Bosutinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
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	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Bosutinib is taken orally once 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			

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

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

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

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG
- Bone marrow examination for cytogenetic analysis.
- Analysis by RQ-PCR BCR-ABL transcript level and screening for BCR-ABL kinase–domain mutation
- Hepatitis B virus (HBV) screening required before initiating treatment with BCR-ABL tyrosine kinase inhibitors (TKIs)

* (See Adverse Effects /Regimen Specific Complications for further information)

Regular tests:

- FBC, renal and liver profile 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

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

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 8 or 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 modification of bosutinib in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
<1	and/or	<50	Hold bosutinib until ANC ≥ $1x10^9$/L and platelets ≥ $50x10^9$/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 cytopenia recurs, reduce dose by 100 mg upon recovery and resume treatment. Doses < 300 mg/day have been used; however, efficacy has not been established.

Renal and Hepatic Impairment:

Table 2: Dose modification of bosutinib in renal impairment

Renal Impairment	
CrCl (ml/min)	**Dose**
30-50	400mg daily
<30	300mg daily
Dose escalation to 500 mg once daily for patients with moderate renal impairment or to 400 mg once daily in patients with severe renal impairment may be considered in those who did not experience severe or persistent moderate adverse reactions, under any of the following circumstances. Circumstances for dose escalation - Failure to achieve complete haematologic response (CHR) by week 8 - Failure to achieve complete cytogenetic response (CCyR) by week 12	

Table 3: Dose modification of bosutinib in 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.

Management of adverse events:

Table 4: Dose Modification of bosutinib for 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. Doses <300 mg/day have been used in patients; however, efficacy has not been established.
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: Minimal-Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

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

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **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.
- **Hepatitis B Virus (HBV):** Cases of reactivation of HBV have occurred in patients who are chronic carriers of HBV after they received BCR-ABL TKIs. Some cases of HBV reactivation resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Experts in liver disease and the treatment of HBV should be consulted before treatment in patients with positive HBV serology (including those with active disease) is initiated and for patients who test positive for HBV infection during treatment. Patients who are carriers of HBV and require treatment with BCR-ABL TKIs should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.
- **Photosensitivity**: Exposure to direct sunlight or ultraviolet (UV) radiation should be avoided or minimised due to the risk of photosensitivity associated with bosutinib treatment. Patients should be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

DRUG INTERACTIONS:

- The concomitant use of bosutinib with strong or moderate CYP3A inhibitors should be avoided, as an increase in bosutinib plasma concentration will occur. Selection of an alternate concomitant medicinal product with no or minimal CYP3A inhibition potential, if possible, is recommended. If a strong or moderate CYP3A inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy or a dose reduction in bosutinib should be considered.
- Grapefruit products, including grapefruit juice and other foods that are known to inhibit CYP3A should be avoided.
- The concomitant use of bosutinib with strong or moderate CYP3A inducers should be avoided as a decrease in bosutinib plasma concentration will occur
- Proton pump inhibitors may decrease bosutinib drug levels. Short-acting antacids should be considered as an alternative to PPIs and administration times of bosutinib and antacids should be separated (i.e. take bosutinib in the morning and antacids in the evening) whenever possible.
- Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients taking anti-arrhythmic medicinal products or other medicinal products that may lead to QT prolongation.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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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. BCR-ABL tyrosine inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) - Important Safety Information from Novartis, Pfizer, BMS and Ariad as approved by the HPRA Available at http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---bcr-abl-tyrosine-kinase-inhibitors-(imatinib-dasatinib-nilotinib-bosutinib-ponatinib).pdf?sfvrsn=0
5. BOSULIF® Summary of Product Characteristics. Accessed Jan 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/bosulif-epar-product-information_en.pdf
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	20/12/2013		Dr Eibhlin Conneally
2	03/05/2016	Updated dose modifications in renal impairment, drug interactions and inclusion of recommendations relating to testing for HBV and treatment of patients with HBV and BCR-ABL TKIs	Dr Eibhlin Conneally
3	21/05/2018	Updated with new NCCP regimen template	Dr Eibhlin Conneally
4	22/03/2021	Amended dose modifications (haematological and adverse events), amended adverse effects.	Dr Eibhlin Conneally

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.