Nilotinib

Indication

Chronic phase and accelerated phase Philadelphia chromosome positive (Ph+) CML with resistance or intolerance to prior therapy including imatinib.
(NICE TA241)

Newly diagnosed Ph+ chronic myelogenous leukaemia (CML) in the chronic phase.
(NICE TA251)

ICD-10 codes

C92.1

Regimen details

Chronic or accelerated phase CML with resistance or intolerance to prior therapy (2nd line)

Days	Drug	Dose	Route
1-28 (ongoing)	Nilotinib	400mg BD	PO

Newly diagnosed CML in the chronic phase (1st line)

Days	Drug	Dose	Route
1-28 (ongoing)	Nilotinib	300mg BD	PO

Cycle frequency

Continuous

Number of cycles

Continued as long as the patient continues to benefit.

Administration

Nilotinib is available as 150mg and 200mg hard capsules which should be swallowed whole with water. Doses should be taken 12 hours apart and NOT with food. Food should be avoided for two hours before the dose and one hour after the dose is taken. (Food increases the bioavailability of nilotinib).
If patients are unable to swallow the capsule, the contents may be dispersed in one teaspoon of apple sauce (puree) and taken immediately.

Patient should be advised to avoid grapefruit and grapefruit juice.

Pre-medication

When used first line, adequate hydration and allopurinol 300mg OD (100mg OD if CrCl <20mL/min) to prevent tumour lysis syndrome is recommended prior to initiation of nilotinib.

Emetogenicity

Nilotinib has low emetic potential

Additional supportive medication

Anti-emetics as per local policy, if required
Loperamide if required

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
Coagulation screen	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Blood glucose	14 days
Fasting cholesterol and lipid profile	14 days

Prior to commencing treatment:
Confirm the presence of t (9;22) and/or BCR-ABL transcript (or other TKI sensitive target)
Consider initial hydroxyurea / leucopheresis in the event of hyperleucocytosis
Hepatitis B (HBV) serology testing – cases of reactivation of HBV have occurred in patients who are chronic carriers of HBV after they received BCR-ABL tyrosine kinase inhibitors.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Every 2 weeks for the first 2 months, then monthly
Coagulation screen	3 monthly
U+Es (including creatinine)	Monthly
LFTs	Monthly
Blood glucose	Monthly
Fasting cholesterol and lipid profile	3 and 6 months after initiating therapy, then yearly

Marrow assessment (karyotype, FISH), peripheral blood BCR-ABL1/ABL1 or other relevant marker for disease monitoring.

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	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Bilirubin	< 3 x ULN
AST/ALT	< 5 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x10^9/L or platelets < 50 x10^9/L consultant decision to treat.

Chronic phase CML (1st or 2nd line)

Neutrophils		Platelets	Action
< 1.0 x10^9/L	and/or	< 50 x 10^9/L	Stop nilotinib and monitor FBC. If counts recover within 2 weeks, resume at previous dose. If counts remain low consider dose reduction to 400mg OD (dose re-escalation may be considered – consultant decision).

Accelerated phase CML (2nd line)

Neutrophils		Platelets	Action
< 0.5 x10^9/L	and/or	< 10 x10^9/L	Stop nilotinib and monitor FBC. If counts recover (neutrophils > 1.0 x10^9/L and platelets > 20 x10^9/L) within 2 weeks, resume at previous dose. If counts remain low consider dose reduction to 400mg OD (dose re-escalation may be considered – consultant decision).

- **Renal impairment**

There is no data regarding treatment in impaired renal function. Since nilotinib and its metabolites are not renally excreted, a decrease in clearance is not anticipated in patients with renal impairment.

- **Hepatic impairment**

Nilotinib elimination is primarily via hepatic mechanisms. Dose adjustment is not considered necessary in patients with hepatic impairment. However, patients with hepatic impairment should be treated with caution.

For Grade 3-4 bilirubin and hepatic transaminase elevations, doses should be reduced to 400mg OD or interrupted (consultant decision).

- **Other toxicities**

If grade 3 – 4 serum lipase elevation (> 2 x ULN) reduce dose to 400mg OD or withhold treatment (consultant decision).

Patients with a cardiac medical history should be treated with caution (patients with uncontrolled or significant cardiac disease were excluded from clinical trials).

Increases in total serum cholesterol levels have been reported with nilotinib. Lipid profiles should be determined prior to initiating therapy, at month 3 and 6 after initiating therapy and at least yearly during chronic therapy.

Increases in blood glucose levels have been reported with nilotinib. Blood glucose levels should be assessed prior to initiating therapy and monitored during treatment.

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

- **Serious side effects**

Myelosuppression
Sudden death (in patients with cardiac history)
QT prolongation

- **Commonly occurring side effects**

Myelosuppression
Nausea, abdominal pain
Headache
Rash
Alopecia
Pruritus
Myalgia
Fatigue
Raised transaminases
Hyperbilirubinaemia
Hypophosphataemia
Hyperglycaemia
Hypercholesterolaemia, raised triglycerides

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

Potent CYP3A4 inhibitors (including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin) avoid concomitant treatment – increases nilotinib exposure.

Moderate CYP3A4 inhibitors: Consider switching to an alternative medicinal product with no or minimal CYP3A4 inhibition – may increase nilotinib exposure.

CYP3A4 inducers (including dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital and St John's Wort) avoid concomitant use - may induce nilotinib metabolism, potentially increasing the risk of therapeutic failure.

Nilotinib is a moderate CYP3A4 inhibitor. Systemic exposure of other drugs primarily metabolised by CYP3A4 may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for drugs that are CYP3A4 substrates and have a narrow therapeutic index (including alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with nilotinib.

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.

Domperidone: potential to increase QT interval prolongation and to induce "torsade de pointes"- arrhythmias; co-administration of domperidone should be avoided. It should only be used, if other medicinal products are not efficacious, with an individual benefit-risk assessment and patients monitoring for QT prolongation.

The absorption and bioavailability of nilotinib are increased if it is taken with food, resulting in a higher serum concentration. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

Warfarin: consider alternative anticoagulant, or use with caution as nilotinib may increase INR.

Additional comments

Men and women of childbearing potential must be advised to use effective contraception during treatment and for up to two weeks after discontinuation.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take nilotinib.

References

- Dasatinib, nilotinib and high-dose imatinib for the treatment of chronic myeloid leukaemia (NICE TA241) accessed 1 April 2015 via www.nice.org.uk
- Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (NICE TA251) accessed 1 April 2015 via www.nice.org.uk
- European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Baccarani M, Deininger MW et al . Blood. 2013 Aug 8;122(6):872-84. doi: 10.1182/blood-2013-05-501569.
- Summary of Product Characteristics Nilotinib (Novartis), accessed 2 April 2015 via http://www.medicines.org.uk

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