Gilteritinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.* * In the event that patients re-initiate gilteritinib post haematopoietic stem cell transplant (HSCT) as maintenance therapy, gilteritinib treatment should be restricted to patients who are minimal residual disease (MRD)-positive post-transplant.	C92	00684a	CDS 01/10/2025

* This applies to post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

- The recommended starting dose of gilteritinib is 120 mg (3 x 40mg tablets) once daily.
- Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs.
- 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.
- In the absence of a response (patient did not achieve a composite complete remission (CRc) after 4 weeks of treatment, the dose can be increased to 200 mg (5 x 40mg tablets) ONCE daily, if tolerated or clinically warranted.

Drug	Dose	Route	Cycle
Gilteritinib	120mg once daily	PO	Continuous
Gilteritinib is available as 40mg tablets and can be taken with or without food. The tablets should be swallowed whole with water and should not be broken or crushed. Gilteritinib should be administered at about the same time each day. If a dose is missed or not taken at the usual time, 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 but should return to the normal schedule the following day.			

ELIGIBILITY:

- Indication as above
- ECOG 0-2
  - (patients with ECOG 3 may be considered at consultant discretion)
- Adequate organ function

CAUTIONS:

- Clinically significant abnormality of coagulation profile, such as disseminated intravascular coagulation.
- Symptomatic congestive heart failure
- Active uncontrolled infection
- Clinically active central nervous system leukaemia
- Treatment with concomitant drugs that are strong inducers of CYP3A4 or strong inhibitors or inducers of P-gp or substrates of MATE1 with the exception of drugs that are considered absolutely essential for the care of the subject. If combination cannot be avoided, close monitoring of gilteritinib-related adverse effects is advised.

EXCLUSIONS:

- Hypersensitivity to gilteritinib or any of the excipients.
- Pregnancy
- Women of childbearing potential not using effective contraception
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test.
- Lipase and amylase
- Bone profile
- LDH and Creatinine kinase(CK)
- Coagulation profile
- ECHO or MUGA
- ECG
- Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment
- Virology screening* - Hepatitis B virus (HBV) serology [HBV sAg, HBV sAb, HBV cAb], hepatitis C virus (HCV) serology, human immunodeficiency virus (HIV) serology, cytomegalovirus (CMV) serology [IgG] and additional screening as clinically indicated

*(See Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

- FBC, renal and liver profile, bone profile, LDH and CK should be monitored at a minimum on day 1 and day 15 of cycle 1 and at least monthly for the duration of treatment or as clinically indicated depending on blood counts.
- Amylase as clinically indicated
- ECG on day 8, 15 of cycle 1 and prior to the start of the next three subsequent months of treatment and as clinically indicated.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose interruptions and reductions are permitted for the management of gilteritinib induced toxicities, as outlined in Table 1 below.

Table 1: Gilteritinib dose interruption, reduction and discontinuation in patients with replased or refractory AML

Criteria	Gilteritinib Dosing
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.
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.
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.

	• Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in CRc[c,d].

[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.

[c] 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 all criteria for CR except for incomplete haematological recovery with residual neutropenia <1 x 10^9/L with or without complete platelet recovery).

[d].In the event that patients re-initiate gilteritinib post haematopoietic stem cell transplant (HSCT) as maintenance therapy, gilteritinib treatment should be restricted to patients who are minimal residual disease (MRD)-positive post-transplant.

Renal and Hepatic Impairment:

Table 2: Dose modification of gilteritinib in renal and hepatic impairment

Renal Impairment	Recommended dose modification	Hepatic Impairment	Recommended dose modification
CrCl ≥ 30 mL/min	No dose adjustment is needed	Child-Pugh A/B or mild/moderate	No dose adjustment is needed
CrCl < 30 mL/min and In Haemodialysis	No need for dose adjustment is expected	Child-Pugh C and severe	Not recommended
Recommendations from Giraud et al 2023			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

Gilteritinib: Minimal-Low **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for Inclusion in NCIS (Medical Oncology) - Available on NCCP website
- NCCP Supportive Care Antiemetic Medicines for Inclusion in NCIS (Haemato-oncology) - Available on NCCP website

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Tumour Lysis Syndrome prophylaxis **(Refer to local policy)**
- Contraception **(see Regimen Specific complications)**

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.
- **Differentiation syndrome:** Gilteritinib has been associated with differentiation syndrome. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with hemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, gilteritinib should be interrupted until signs and symptoms are no longer severe, as per Table 1 above. Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment.
- **Posterior reversible encephalopathy syndrome (PRES):** PRES has been reported in patients receiving gilteritinib. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of gilteritinib in patients who develop PRES is recommended.
- **Prolonged QT interval:** Gilteritinib has been associated with 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. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during gilteritinib treatment. Gilteritinib should be interrupted in patients who have a QTcF >500 msec, as per Table 1 above. 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:** There have been reports of 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 when the signs and symptoms of pancreatitis have resolved**.**
- **Concomitant use of inducers of CYP3A4/P-gp:** Concomitant use of strong CYP3A4/P-gp inducers

should be avoided due to the risk of decreased efficacy of gilteritinib. Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A, P-gp and/or breast cancer resistant protein (BCRP) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib.

- Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient.
- **Embryofoetal toxicity and contraception**: Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with gilteritinib and to use effective contraception during treatment with gilteritinib and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of gilteritinib.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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2. Perl AE, Larson RA, Podoltsev NA, et al. Follow-up of patients with R/R FLT3- mutation-positive AML treated with gilteritinib in the phase 3 ADMIRAL trial. Blood 2022;139:3366-3375 https://pubmed.ncbi.nlm.nih.gov/35081255/
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Gilteritinib (Xospata®) Summary of Product Characteristics. Last updated: 09/07/2024. Accessed April 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/xospata-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/10/2025		Dr. Janusz Krawczyk

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