NILOTINIB

An option for 1st line treatment of adults with chronic phase Ph+ve CML, where there are clinical reasons not to use imatinib
Blueteq registration is required before 1st line treatment may start

For 2nd line use in adults with chronic or accelerated phase Ph+ve CML with resistance or intolerance to imatinib

All patients should be screened for hepatitis B virus before starting treatment
This screen must include HBV surface antigen and anti-HBV core antibody

Drug/Dosage:	**1st line Nilotinib**	300mg po twice daily, approximately 12 hours apart
	2nd line Nilotinib	initiate at 400mg po twice daily, approximately 12 hours apart (same dosing schedule for chronic and accelerated phase)

Administration: Nilotinib is available as 150mg and 200mg capsules.
Capsules should be swallowed whole with water, and must not be taken with food. No food should be consumed for 2 hours before each dose, and for one hour after each dose. (Food increases bioavailability of nilotinib)
The patient should also avoid grapefruit and grapefruit juice while on nilotinib.

Other Drugs: Allopurinol 300mg po od for the first four weeks (may be omitted in the context of treatment change in patients with good haematological disease control)

Frequency: continuous therapy, until disease progression or no longer tolerated

Main Toxicities: myelosuppression; peripheral oedema; fatigue; rash and pruritis; diarrhoea or constipation; muscle cramps; headache; lipase increased; cardiac side effects, including prolonged QT interval and palpitations

Anti- emetics: mildly emetogenic

Regular Investigations:	FBC	every 2 weeks for first 2 months, then monthly, then increasing to 3 – 4 monthly in stable responders
	Peripheral blood PCR	3 monthly initially, to assess molecular response, then 3-4 monthly in stable responders
	Bone marrow cytogenetics	annually until CCR and MMR achieved, and thereafter if concerns or loss of molecular response
	LFTs and U&Es	monthly initially, then every 3 – 6 months
	Mg^{2+}	baseline, and as indicated
	Serum lipase	monthly initially, then as indicated

Comments: Elimination of nilotinib is mainly through hepatic metabolism. Nilotinib is a substrate and an inhibitor of CYP3A4. Therefore, concomitant use of medicines that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, St Johns wort) and nilotinib should be avoided, as this may increase the risk of therapeutic failure.

Concomitant use of nilotinib and medicines that potently inhibit CYP3A4 (e.g. itraconazole, voriconazole, erythromycin, clarithromycin, ritonavir, telithromycin) may increase exposure to nilotinib and is not recommended by the manufacturer.

Reason for Update: Hep B statement added; indications updated	Approved by Chair of Alliance TSSG: Dr A Laurie
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Prepared by: S Taylor	Checked by: C Tucker

Proton pump inhibitors should be avoided if at all possible as a raised pH reduces absorption of nilotinib.

H_2 antagonists, if necessary, should be taken 10 hours before a dose of nilotinib and/or 2 hours after nilotinib, as this has been shown not to affect nilotinib pharmacokinetics. Aluminium hydroxide/magnesium hydroxide products (eg Gaviscon) may be used, but should not be administered within 2 hours prior to, or 2 hours following, the administration of nilotinib.

Patients with cardiac disease or risk factors for arrhythmias should be monitored carefully. Correct hypokalaemia and hypomagnesaemia before treating with nilotinib.
Avoid the concomitant use of drugs that may lead to QT prolongation e.g chloroquine, clarithromycin, haloperidol, domperidone, ondansetron. Nilotinib should also be used with caution in patients on anti-arrhythmic agents such as amiodarone, disopyramide, procainamide, quinidine or sotalol.

Warfarin should only be used with caution and close monitoring, as nilotinib may inhibit its metabolism. Alternative anticoagulants should be considered.

Dose Modifications

Haematological Toxicity: Treatment decisions for patients whose neutrophils are below 1.0 x10^9/l or platelets below 50 x10^9/l should be made by a Consultant.

Chronic Phase CML (1st or 2nd line use):	Neutrophils < 1.0 x 10^9/L or Platelets < 50 x 10^9/L	Stop nilotinib and monitor FBC weekly. If counts recover to above these limits within 2 weeks or less, resume treatment at original start dose. If blood counts remain low after 2 weeks, a dose reduction to 400mg once daily may be required.

If clinically appropriate, consider re-escalation of the dose.

Accelerated Phase CML (2nd line use):	Neutrophils < 0.5 x 10^9/L or Platelets < 10 x 10^9/L	Stop nilotinib and monitor FBC weekly. If neuts > 1.0 x 10^9/L and platelets > 20 x 10^9/L within 2 weeks or less, resume treatment at original start dose. If blood counts remain low after 2 weeks, a dose reduction to 400mg once daily may be required.

If clinically appropriate, consider re-escalation of the dose to 400mg twice daily.

Renal Impairment: There is no data in patients with renal impairment. However, as nilotinib and its metabolites are not renally excreted, a decrease in nilotinib clearance is not expected.

Hepatic Impairment: Since nilotinib is mainly metabolised, exposure to nilotinib is expected to increase if liver function is impaired, and so it should only be used with caution in patients with hepatic impairment.
If bilirubin > 3 x ULN or transaminases > 5 x ULN during treatment, nilotinib dose should be reduced to 400mg once daily or interrupted.

Elevated serum lipase: Grade 3 – 4 serum lipase elevations (> 2 x ULN) require either a nilotinib dose reduction to 400mg once daily or treatment interruption.

Patient Information: Macmillan leaflet for Nilotinib

References:
Le Coutre et al; Blood 2008; 111 (4): 1834 – 1839
Kantarijian, H et al; Blood 2007; 110 (10); 3540 – 3546
Saglio, G et al; NEJM 2010; 362: 2251 - 2259

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