Bosutinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Protocol Code
Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotonib and dasatinib are not considered appropriate treatment options.	C92	00224a

ELIGIBILTY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hepatic impairment
- Serum creatinine > 1.5xULN
- Pregnancy
- Breastfeeding
- Hypersensitivity to bosutinib or any of the excipients

USE WITH CAUTION:

Use with caution in patients with

- Uncontrolled or significant cardiac disease (e.g. recent MI, CHF or unstable angina)
- Recent or ongoing clinically significant gastrointestinal disorder

TESTS:

Baseline tests: FBC, U&Es, LFTs, ECG, bone marrow examination for cytogenetic analysis. Analysis by RQ-PCR BCR-ABL transcript level and screening for BCR-ABL kinase–domain mutation

Regular tests:

- FBC, U&Es, LFTs weekly for the first month and then monthly thereafter or as clinically indicated.

- ECG should be repeated 7 days after start of treatment and as clinically indicated, including 7 days after dose changes.
- BCR-ABL transcript analysis every 3 months

TREATMENT:

Bosutinib is administered daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Bosutinib	500mg daily	PO once daily with food.	Continuous

Missed doses should not be replaced.
Normal dosing should be resumed at the next scheduled dose.
If a patient vomits within a few hours of taking the drug do not repeat the dose
Bosutinib is available as 100mg and 500mg tablets

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Consider dose escalation to 600mg once daily with food in patients who do not achieve complete haematologic response (CHR) by week 8or complete cytogenetic response (CCyR) by week 12 and who do not have grade ≥ 3 adverse reactions.
  Doses > 600mg/day have not been studied and therefore should not be given.

Haematological :

Table 1: Dose adjustments for haematological toxicity

ANC< 1 x 10^9/L and/or Platelets < 50 x 10^9/L	Hold bosutinib until ANC ≥ 1.0x 10^9/L and platelets ≥ 50 x 10^9/L. Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for > 2 weeks, reduce dose by 100 mg and resume treatment. If cytopoenia recurs, reduce dose by 100 mg upon recovery and resume treatment. Doses < 300 mg/day have not been evaluated.

Renal impairment: Patients with serum creatinine >1.5 x ULN were excluded from

CML studies. A trend to increasing exposure (AUC) in patients with moderate renal impairment during studies was observed.

Hepatic impairment:

Table 2: Dose adjustments for hepatic impairment

Transaminase (AST, ALT)	Bilirubin	AP	Dose Modification
>5xULN			Interrupt bosutinib therapy until recovery to ≤ 2.5 x ULN. Therapy may be resumed at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinuation of bosutinib should be considered.
≥3xULN and	>2xULN and	<2xULN	Discontinue bosutinib.

Table 3: Dose modification schedule for bosutinib based on adverse events

Adverse reactions	Recommended dose modification / discontinuation
Non-Haematologic Clinically significant grade 2 or > Grade 3	Bosutinib therapy should be interrupted and may be resumed at 400mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 500mg once daily should be considered.
Grade ≥3 Diarrhoea	Therapy should be interrupted and may be resumed at 400 mg once daily upon recovery to grade ≤1
Lipase elevation accompanied by abdominal symptoms	Bosutinib treatment must be interrupted and appropriate diagnostic measures considered to exclude pancreatitis.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low risk (Refer to local policy).

PREMEDICATIONS:

Not usually required.

TAKE HOME MEDICATIONS:

Medication may be required (particularly on initiating Bosutinib) for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mgafter each loose stool (max 16 mg /day) or see local policy.

OTHER SUPPORTIVE CARE:

No specific recommendations.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details..

- **Diarrhoea and vomiting:** Patients with diarrhoea and vomiting should be managed using standard-of-care treatment. In addition, these events can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib. The antiemetic agent, domperidone, should be avoided. It should only be used, if other medicinal products are not efficacious. In these situations an individual benefit-risk assessment is mandatory and patients should be monitored for occurrence of QT prolongation.
- **Fluid retention:** Treatment with bosutinib may be associated with fluid retention including pericardial effusion, pleural effusion and pulmonary oedema. Patients should be monitored and managed using standard-of-care treatment. In addition, these events can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib.
- **Infections:** Bosutinib may predispose patients to bacterial, fungal, viral or protozoan infections.
- **Proarrhythmic potential:** Bosutinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, who have uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, or who are taking medicinal products that are known to prolong the QT interval (e.g. anti-arrhythmic medicinal products and other substances that may prolong QT

DRUG INTERACTIONS:

- Potent inhibitors of CYP3A may lead to increased toxicity of bosutinib. Patients should also be counselled with regard to consumption of grapefruit and grapefruit juice.
- Avoid the concomitant administration of P-gp inhibitors.
- Potent inducers of CYP3A may reduce the efficacy of bosutinib.
- Proton pump inhibitors may decrease bosutinib drug levels.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Bosutinib - L01XE14

REIMBURSEMENT CATEGORY:

00224a	Bosutinib is available for reimbursement, for this indication, under the High Tech Arrangements on the PCRS drug reimbursement schemes.

PRESCRIPTIVE AUTHORITY:

Consultant haematologist.

REFERENCES:

1. Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood. 2011;118(17):4567–4576.
2. Cortes JE, Kim DW, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol. 2012;30(28):3486–3492.
3. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012;119(15):3403–3412.
4. BOSULIF®Summary of Product Characteristics Accessed 11/11/2013 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002373/WC500141721.pdf

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