gilteritinib.
QTcF interval >500 msec	• Interrupt gilteritinib. • Resume gilteritinib at a reduced dose (80 mg or 120 mg[b]) when QTcF interval returns to within 30 msec of baseline or ≤ 480 msec.
QTcF interval increased by >30 msec on ECG on day 8 of cycle 1	• Confirm with ECG on day 9. • If confirmed, consider dose reduction to 80 mg
Symptoms of pancreatitis	• Interrupt gilteritinib until pancreatitis is resolved. • Resume treatment with gilteritinib at a reduced dose (80 mg or 120 mg[b]).
Other Grade 3[a] or higher toxicity considered related to treatment.	• Interrupt gilteritinib until toxicity resolves or improves to Grade 1[a]. • Resume treatment with gilteritinib at a reduced dose (80 mg or 120 mg[b]).
Planned HSCT	• Interrupt treatment with gilteritinib one week prior to administration of the conditioning regimen for HSCT.
a. Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening. b. The daily dose can be reduced from 120 mg to 80 mg or from 200 mg to 120 mg.	

Repeat every 28 days

Day	Drug	Dose	Route	Administration
Day 1	**GILTERITINIB**	**120mg**	PO	OD at the same time each day Swallow whole with water, do not crush or break tablet. Can be taken with or without food. Available as 40mg tablets NB see monitoring parameters for information regarding dose escalation in the absence of a response.
	Metoclopramide	10mg	PO	TDS PRN Do not take for more than 5 days continuously. (dispense 28 tablets on cycle 1, then only if specified)
	Loperamide	2mg-4mg	PO	Take 4mg initially then 2mg after each loose stool when required (max 16mg a day) (dispense 1 original pack on cycle 1, then when required)
	Allopurinol	300mg	PO	OD Cycle 1 only. Clinician to assess patient, and delete if not required.
	If cytopenic consider adding anti-viral, anti-fungal, antibiotic prophylaxis			