**INDICATION**

Licensed / NICE

- Untreated chronic-phase Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) (TA426) who cannot have imatinib for clinical reason* (BLUETEQ required) or
- Chronic- or accelerated-phase Ph+ CML in adults who cannot have imatinib or their disease is imatinib-resistant (TA425)

Licensed / Unfunded Indication

- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy

*NHS England Circular 1732

**TREATMENT INTENT**

Disease modification

**PRE-ASSESSMENT**

1. Investigations to include FBC, blood film and manual differential, coagulation screen, urea, creatinine, electrolytes, liver function tests, calcium, lipid profile, glucose, amylase, urate, CK.
2. Ensure diagnosis is confirmed prior to commencing treatment (usually PCR on peripheral blood and bone marrow aspirate morphology with FISH for Ph chromosome). Results of full karyotype are important to exclude major route abnormality but treatment can be commenced prior to the karyotype becoming available. For second line treatment for resistance, it is recommended to carry out bone marrow, cytogenetics and kinase domain mutation screen testing prior to switch of treatment.
3. Pregnancy Test - for all women of childbearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
4. Record performance status (WHO/ECOG).
5. Record height and weight.
6. Record blood pressure
7. ECG (most TKIs can affect the QT interval)
8. Consider echo in selected patients at risk of cardiac disease
9. Hepatitis B (including HB surface Ag and HB core antibodies) and C testing (reactivation of HBV has been reported with TKIs)
10. SOKAL risk score should be documented at diagnosis for all CML patients (LINK)
11. QRISK3 score (LINK - some TKIs have been associated with increased risk of cardiovascular disease and vascular risk factors should be considered and managed as appropriate)
12. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.

13. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines). There is a degree of uncertainty but most evidence supports that it is safe to continue dasatinib for male considering parenting. As dasatinib may cause reduced fertility, consider sperm storage/ cryopreservation in appropriate patients.

14. Treatment should be agreed in the relevant MDT.

15. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.

**DRUG REGIMEN**

**DASATINIB**

100mg PO once daily in chronic phase CML

140mg PO once a day in accelerated myeloid or lymphoid blast phase CML or Ph+ ALL

Tablets can be taken with or without food.

**TREATMENT-FREE PERIOD**

Refer to Interim Expert Opinion document available on NSSG website [LINK]

**DOSE MODIFICATIONS**

| Chronic Phase CML | ANC < 0.5 x10^9/L and/or Platelets < 50 x10^9/L | 1. Stop treatment until ANC 1 x10^9/L and platelets ≥ 50 x10^9/L.  
2. Resume treatment at the original starting dose.  
3. If platelets < 25 x10^9/L and/or recurrence of ANC < 0.5 x10^9/L for > 7 days, repeat step 1 and resume treatment at a reduced dose of 80 mg once daily (second episode) or discontinue (third episode).  
4. Consider GCSF if recurrent neutropenia. |
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<td>(starting dose 100 mg once daily)</td>
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| Accelerated and Blast Phase CML and Ph+ ALL | ANC < 0.5 x10^9/L and/or Platelets < 10 x10^9/L | 1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy).  
2. If cytopenia is unrelated to leukaemia, stop treatment until ANC ≥ 1 x10^9/L and platelets ≥ 20 x10^9/L and resume at the original starting dose.  
3. If recurrence of cytopenia, repeat step 1 and resume treatment at a reduced dose of 100mg once daily (second episode) or 80mg once daily (third episode).  
4. If cytopenia is related to leukaemia, consider dose escalation to 180mg once daily. |
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<td>(starting dose 140mg once daily)</td>
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DOSE MODIFICATIONS (continued)

Hepatic and renal impairment

Dose reduction of dasatinib may be necessary in selected patients but should be avoided where possible. Clinical significant reduction in body clearance is not expected in patients with renal insufficiency. Use with caution in moderate to severe hepatic impairment and monitor haematological response.

<table>
<thead>
<tr>
<th>Other non-haematological toxicities</th>
<th>Starting dose</th>
<th>1st dose reduction</th>
<th>2nd dose reduction</th>
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</thead>
<tbody>
<tr>
<td>Chronic Phase CML</td>
<td>100mg od</td>
<td>80mg od</td>
<td>50mg od</td>
</tr>
<tr>
<td>advanced phase CML or Ph+ ALL</td>
<td>140mg</td>
<td>100mg od</td>
<td>50mg od</td>
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**Grade 2**: interrupt treatment until the event has resolved or returned to baseline. Resume at the same dose if this is the first occurrence and at a reduced dose if this is a recurrent event.

**Grade 3 or 4**: treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose level.

DOSE ESCALATION

In clinical studies in adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML or Ph+ ALL) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dose. Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

INVESTIGATIONS

- See pre-assessment above
- BCR-ABL monitoring, as per ELN guidelines.
- Monitoring for toxicity:
  - Weekly in first month on treatment: ECG (at baseline and at least one ECG following TKI initiation for all patients. Additional weekly ECG if new symptoms or abnormal at baseline), FBC, U&E, LFT, Bone
  - Monthly for next 2 months: ECG as clinically indicated, FBC, U&E, LFT and Bone, glucose, amylase, CK
  - 3-4 monthly: Lipids, glucose, amylase, CK, FBC, U&E, LFT, Bone
  - TSH should be monitored during TKI therapy on a yearly basis (or when clinically indicated)
  - CXR should be performed in all patients who are SOB for assessment of pleural effusion
  - Consideration should also be given to Echo in selected patients – for exclusion of pericardial effusion and assessment of left ventricular function as this can be affected by all TKIs
CONCURRENT MEDICATION

Not usually required.
Consider allopurinol in selected patients.

EMETIC RISK

Low

DRUG INTERACTIONS

(Consult with pharmacist and refer to SPC for full details)

- Concomitant use of CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St John’s Wort) as they may significantly reduce exposure to dasatinib, potentially increasing the risk of therapeutic failure.
- Caution should be taken when co-administering dasatinib with CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin), as they could increase dasatinib exposure.
- Caution should be taken when co-administering dasatinib with a CYP3A4 substrate with narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot analogues) as they could increase exposure to the CYP3A4 substrate.
- Concomitant use of H₂ antagonists, proton pump inhibitors or aluminium hydroxide / magnesium hydroxide may reduce exposure to dasatinib therefore should be administered 2 hours prior to 2 hours after dasatinib.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

(Consult with pharmacist and refer to SPC for full details)

- Pleural effusions (can occur late, even after years of dasatinib treatment). Management usually requires temporary interruption of the treatment. In recurrent cases diuretics or steroids can be used. After resolution of the first episode, dasatinib can usually be restarted at the same dose but dose reduction is recommended in the event of recurrence.
- Cytopenias grade 3/4 incidence 15-20% (thrombocytopenia more common than with imatinib)
- Pulmonary arterial hypertension (approx. incidence 0.5% with dasatinib)
- Liver abnormalities (50% incidence all grades)
- Rash and headaches more common than with imatinib
- Gastrointestinal side effects less common than with imatinib

TKI should be discontinued 1 week before major surgery and restarted when risk of bleeding is considered to be minimal.
BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation

- Test patients for infection with hepatitis B virus (HBV) before starting treatment with BCR-ABL tyrosine kinase inhibitors
- Consult experts in liver disease and in the treatment of HBV before starting treatment with BCR-ABL tyrosine kinase inhibitors in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV during treatment
- Patients who are carriers of HBV who require treatment with BCR-ABL tyrosine kinase inhibitors should be closely monitored for signs and symptoms of active HBV infection throughout treatment and for several months after stopping
- Suspected adverse drug reactions to BCR-ABL tyrosine kinase inhibitors should be reported via the Yellow Card scheme

TREATMENT RELATED MORTALITY

Very low (<1%).

REFERENCE


REVIEW

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<tbody>
<tr>
<td>Dr Adam Mead</td>
<td>Adverse effects reviewed, treatment intent and mortality added</td>
<td>Sep 2016</td>
<td>2.1</td>
<td></td>
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<tr>
<td>Dr Mead and Cheuk-ke Cheung</td>
<td>Indication and BCR-ABL section added</td>
<td>Mar 2017</td>
<td>2.2</td>
<td></td>
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<tr>
<td>Cheuk-ke Cheung</td>
<td>Update of NHSE funding position for 1st line indication</td>
<td>Apr 2017</td>
<td>2.3</td>
<td></td>
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<tr>
<td>Cheuk-ke Jackie Cheung, Haematology Pharmacist, NSSG Myeloid Group</td>
<td>Annual protocol meeting</td>
<td>Oct 2019</td>
<td>2.4</td>
<td>Oct 2021</td>
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