NILOTINIB

INDICATION

Licensed & Funded indications

- Untreated chronic-phase Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) where imatinib is not appropriate **(BLUETEQ required – NICE TA 426)** or
- Chronic- or accelerated-phase Ph+ CML in adults where imatinib is not appropriate or their disease is imatinib-resistant **(no BLUETEQ required – NICE TA 425)**

Available as 50mg, 150mg and 200mg capsules

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Investigations to include FBC, blood film and manual differential, coagulation screen, urea and electrolytes, liver function tests, bone profile, lipid profile, fasting glucose or HbA1c, BNP, amylase, urate, CK, HIV, Hepatitis B (including HB surface Ag and HB core antibodies) and C testing.
2. Ensure diagnosis is confirmed prior to commencing treatment (usually PCR on peripheral blood and bone marrow aspirate morphology with FISH for Ph chromosome). Results of full karyotype are important to exclude major route abnormality (extra Philadelphia (Ph) chromosome, trisomy 8, isochromosome 17q or trisomy 19) but treatment can be commenced prior to the karyotype becoming available. For second line treatment for resistance, it is recommended to carry out bone marrow, cytogenetics and kinase domain mutation screen testing prior to switch of treatment.
3. Pregnancy Test - for all women of childbearing age unless they are postmenopausal or have undergone a hysterectomy.
4. Record performance status (WHO/ECOG).
5. Record height and weight.
6. Record blood pressure
7. ECG (most TKIs can affect the QT interval)
8. Consider echocardiogram in selected patients at risk of cardiac disease
9. ELTS or SOKAL risk score should be documented at diagnosis for all CML patients (LINK)
10. QRISK3 score (LINK - some TKIs have been associated with increased risk of cardiovascular disease and vascular risk factors should be considered and managed as appropriate)
11. 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.
12. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines). There is a degree of uncertainty but most evidence supports that it is safe to continue nilotinib for male considering parenting. As

nilotinib may cause reduced fertility, consider sperm storage/ cryopreservation in appropriate patients.

13. Treatment should be agreed in the relevant MDT.
14. Ensure pre-treatment counselling in line with national recommendations for oral systemic anti-cancer therapy (SACT).

DRUG REGIMEN

Newly diagnosed CML in the chronic phase OR if intolerant to prior TKI

NILOTINIB 300mg PO TWICE daily. Consider increase dose to 400mg TWICE daily if suboptimal response (off-label).

For patients in sustained MMR and troublesome side effects, dose can be reduced to 400mg once daily.

Resistant CML

NILOTINIB 400 mg PO TWICE daily

Dose should be taken approximately 12 hours apart and must not be taken with food. No food should be consumed for 2 hours before and one hour after each dose. Avoid grapefruit and grapefuit juice.
For patients unable to swallow capsules, the contents of each capsule may be dispersed in only one teaspoon of apple sauce and taken immediately. No additional food should be eaten.

DOSE MODIFICATIONS

	Increased dose (Dose Level +1)	Starting dose	Dose Level -1	Dose Level -2
Chronic Phase CML	400mg BD	**300mg BD**	400mg OD (or 200mg BD)	300mg OD (or 150mg BD)
Resistant CML/ acccelerated phase CML	n/a	**400mg BD**	400mg OD (or 200mg BD)	300mg OD (or 150mg BD)

Dose Adjustments for Haematological Toxicities

Newly diagnosed chronic phase CML/prior intolerance to TKI at 300 mg twice daily and **Imatinib-resistant CML in chronic phase** at 400 mg twice daily	ANC <1 x 10^9/L and/or Platelet <50 x 10^9/L	1. Stop nilotinib and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/L and/or platelets > 50 x 10^9/L 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Imatinib-resistant CML in accelerated phase at 400 mg twice daily	ANC <0.5 x 10^9/L and/or Platelet <10 x 10^9/L	1. Stop nilotinib and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC > 1 x 10^9/L and/or platelets > 20 x 10^9/L. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.

Non-Haematological Toxicities

Criteria	Action
Grade 3 or 4 elevations in serum lipase/amylase	Interrupt nilotinib or reduce dose to 400mg daily.
Grade 3 and 4 bilirubin and hepatic transaminase elevations	Interrupt nilotinib or reduce dose to 400mg daily.
Other moderate or severe non-haematological toxcicities	Interrupt nilotinib, monitor patients and treat accordingly. Restart at one dose level lower. If clinically appropriate, consider re-escalating back to starting dose once resolved

Renal / Hepatic Impairment

Renal impairment	Hepatic impairment
No dose adjustment is required in any stage of renal impairment.	No initial dose adjustment is required. Use with caution in moderate to severe hepatic impairment and monitor haematological response.

INVESTIGATIONS & ON-TREATMENT MONITORING

Monitoring for Nilotinib		Frequency of Monitoring (Month 1)	Frequency of Monitoring (Month 2 and 3)	Frequency of Monitoring Once Stable
HIV, Hepatitis B and C serology	Baseline	N/A	N/A	N/A
Document Q-RISK score	Baseline	N/A	N/A	Annually
FBC	Baseline	1-2 weekly	Monthly	3 monthly
Biochemistry (U&Es, LFTs, bone profile)	Baseline	1-2 weekly	Monthly	3 monthly
BCR-ABL monitoring	Baseline	N/A	Monthly	3 monthly *
Lipid profile	Baseline	N/A	N/A	Annually
BNP	Baseline	N/A	N/A	Annually
HbA1c	Baseline	N/A	N/A	Annually
TFTs	Baseline	N/A	N/A	As clinically indicated
Amylase	Baseline	N/A	N/A	As clinically indicated
Creatine kinase	Baseline	N/A	N/A	As clinically indicated
Blood pressure	Baseline	N/A	Monthly	3 monthly
ECG	Baseline	At least 1 ECG following initiation	As clinically indicated	As clinically indicated
Echocardiogram & Chest X-ray #	As clinically indicated	N/A	As clinically indicated	As clinically indicated
ABL1 kinase domain mutation	At diagnosis	N/A	N/A	At warning or failure of response

* BCR-ABL monitoring every 3 months until the achievement of a stable MMR (<MR 3 – sustained for 1 year), and thereafter at 3-6 months as clinically indicated, as per BSH/ELN guidelines.

CXR should be performed in all patients who are SOB for assessment of pleural effusion Consideration should also be given to Echo in selected patients – for exclusion of pericardial effusion and assessment of left ventricular function as this can be affected by all TKIs.

TREATMENT-FREE PERIOD

- Any patient considering discontinuation should be discussed at an MDT meeting
- Patients should be on approved TKI therapy for at least 3 years (but preferably 5 years) and should not have:
  - A prior history of accelerated or blast phase CML
  - Previous resistance to any TKI
  - Previous detection of a BCR-ABL1 KD mutation
- Patients should have MR4 (<0.01% by IS) for the last 2 years (at least 4 consecutive BCR-ABL tests, at least 3 months apart)

- Prior to treatment-free period, typically we recommend de-escalation to 50% of standard dose for 12 months prior to discontinuation with monthly monitoring

Time point after de-escalation	Frequency of Monitoring
Month 1 to 12	Monthly

- Following discontinuation, monitoring should be as follows:

Time point after discontinuation	Frequency of Monitoring
Month 1 to 6	Monthly
Month 7 to 12	6 weekly
Month 13 to 36	2 monthly
Month 36 (3 Years) onwards	3 to 6 monthly

Note: During discontinuation/de-escalation there should be access to a lab with at least MR4/5 sensitivity able to provide results within 14 days.

Reinitiation of TKI following loss of confirmed MMR (> 0.1%)

TKI should restarted within 1 month at full dose.
BCR-ABL testing should be performed monthly until re-establishment of MMR
If MR3 is not achieved by 6 months, BCR-ABL1 KD mutation analysis should be performed
It is noted that after discontinuation of TKI therapy to attempt treatment-free period, patients may experience musculoskeletal symptoms (e.g. myalgia, arthralgia, bone pain) more frequently than before treatment discontinuation.

Note: Treatment-free periods for TKIs for patients in MMR are exempt from the NHS England Treatment Break Policy. The TKI can be restarted without completing a treatment break form.

CONCURRENT MEDICATION

Not usually required.
Allopurinol 300mg PO once daily for 14 days can be considered if WBC >10
Consider GCSF support in patients with recurrent neutropenia.
Consider erythropoietin-stimulating agents (ESA) in anaemic patients.

EMETIC RISK

Low

DRUG INTERACTIONS
(Consult with pharmacist and refer to SPC for full details)

- Avoid concomitant use of nilotinib with CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, phenobarbital or St John's Wort) as they may significantly reduce exposure to nilotinib, potentially increasing the risk of therapeutic failure.

- Avoid concomitant use of nilotinib with strong CYP3A4 inhibitors (eg. ketaconazole, itraconazole, voriconazole, ritonavir, clarithromycin and telithromycin) as some can increase exposure to nilotinib 3 fold. Moderate CYP3A4 inihibitors should also ideally be substituted with other products with no or minimal CYP3A4 inhibition due to increased exposure to nilotinib. Avoid grapefruit and grapefruit juice.
- Caution should be taken when co-administering nilotinib with any CYP3A4 substrate with a narrow therapeutic index (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) as this could increase exposure to the substrate. Increase monitoring and adjust CYP3A4 substrate doses as necessary.
- Concomitant use of H_2 antagonists or antacids may reduce exposure to nilotinib. H_2 antagonists should be adminsistered 10 hours before or 2 hours after nilotinib. Antacids should be administered 2 hours before or 2 hours after nilotinib. Nilotinib may be used with proton pump inhibitors.
- Concomitant use of statins that are mainly eliminated by CYP3A4 may increase the potential for statin-induced myopathy, including rhabdomyolysis. Consider alternative statins that do not have this effect such as rosuvastatin or pravastatin. Alternatively atorvastatin can be used at lower doses.
- Nilotinib should be used with caution in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicinal products that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, haloperidol, methadone and moxifloxacin

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ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
(Consult with pharmacist and refer to SPC for full details)

Caution should be exercised in patients with a history of congestive heart failure and QT prolongation, and alternative TKIs should be considered.

Neutropenia, thrombocytopenia, anaemia, rash, pruritus, headache, nausea, alopecia, upper abdominal pain, fatigue, myalgia, derranged LFTs (hyperbilirubinaemia very common), infections, electrolyte disturbances, increased lipase, cholesterol and blood triglycerides.

Nilotinib has been associated with an increased risk of cardiovascular complications. Careful attention to vascular risks is important during nilotinib therapy. If a vascular event occurs during nilotinib treatment, consider a change of TKI. Nilotinib should be used with caution in patients with known vascular disease or with vascular risk factors with careful consideration of risk versus benefit.

QT prolongation - use with caution in patients who have or who are at significant risk of developing prolongation of QTc, such as those:

- with congenital long QT prolongation
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- Taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation

TKI should be discontinued 1 week before major surgery and restarted when risk of bleeding is considered to be minimal. Discuss with haematologist during surgery planning.

BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation

- Test patients for infection with hepatitis B virus (HBV) before starting treatment with BCR-ABL tyrosine kinase inhibitors
- Consult experts in liver disease and in the treatment of HBV before starting treatment with BCR-ABL tyrosine kinase inhibitors in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV during treatment
- Patients who are carriers of HBV who require treatment with BCR-ABL tyrosine kinase inhibitors should be closely monitored for signs and symptoms of active HBV infection throughout treatment and for several months after stopping
- Suspected adverse drug reactions to BCR-ABL tyrosine kinase inhibitors should be reported via the Yellow Card scheme

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TREATMENT RELATED MORTALITY

Very low (<1%)

REFERENCES

1. NICE (2018) TA425. Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia. Last updated: 21/12/2018. Accessed via: https://www.nice.org.uk/guidance/ta425
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3. Novartis. Nilotinib Summary of Product Characteristics. Updated 22/2/2022. Accessed on 15/8/2023 via http://www.medicines.org.uk/
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5. Smith G et al (2020). A British Society of Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. B J Haem 191: 171-193
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7. Hochhaus et al (2017) Chronic Myeloid Leukaemia: ESMO Clinical Practice Guidelines. Ann Oncol 28(S4):iv41-51
8. Giraud, E.L. et al. (2023) 'Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: An update', The Lancet Oncology, 24(6). doi:10.1016/s1470-2045(23)00216-4

REVIEW

Name	Revision	Date	Version	Review date
Dr Adam Mead	Adverse effects reviewed, treatment intent and mortality added. Full review of Indications, Pre-assessment, Drug regimen, Dose modifications, Haematology	Nov 2016	2.0	

	toxicity, monitoring of disease respond, investigations and drug interaction sections			
Cheuk-kie Cheung (Pharmacist) and Dr Mead	Review if indication, pre-assesment and adverse regimen specific complications	Mar 2017	2.1	
Cheuk-kie Cheung	Update of NHSE funding position for 1st line indication	Apr 2017	2.2	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Treatment free period information added. Annual protocol meeting	Oct 2019	2.3	Oct 2021
Dr Oni Chowdhury and Prof Adam Mead, Consultant Haematologists. Yen Lim, Zishaan Ramzan Haematology Pharmacists. NSSG Myeloid Group.	Updated as per BSH/ELN guidelines and SPC. Addition of monitoring table, treatment-free period and reinitiation guidance. Annual protocol meeting 2022. Dosing information updated with indications.	Aug 2023	3.0	Nov 2025