Bosutinib

Indication
Chronic phase, accelerated phase, and blast phase Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) patients previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

(Funding via the CDF)

ICD-10 codes
C92.1

Regimen details

Day	Drug	Dose	Route
1-28 (continuously)	Bosutinib	500mg OD	PO

If this dose is tolerated, dose escalation to 600 mg OD may be considered in the following circumstances:
- Failure to achieve complete haematological response by week 8
- Failure to achieve complete cytogenetic response by week 12

Cycle frequency
Continuous as above

Number of cycles
As above, continued until disease progression or unacceptable toxicity.

Administration
Bosutinib is available as 100mg and 500mg film coated tablets. Doses should be swallowed whole with food.

Patients should be advised to avoid grapefruit and grapefruit juice.

Pre-medication
Consider the use of adequate hydration and allopurinol 300mg OD (100mg OD if CrCl <20mL/min) to prevent tumour lysis syndrome.

Emetogenicity
Bosutinib has low emetic potential.

Additional supportive medication
Antiemetics (avoid domperidone) 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
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.

A baseline ECG is recommended prior to initiating therapy with bosutinib and then as clinically indicated to monitor for an effect on the QTc interval.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Weekly for the first 4 weeks, then monthly
Coagulation screen	3 monthly
U+Es (including creatinine)	Monthly
LFTs	Monthly
Magnesium	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
CrCl	> 50 mL/min
Bilirubin	< 2 x ULN
AST/ALT	< 3 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L, withhold treatment until counts have recovered. If recovery within 2 weeks resume at previous dose. If counts still low after 2 weeks, resume treatment with 100mg dose reduction. If recurs, await recovery and resume treatment with further 100mg dose reduction.

(Doses < 300mg OD have not been studied)

If clinically appropriate, re-escalation of the dose may be considered (consultant decision).

- **Renal impairment**

CrCl (mL/min)	**Bosutinib dose**
> 50	500mg OD
30-50	400mg OD
< 30	300mg OD

If these doses are tolerated, dose escalation by 100mg OD (to 500mg OD if CrCl 30-50mL/min or to 400mg OD if CrCl < 30 mL/min) may be considered in the following circumstances:
- Failure to achieve complete haematological response by week 8
- Failure to achieve complete cytogenetic response by week 12

- **Hepatic impairment**

Bosutinib treatment has been associated with elevations in transaminases.

AST/ALT (x ULN)		**Bilirubin** (x ULN)	**Bosutinib dose**
≥ 3	and	> 2	Discontinue
> 5			Withhold treatment. If ≤ 2.5 x ULN within 4 weeks resume at 400mg OD. If not recovered within 4 weeks, discontinue.

- **Other toxicities**

Toxicity	**Definition**	**Bosutinib dose**
Diarrhoea	Grade 3-4	Withhold Bosutinib. Resume at a dose of 400 mg OD upon recovery to ≤ grade 1.

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

- **Serious side effects**

Myelosuppression
QTc prolongation
Pericardial effusion

- **Commonly occurring side effects**

Myelosuppression
Elevated transaminases
Fluid retention including pericardial effusion, pleural effusion and pulmonary oedema
Diarrhoea
Nausea and vomiting
Elevation of serum lipase
Renal impairment (with long term use)

- **Other side effects**

Rash

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 bosutinib exposure.

Moderate CYP3A4 inhibitors: Consider switching to an alternative medicinal product with no or minimal CYP3A4 inhibition, or consider bosutinib dose reduction – may increase bosutinib exposure.

CYP3A4 inducers (including dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital and St John's

Wort) avoid concomitant use - may induce bosutinib metabolism, potentially increasing the risk of therapeutic failure.

Bosutinib 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.

Proton pump inhibitors (PPIs): reduced gastric acidity may impair absorption of bosutinib. Use with caution and consider short acting antacids or separate administration times (i.e. take bosutinib in the morning and antacids in the evening) whenever possible.

Nephrotoxic drugs should be avoided wherever possible

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

Caution should be used if bosutinib is administered with medicinal products that are substrates of P-glycoprotein (P-gp). Bosutinib may increase the plasma concentrations of these agents, including digoxin, colchicine, tacrolimus, quinidine, etoposide, doxorubicin, vinblastine, dexamethasone and HIV-type 1 antiretroviral therapy agents.

Additional comments

Women of childbearing potential must be advised to use effective contraception during treatment.

Patients with uncontrolled or significant cardiac disease (e.g. recent myocardial infarction, congestive heart failure or unstable angina) were excluded from clinical studies. Caution should be exercised if bosutinib is used in patients with these disorders.

References

- 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 Bosutinib (Pfizer), accessed 8 April 2015 via http://www.medicines.org.uk
- NHS England Cancer Drug Fund List. Accessed 8 April 2015 via www.england.nhs.uk

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