DASATINIB

An option for first-line use in 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 use in adults with chronic phase 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: **Dasatinib** chronic phase CML: initiate at 100mg po once daily
accelerated phase CML: initiate at 140mg po once daily

Dose escalation to 140mg once daily (chronic phase) or 180mg once daily (accelerated phase only) may be considered in patients who do not achieve a haematological or cytogenetic response at the initial dose.

Administration: Available as 20mg, 50mg, 80mg, 100mg & 140mg tablets, which are not scored or divisible. Swallow tablets whole, with or without a meal, at the same time of day each day. Grapefruit and grapefruit juice should be avoided while on dasatinib.

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; fluid retention, commonly presenting as periorbital oedema; pleural effusion; rash; diarrhoea; muscle cramps; headache; cardiotoxicity (see Comments)

Anti- emetics: none usually needed, but some patients may have mild nausea

Regular Investigations:

FBC	**chronic phase:** every 2 weeks for 3 months, then increasing to 3 - 4 monthly in stable responders **accelerated phase:** weekly for the 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
Cytogenetics	annually until CCR and MMR achieved, and thereafter if concerns or loss of molecular response
LFTs & U&Es	monthly initially, then every 3 – 6 months
Mg^{2+}	baseline, and as indicated

Interactions: Elimination of dasatinib is mainly through hepatic metabolism. Dasatinib 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 dasatinib should be avoided, as this may increase the risk of therapeutic failure.

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

Reason for Update: 70mg tablets no longer available; Hep B statement added; indications updated; FBC monitoring updated	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 4b	Date: 5.12.16
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Prepared by: S Taylor	Checked by: C Tucker

H_2 blockers or proton pump inhibitors should not be prescribed to patients on dasatinib as a raised pH has been shown to reduce dasatinib absorption, and hence exposure, by more than 60%. Aluminium / magnesium hydroxide products, e.g. Gaviscon, may be used, but should not be administered within 2 hours prior to, or until 2 hours following a dasatinib dose.

Comments: QT prolongation has been observed in Phase II trials of dasatinib. Patients with cardiac disease or risk factors for arrhythmias should be monitored carefully. Hypokalaemia and hypomagnesaemia should be corrected before treating with dasatinib.

Dose Modifications

Haematological Toxicity: Treatment decisions for patients with myelosuppression should be made by a Consultant and / or consider discussion with tertiary centre for current opinion.

Chronic Phase CML	Neutrophils < 0.5 x 10^9/L or Platelets 25 - 49 x 10^9/L	Stop dasatinib until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L. Then resume treatment at original start dose.
	Platelets < 25 x 10^9/L	Stop dasatinib until platelets ≥ 50 x 10^9/L (and neuts ≥ 1.0 x 10^9/L). If 1st occurrence, resume treatment at reduced dose of 80mg od; if 2nd episode, discontinue (or consider 50mg od dose, if newly diagnosed patient)
	Recurrence of neutrophils < 0.5 x 10^9/L for > 7 days	Stop dasatinib until neuts ≥ 1.0 x 10^9/L (and platelets ≥ 50 x 10^9/L). Then resume treatment at reduced dose of 80mg po od if previously on 100mg od; if 3rd episode, discontinue (or reduce to 50mg od, if newly diagnosed patient).
Accelerated Phase CML	Neutrophils < 0.5 x 10^9/L or Platelets < 10 x 10^9/L	If cytopenia unrelated to leukaemia, stop dasatinib until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 20 x10^9/L. Then resume treatment as follows: First episode: continue at original start dose. Second episode: resume treatment at 100mg daily. Third episode: resume treatment at 80mg daily.

If cytopenia related to leukaemia, consider dasatinib dose increase to 180mg po od.

Non-haem toxicity:
Grade 2: interrupt until resolved, then resume at original dose if 1st occurrence, but with a dose reduction if further occurrence.
Grade 3+: interrupt until resolved, then resume with a dose reduction.
Recommended step-wise dose reductions for chronic phase: 100mg→80mg→50mg
Recommended step-wise dose reductions for accelerated phase: 140mg→100mg→50mg

Renal Impairment: The renal route accounts for < 4% clearance of dasatinib and its metabolites, so accumulation of dasatinib is not expected in renal impairment.

Hepatic Impairment: As dasatinib is extensively metabolised, it should be used with caution in patients with moderate or severe hepatic impairment. However, patients with moderate or severe hepatic impairment may receive the usual recommended starting dose.

Patient Information: Macmillan leaflet for dasatinib

References:
Talpaz, MD et al; NEJM 2006; 354 (24): 2531 – 2541
Hochhaus, A et al; Blood 2007; 109 (6): 2303 - 2309

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