

DASATINIB

INDICATION

Licensed & Funded Indications

- Untreated chronic-phase Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) where imatinib is not appropriate (**BLUETEQ required – NICE TA 426**) or
- Chronic- or accelerated-phase Ph+ CML in adults where imatinib is not appropriate or their disease is imatinib-resistant (**no BLUETEQ required – NICE TA 425**)

Licensed / Unfunded Indication

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

Available as 20mg, 50mg, 80mg, 100mg and 140mg tablets

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Investigations to include FBC, blood film and manual differential, coagulation screen, urea and electrolytes, liver function tests, bone profile, lipid profile, fasting glucose or HbA1c, BNP, amylase, urate, CK, HIV, Hepatitis B (including HB surface Ag and HB core antibodies) and C testing.
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 (extra Philadelphia (Ph) chromosome, trisomy 8, isochromosome 17q or trisomy 19) 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 or have 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 echocardiogram in selected patients at risk of cardiac disease
9. ELTS or SOKAL risk score should be documented at diagnosis for all CML patients ([LINK](#))
10. 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)

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1 of 8

ML.7 Dasatinib	Authorised by Myeloid Lead Prof Adam Mead	Aug 2023	Version 3.0
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11. 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.
12. 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 males considering parenting. As dasatinib may cause reduced fertility, consider sperm storage/ cryopreservation in appropriate patients.
13. Treatment should be agreed in the relevant MDT.
14. Ensure pre-treatment counselling in line with national recommendations for oral systemic anti-cancer therapy (SACT).

DRUG REGIMEN

DASATINIB 100mg PO once daily in chronic phase CML. In elderly/frail patients, or those with comorbidities, a lower starting dose of 50mg can be used with subsequent uptitration of the dose as required depending on tolerance and response.

140mg PO once a day in accelerated myeloid or lymphoid blast phase CML (or Ph+ ALL – not funded)

Tablets can be taken with or without food. Avoid grapefruit or grapefruit juice. For patients unable to swallow tablets, a liquid preparation is available.

DOSE MODIFICATIONS

	Increased dose (Dose Level +1)	Starting dose	Dose Level -1	Dose Level -2	Dose Level -3
Chronic Phase CML	140mg od	100mg od	80mg od	50mg od	20mg od
Accelerated or blast phase CML or Ph+ ALL	180mg od	140mg od	100mg od	50mg od	N/A

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.

Dose Adjustment for Haematological Toxicities

<p>Chronic Phase CML (starting dose 100 mg once daily)</p>	<p>ANC < 0.5 x10⁹/L and/or Platelets < 50 x10⁹/L</p>	<ol style="list-style-type: none"> 1. Stop treatment until ANC ≥ 1 x10⁹/L and platelets ≥ 50 x10⁹/L. 2. Resume treatment at the original starting dose. 3. If platelets < 25 x10⁹/L and/or recurrence of ANC < 0.5 x10⁹/L for > 7 days, repeat step 1 and resume treatment at dose level -1 (second episode). For third episode, further reduce dose to dose level -2 (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy including imatinib). 4. Consider GCSF if recurrent neutropenia.
<p>Accelerated and Blast Phase CML and Ph+ ALL (starting dose 140mg once daily)</p>	<p>ANC < 0.5 x10⁹/L and/or Platelets < 10 x10⁹/L</p>	<ol style="list-style-type: none"> 1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, stop treatment until ANC ≥ 1 x10⁹/L and platelets ≥ 20 x10⁹/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat step 1 and resume treatment at dose level -1 (second episode) or dose level -2 (third episode). 4. If cytopenia is related to leukaemia, consider dose escalation to 180mg once daily.

Non-Haematological Toxicities

Criteria	Action
Pleural effusion	Interrupt dasatinib until patient is examined, asymptomatic or returned to baseline. If not approved in 1 week, consider diuretics and/or corticosteroids. Following resolution of the first episode, restart at same dose level. Following resolution of a subsequent episode, or if the first episode was severe, restart at one dose level lower.
Other Grade 2 toxicities	Interrupt dasatinib 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 toxicities	Interrupt dasatinib the event has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose level.

Renal / Hepatic Impairment

Renal impairment	Hepatic impairment
No dose adjustment is required in any stage of renal impairment.	No initial dose adjustment is required. Use with caution in moderate to severe hepatic impairment and monitor haematological response.

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3 of 8

ML.7 Dasatinib	Authorised by Myeloid Lead Prof Adam Mead	Aug 2023	Version 3.0
-------------------	--	----------	----------------

INVESTIGATIONS & ON-TREATMENT MONITORING

Monitoring for Dasatinib		Frequency of Monitoring (Month 1)	Frequency of Monitoring (Month 2 and 3)	Frequency of Monitoring Once Stable
HIV, Hepatitis B and C serology	Baseline	N/A	N/A	N/A
Document Q-RISK score	Baseline	N/A	N/A	Annually
FBC	Baseline	1-2 weekly	Monthly	3 monthly
Biochemistry (U&Es, LFTs, bone profile)	Baseline	1-2 weekly	Monthly	3 monthly
BCR-ABL monitoring	Baseline	N/A	Monthly	3 monthly *
Lipid profile	Baseline	N/A	N/A	Annually
BNP	Baseline	N/A	N/A	Annually
HbA1c	Baseline	N/A	N/A	As clinically indicated
TFTs	Baseline	N/A	N/A	As clinically indicated
Amylase	Baseline	N/A	N/A	As clinically indicated
Creatine kinase	Baseline	N/A	N/A	As clinically indicated
Blood pressure	Baseline	N/A	Monthly	3 monthly
ECG	Baseline	At least 1 ECG following initiation	As clinically indicated	As clinically indicated
Echocardiogram & Chest X-ray#	As clinically indicated	N/A	As clinically indicated	As clinically indicated
ABL1 kinase domain mutation	At diagnosis	N/A	N/A	At warning or failure of response

* BCR-ABL monitoring every 3 months until the achievement of a stable MMR (<MR 3 – sustained for 1 year), and thereafter at 3-6 months as clinically indicated, as per BSH/ELN guidelines.

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.

TREATMENT-FREE PERIOD

- Any patient considering discontinuation should be discussed at an MDT meeting.
- Patients should be on approved TKI therapy for at least 3 years (but preferably 5 years) and should not have:
 - A prior history of accelerated or blast phase CML
 - Previous resistance to any TKI
 - Previous detection of a BCR-ABL1 KD mutation
- Patients should have MR4 (<0.01% by IS) for the last 2 years (verified by at least 4 consecutive BCR-ABL tests at least 3 months apart)
- Prior to treatment-free period, typically we recommend de-escalation to 50% of standard dose for 12 months prior to discontinuation with monthly monitoring

Time point after de-escalation	Frequency of Monitoring
Month 1 to 12	Monthly

- Following discontinuation, monitoring should be as follows:

Time point after discontinuation	Frequency of Monitoring
Month 1 to 6	Monthly
Month 7 to 12	6 weekly
Month 13 to 36	2 monthly
Month 36 (3 Years) onwards	3 to 6 monthly

Note: During discontinuation/de-escalation there should be access to a lab with at least MR4/5 sensitivity able to provide results within 14 days.

Reinitiation of TKI following loss of confirmed MMR (> 0.1%)

TKI should be restarted within 1 month at full dose.
 BCR-ABL testing should be performed monthly until re-establishment of MMR.
 If MR3 is not achieved by 6 months, BCR-ABL1 KD mutation analysis should be performed.
 It is noted that after discontinuation of TKI therapy to attempt treatment-free period, patients may experience musculoskeletal symptoms (e.g. myalgia, arthralgia, bone pain) more frequently than before treatment discontinuation.

Note: Treatment-free periods for TKIs for patients in MMR are exempt from the NHS England Treatment Break Policy. The TKI can be restarted without completing a treatment break form.

CONCURRENT MEDICATION

Not usually required.
 Allopurinol 300mg PO once daily for 14 days can be considered if WBC >10
 Consider GCSF support in patients with recurrent neutropenia.
 Consider erythropoietin-stimulating agents (ESA) in anaemic patients.

EMETIC RISK

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5 of 8

ML.7 Dasatinib	Authorised by Myeloid Lead Prof Adam Mead	Aug 2023	Version 3.0
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Low

DRUG INTERACTIONS

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

- Concomitant use of potent 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 potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin), as they could increase dasatinib exposure. Avoid where possible. Grapefruit juice should also be avoided. If the interaction cannot be avoided, consider a dose decrease of dasatinib to:
 - 40mg daily if taking 140mg daily
 - 20mg daily if taking 100mg or 70mg daily
- 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 this could increase exposure to the CYP3A4 substrate.
- Concomitant use of H₂ antagonists, proton pump inhibitors or antacids may reduce exposure to dasatinib. H₂ antagonists and proton pump inhibitors should be avoided and antacids should be administered 2 hours prior to, or 2 hours after, the dasatinib dose.
- Concomitant use of statins that are mainly eliminated by CYP3A4 may increase the potential for statin-induced myopathy, including rhabdomyolysis. Consider alternative statins that do not have this effect such as rosuvastatin or pravastatin. Alternatively atorvastatin can be used at lower doses with close monitoring.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Caution should be exercised in patients with a history of pulmonary hypertension, and alternative TKIs should be considered.

- 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. Discuss with haematologist during surgery planning.

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6 of 8

ML.7 Dasatinib	Authorised by Myeloid Lead Prof Adam Mead	Aug 2023	Version 3.0
-------------------	--	----------	----------------

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

1. NICE TA425. Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia. Last updated: 21/12/2018. Accessed via: <https://www.nice.org.uk/guidance/ta425>
2. NICE TA426. Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia. Last updated: 21/12/2018. Accessed via: <https://www.nice.org.uk/guidance/ta426>.
3. Bristol-Myers Squibb. Dasatinib Summary of Product Characteristics. Updated 19/10/2022. Accessed on 15/8/2023 via <http://www.medicines.org.uk/>
4. MHRA (2016) Drug Safety Update: BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation[[Link](#)]
5. Smith G et al (2020). A British Society of Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. B J Haem 191: 171-193
6. Hochhaus A et al (2020). European LeukemiaNet 2020 recommendations for treating chronic myeloid leukaemia. Leukemia 34: 966-984Hochhaus et al (2017) Chronic Myeloid Leukaemia: ESMO Clinical Practice Guidelines. Ann Oncol 28(S4):iv41-51
7. Giraud, E.L. et al. (2023) 'Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: An update', The Lancet Oncology, 24(6). doi:10.1016/s1470-2045(23)00216-4

REVIEW

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7 of 8

ML.7 Dasatinib	Authorised by Myeloid Lead Prof Adam Mead	Aug 2023	Version 3.0
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Name	Revision	Date	Version	Review date
Dr Adam Mead	Adverse effects reviewed, treatment intent and mortality added	Sep 2016	2.1	
Dr Mead and Cheuk-ke Cheung	Indication and BCR-ABL section added	Mar 2017	2.2	
Cheuk-kie Cheung	Update of NHSE funding position for 1 st line indication	Apr 2017	2.3	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Oct 2019	2.4	Oct 2021
Dr Oni Chowdhury and Prof Adam Mead, Consultant Haematologists. Yen Lim, Zishaan Ramzan Haematology Pharmacist. NSSG Myeloid Group.	Updated as per BSH/ELN guidelines and SPC. Addition of monitoring table, treatment-free period and reinitiation guidance. Annual protocol meeting 2022.	Aug 2023	3.0	Nov 2025

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8 of 8

ML.7 Dasatinib	Authorised by Myeloid Lead Prof Adam Mead	Aug 2023	Version 3.0
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