Gilteritinib (AML)

Indication
Monotherapy for relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]).

ICD-10 codes
C92

Regimen details

Drug	Dose	Route
Gilteritinib	120mg OD*	Oral

*In the absence of response after 4 weeks of treatment (i.e. patient did not achieve composite complete remission CRc) the dose can be increased to 200mg once daily, if tolerated or clinically warranted

Cycle frequency
Continuous

Number of cycles
Continued until the patient is no longer clinically benefiting from gilteritinib, experiences unacceptable toxicity, is considered to be cured or receives a haematopoietic stem cell transplant (HSCT).

Administration
Gilteritinib is available as 40mg tablets.

Tablets should be swallowed whole with water, either with or without food, 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.

Pre-medication
Nil

Emetogenicity
This regimen has low emetic potential (no routine anti-emetics are required)

Additional supportive medication
Allopurinol 300mg PO once daily for 7 days on cycle 1
Antiviral prophylaxis as per local policy
Antifungal prophylaxis as per local policy

Extravasation
N/A

Investigations – pre first cycle

Patients must have confirmed FLT3 mutation prior to starting treatment. NB. Clonal evolution can be seen in relapsed AML, whereby mutations, such as FLT3-ITD mutations, that were not originally detectable at diagnosis can appear at relapse, and those initially present can be lost. Around 20% of patients with AML have a newly detectable mutation or lose a previously detectable FLT3-ITD or FLT3-TKD mutation at relapse (McCormick et al., Arch Pathol Lab Med. 2010;134:1143–51). This highlights the importance of testing for FLT3-ITD and FLT3-TKD variants at AML diagnosis and also at relapse, including in patients who lacked FLT3 mutations at initial AML diagnosis.

Investigation	Validity period
FBC	7 days
Coagulation screen	7 days
U&E (including creatinine)	7 days*
LFTs	7 days
Magnesium	7 days*
Creatine Kinase	Prior to treatment initiation
ECG	Prior to treatment initiation

* Hypokalaemia or hypomagnesaemia may increase QT prolongation risk; correct electrolyte abnormalities prior to initiating treatment as required once treatment commenced.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	On day 15 of the first cycle, then monthly
U&E (including creatinine)	On day 15 of the first cycle, then monthly
LFTs	On day 15 of the first cycle, then monthly
Magnesium	On day 15 of the first cycle, then monthly
Creatine kinase	On day 15 of the first cycle, then monthly
ECG	On day 8 and day 15 of cycle 1, then prior to the start of cycles 2, 3 and 4.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	See haematological toxicity
Platelets	See haematological toxicity
Creatinine Clearance	>30ml/min
ALT/AST	<5 x ULN
Bilirubin	≤1.5 x ULN
QTc interval	<500 msec <30msec increase on cycle 1 day 8 (see below)

Dose modifications

- **Haematological toxicity**

No dose adjustment is required for disease related cytopenias.

- **Renal impairment**

No dose adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment.

- **Hepatic impairment**

No dose adjustment is required for patients with mild or moderate (Child Pugh Class A or B) hepatic impairment. Gilteritinib is not recommended in severe hepatic impairment (Child Pugh C) as safety and efficacy have not been evaluated in the population.

- **Other toxicities**

QT prolongation

Toxicity	Definition	Dose adjustment
QTc interval	Increased by >30 msec from baseline on day 8 of cycle 1	Confirm with ECG on day 9. If confirmed, consider dose reduction to 80mg daily.
	>500 msc	Interrupt gilteritinib Once QTc interval returns to within 30 msec of baseline or ≤480 msec resume gilteritinib at a reduced dose (80mg if previously taking 120mg or 120mg if previously taking 200mg)

If gilteritinib is re-introduced at a reduced dose following an event of QT prolongation, ECG should be performed after 15 days of dosing and prior to the start of the next three months of treatment.

Other toxicities

Toxicity	Management and dose adjustment
Differentiation syndrome	If suspected, administer corticosteroids and initiate haemodynamic monitoring Interrupt gilteritinib if signs/symptoms persist for more than 48 hours after initiation of corticosteroids Resume gilteritinib at the same dose when signs or symptoms improve to Grade 2 or lower Corticosteroids may be tapered after resolution of symptoms and should be administered for a minimum of 3 days.
Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue gilteritinib
Pancreatitis	Interrupt gilteritinib until pancreatitis is resolved Resume gilteritinib at a reduced dose (80mg if previously taking 120mg or 120mg if previously taking 200mg)
Other Grade 3 or high toxicity considered related to treatment	Interrupt gilteritinib until toxicity resolves or improves to Grade 1 Resume gilteritinib at a reduced dose (80mg if previously taking 120mg or 120mg if previously taking 200mg)

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Posterior reversible encephalopathy syndrome (PRES)
Pancreatitis
QT interval prolongation
Differentiation syndrome

- **Frequently occurring side effects**

Dizziness
Hypotension
Cough, dyspnoea

Diarrhoea
Nausea
Constipation
Raised transaminases
Arthralgia, myalgia
Fatigue
Peripheral oedema
Asthenia

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A or P-gp Inducers (e.g. phenytoin, rifampicin and St John's Wort): avoid as they can decrease gilteritinib concentrations

CYP3A, P-gp or BCRP inhibitors (e.g. voriconazole, itraconazole, posaconazole, clarithromycin, erythromycin, captopril, carvedilol, ritonavir, azithromycin): increase gilteritinib plasma concentrations, use alternative or monitor closely for toxicity.

Additional comments

For planned HSCT, stop treatment with gilteritinib one week prior to administration of the conditioning regimen for HSCT.

References

- National Institute for Health and Care Excellence (NICE TA642) accessed 10th February 2022 via www.nice.org.uk
- Summary of Product Characteristics – Gilteritinib (Astellas) accessed 10th February 2022 via www.medicines.org.uk
- Perl, A. *et al*. Gilteritinib or Chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med 2019; 381:1728-1740.

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