BOSUTINIB

For use in adults with chronic phase, accelerated phase or blast phase Ph+ve CML, previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not appropriate (NICE approved August 2016)

Blueteq registration is required before treatment may start

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

Drug/Dosage: **Bosutinib** initiate at **500mg** po once daily

For patients who are not experiencing severe, or persistent moderate, side effects, the dose should be increased to **600mg** po once daily in the following circumstances:

- Failure to achieve complete haematologic response by week 8
- Failure to achieve complete cytogenetic response by week 12

Doses greater than 600mg/day have not been studied and therefore should not be given.

Administration: Bosutinib available as 100mg and 500mg tablets, which are not scored or divisible.
Tablets should be swallowed whole once daily with food.
Grapefruit and grapefruit juice should be avoided.

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)
Loperamide to be used as required for management of diarrhoea

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

Main Toxicities: myelosuppression; fluid retention, pericardial effusion; rash; diarrhoea; transaminase elevations (most likely within the first 3 months);
QT prolongation (see below)

Anti- emetics: mildly emetogenic (domperidone should be avoided)

Regular Investigations:		
	FBC	weekly for the first 4 weeks, then monthly, then increasing to 3 – 4 monthly in stable responders
	LFTs	monthly for the first 3 months, then as indicated
	U&Es	baseline, and as indicated
	Mg^{2+}	baseline, and as indicated
	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

Interactions: Bosutinib is a substrate of CYP3A4. Therefore, concomitant use of medicines that induce CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, St Johns wort) and bosutinib should be avoided, as this may increase the risk of therapeutic failure.

Concomitant use of bosutinib and medicines that potently inhibit CYP3A4 (e.g. itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) or moderately inhibit

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(fluconazole, ciprofloxacin, aprepitant, verapamil) may increase exposure to bosutinib and is not recommended by the manufacturer.
If a potent or moderate inhibitor must be used, consider an interruption or dose reduction for bosutinib.

Caution should be exercised when administering bosutinib concomitantly with proton pump inhibitors, as bosutinib displays pH-dependent solubility. (Bosutinib C_{max} and AUC decreased to 54% and 74%, respectively, when co-administered with lansoprazole, compared to values seen when bosutinib was given alone)
Short-acting antacids should be considered as an alternative and administration times of bosutinib and antacids should be separated (i.e. take bosutinib in the morning and antacids in the evening) whenever possible.

Dose Modifications Doses less than 300 mg/day have not been evaluated.

Haematological Toxicity:	Neutrophils < 1.0 x 10^9/L or Platelets < 50 x 10^9/L	Stop bosutinib until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L. Then resume treatment at the same dose if recovery within 2 weeks. If counts remain low for > 2 weeks, reduce dose by 100 mg and resume treatment. If cytopoenia recurs, reduce dose by a further 100 mg upon recovery and resume treatment. Doses less than 300 mg/day have not been evaluated.

Non-haem toxicity: If clinically significant moderate or severe non-haematological toxicity develops, bosutinib should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 500 mg once daily should be considered.
For Grade 3-4 diarrhoea, bosutinib should be interrupted and may be resumed at 400 mg once daily upon recovery to ≤ Grade 1.

Cardiac: QT prolongation has been observed. Patients with cardiac disease or risk factors for arrhythmias should be monitored carefully. Hypokalaemia and hypomagnesaemia should be corrected before treating with bosutinib.

Hepatic toxicity: If ALT / AST > 5 x ULN, interrupt bosutinib until recovery to ≤ 2.5 x ULN and then resume at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinuation of bosutinib should be considered.
If ALT / AST ≥ 3 x ULN occur concurrently with bilirubin >2 x ULN and ALP <2 x ULN, bosutinib should be discontinued

Renal Impairment: If CrCl 30 – 50 ml/min, the recommended dose is 400mg daily.
If CrCl < 30 ml/min, the recommended dose is 300mg daily.

Dose escalation to 500mg (CrCl 30-50) or to 400mg (CrCl < 30) may be considered in those who did not experience severe, or persistent moderate, adverse reactions if::
- failure to achieve complete haematologic response by week 8, *or*
- failure to achieve complete cytogenetic response by week 12

Hepatic Impairment: Contra-indicated in patients with hepatic impairment.

Patient Information: Macmillan leaflet for Bosutinib

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