Thames Valley
Strategic Clinical Network

# GILTERITINIB

## INDICATION

**Licensed & Funded (BLUETEQ required – NICE TA 642)**
Monotherapy for relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]).

**Licensed / Unfunded**
Continuation of gilteritinib as maintenance therapy after haematopoietic stem cell transplantation.

Available as 40mg tablets

---

## TREATMENT INTENT

Disease Modification/Maintenance

---

## PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen, U&Es, LDH, urate, calcium, magnesium, creatinine, creatine kinase, LFTs, glucose, Hepatitis B core antibody and Hepatitis B surface antigen, Hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
2. Ensure bone marrow findings and dates of findings are confirming diagnosis of relapsed and/or refractory AML and are documented in notes prior to administration of therapy.
3. Ensure FLT3 (ITD or TKD) mutational status is confirmed and documented in notes prior to administration of therapy.
4. Urine pregnancy test - before cycle 1 of each new therapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy
5. Baseline ECG.
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
9. Treatment should be agreed in the relevant MDT,
10. Ensure pre-treatment counselling in line with national recommendations for oral systemic anti-cancer therapy (SACT).

---

## DRUG REGIMEN

**GILTERITINIB** **120mg PO once daily,** with or without food.

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

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.

---

## CYCLE FREQUENCY

28 day cycle.

Continuous treatment, until disease progression or unacceptable toxicity.

---

## DOSE MODIFICATIONS

| Dose Level | Dose |
|---|---|
| 1 | 200mg |
| 0 | 120mg |
| -1 | 80mg |

**Haematological Toxicity**
No dose reduction for disease related abnormality.

**Non-Haematological Toxicities**

| Criteria | Action |
|---|---|
| Symptoms of differentiation syndrome | • If differentiation syndrome is suspected, administer corticosteroids and initiate haemodynamic monitoring.<br>• Interrupt gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids.<br>• Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2 or lower. |
| Symptoms of posterior reversible encephalopathy syndrome | • Discontinue gilteritinib. |
| QTc interval >500 msec | • Interrupt gilteritinib.<br>• Resume gilteritinib at one dose level lower when QTc interval returns to within 30 msec of baseline or ≤ 480 msec. |
| QTc interval increased by >30 msec on ECG on day 8 of cycle 1 | • Confirm with ECG on day 9.<br>• If confirmed, consider dose reduction to one dose level lower |

| | |
|---|---|
| Symptoms of pancreatitis | • Interrupt gilteritinib until pancreatitis is resolved.<br>• Resume treatment with gilteritinib at one dose level lower |
| Other Grade 3 or higher toxicity considered related to treatment. | • Interrupt gilteritinib until toxicity resolves or improves to Grade 1.<br>• Resume treatment with gilteritinib at one dose level lower |
| Planned HSCT | • Stop treatment with gilteritinib one week prior to administration of the conditioning regimen for HSCT. **Continuation of gilteritinib after successful HSCT is not commissioned.** |

| Renal impairment | Hepatic impairment |
|---|---|
| GFR ≥30 mL/min: No dose adjustments necessary<br>GFR <30mL/min: No information available, clinical decision | Mild/moderate impairment (Child-Pugh Class A or B): No dose adjustments necessary<br>Severe impairment (Child-Pugh Class C): No information available, clinical decision |

## INVESTIGATIONS

FBC, U&E, LFT at baseline and monthly for the duration of treatment.
Creatine kinase level prior to initiation of treatment, on C1D15. Then check every 3 monthly, or more frequently, as clinically indicated.
ECG should be performed before initiation of treatment, on day 8 and 15 of cycle 1 and prior to the start of the next three subsequent months of treatment.

## CONCURRENT MEDICATION

| Drug | Dose/ |
|---|---|
| Allopurinol | 300mg PO once daily for 7 days on cycle 1 |
| Aciclovir | 200mg PO three times a day,<br>**Only when neutrophil count is <1x10$^9$/L** |
| Antifungal prophylaxis | Voriconazole 400mg PO twice daily on Day 1, then 200mg PO twice daily **or** Posaconazole 300mg PO twice daily on Day 1, then 300mg PO once daily. Follow local antifungal policy.<br>**Only when neutrophil count is <1x10$^9$/L** |

## EMETIC RISK

Low

## DRUG INTERACTIONS

### Effects of other medicinal products on Gilteritinib

Co-administration of CYP3A/P-gp inducers (e.g. phenytoin, rifampin and St. John's Wort) may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided.

Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A and/or P-gp (e.g. **voriconazole**, itraconazole, **posaconazole**, clarithromycin, erythromycin, captopril, carvedilol, ritonavir, azithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A and/or P-gp activity should be considered.

**Voriconazole** and **posaconazole** can be used as fungal prophylaxis at the same time as gilteritinib (at full dose) with monitoring of gilteritinib toxicity, in particularly ECG changes. Dose reduce if toxicity occurs.

### Effects of Gilteritinib on other medicinal products

Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 *in vitro*. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin).

Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors (e.g. escitalopram, fluoxetine, sertraline). Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient.

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Deranged LFTs, increased creatinine kinase, diarrhoea, fatigue, nausea, constipation, cough, peripheral oedema, dyspnoea, dizziness, hypotension, pain in extremity, asthenia, arthralgia and myalgia.
Other clinical significant serious adverse reactions included differentiation syndrome, QT prolongation and posterior reversible encephalopathy syndrome (PRES).

---

## TREATMENT RELATED MORTALITY

2% at 30 days and 7.7% at 60 days.

---

## REFERENCES

1. NICE (2020). TA 642: Gilteritinib for treating relapsed or refractory acute myeloid leukaemia. Published 12.08.2020. Accessed via https://www.nice.org.uk/guidance/ta642
2. Astellas Pharma. Xospata® Summary of Product Characteristics. Updated 02.07.2021. Accessed 26.10.2021 via https://www.medicines.org.uk/emc/product/10832
3. Perl AE et al.(2019) Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. N Engl J Med.2019;381(18):1728-40.
4. Perl AE et al. (2017) Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicenter, first-in-human, open-label, phase 1-2 study. Lancet Oncol. 2017;18(8):1061-1075.

## REVIEW

| Name | Revision | Date | Version | Review date |
|---|---|---|---|---|
| Maria Monro, Haematology Pharmacist<br>Prof Paresh Vyas, Haematology Consultant | New document | May 2020 | 1.0 | May 2021 |
| Yen Lim, Haematology Pharmacist<br>Prof Paresh Vyas, Haematology Consultant | Update following NICE TA642, published August 2020 | Oct 2020 | 1.1 | Oct 2021 |
| Yen Lim, Haematology Pharmacist.<br>Prof Paresh Vyas, NSSG Myeloid Group | Annual protocol meeting. Funding clarification. Reviewed monitoring criteria. | Nov 2022 | 2.0 | Nov 2024 |