Thames Valley
Strategic Clinical Network

IMATINIB

INDICATION

Licensed & Funded indications

- Imatinib is recommended as first-line treatment of adults with chronic phase Ph+ chronic myeloid leukaemia (CML) **[NICE TA426]**
- Imatinib, dasatinib or nilotinib is recommended for the treatment of adults with Ph+ CML who initially present in the accelerated phase or with blast crisis. **[NICE TA 426]**
- Newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy (Ph+ ALL) (see separate ALL protocols)

Licensed / Unfunded Indications

• adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.

• adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

Unlicensed Indication (Please ensure unfunded SACT form complete)

• Philadelphia chromosome positive acute lymphoblastic leukaemia following allogeneic stem cell transplant. When used, aim to start 3 months post-transplant.

Available as 100mg and 400mg, tablets and capsules.

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).
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 imatinib for male considering parenting. As imatinib 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 / CYCLE FREQUENCY

IMATINIB

400mg PO once daily in **chronic phase CML**, can be increased to 600mg OD for selected patients with suboptimal response with no evidence of a mutation and good tolerance of the standard dose. In elderly/frail patients, or those with comorbidities, a lower starting dose of 200mg can be used, with subsequent uptitration of the dose as required depending on tolerance and response.

600mg once daily or 400mg twice a day PO (use maximum tolerated dose) in **accelerated phase or blast crisis CML**, although use of second/third generation TKI should be strongly considered where appropriate

100-400mg PO once daily in **FIP1L1/ PDGFRA** associated chronic eosinophilic leukemia (CEL) or advanced hypereosinophilic syndrome (HES)

400mg PO once daily in **MDS/MPD**

400mg PO once daily in Philadelphia chromosome positive acute lymphoblastic leukaemia following allogeneic stem cell transplant.

Once diagnosis is confirmed imatinib can be initiated first line (hydroxycarbamide should be reserved for patients where leucostasis is a concern whilst awaiting the diagnosis, not usually required if the WBC is <100 x 10^9/L).

Continue treatment until disease progression. The effect of stopping treatment after the achievement of completed cytogenic remission (CCyR) has not been investigated.

For patients unable to swallow tablets, disperse the tablets in a glass of still water or apple juice as follows: approximately 50ml for a 100mg tablet, and 200ml for a 400mg tablet. Stir the suspension and take immediately after tablet(s) completely disintegrate. Capsules can be opened and the contents dispersed in a glass of still water or apple juice.

DOSE MODIFICATIONS

	Increased dose (Dose Level +1)	Starting dose	Dose Level -1	Dose Level -2	Dose Level -3
Chronic Phase CML	600mg od	**400mg od**	300mg od	200mg od	100mg od
Accelerated or blast phase CML or Ph+ ALL	400mg bd	**600mg od**	400mg od	300mg od	200mg od

Dose Escalation

In suboptimal response, consider dose increase to 600mg daily for patients tolerating imatinib in the absence of mutation.

Dose Adjustment for Haematological Toxicities

Indication	Counts	Modification
Chronic phase CML (400mg)	ANC < 1.0 x 10^9/L and/or Plt < 50 x 10^9/L	1. Stop Imatinib until ANC ≥ 1.5 x 10^9/L and Plt ≥ 75 x 10^9/L 2. Resume treatment at previous dose 3. Recurrence of ANC < 1.0 x 10^9/L and/or Plt < 50 x 10^9/L, repeat step 1 and resume Imatinib at one dose band lower. 4. Consider GCSF if recurrent neutropenia
Accelerated phase CML and blast crisis (600mg)	ANC < 0.5 x 10^9/L and/or Plt < 10 x 10^9/L occurring after at least 1 month of treatment	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia unrelated to leukaemia, reduce dose of Imatinib to 400mg. 3. If cytopenia persists for 2 weeks, reduce to 300mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop Imatinib until ANC ≥ 1 x 10^9/L and Plt ≥ 20 x 10^9/L, then resume treatment at 300mg.
HES/CEL (starting dose 100 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop imatinib until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with imatinib at previous dose

Non-haematological Toxicities

Toxicity	Modification
Any severe non-haematological toxicity	Withhold treatment until resolved. Resume treatment depending on the initial severity of the event.

Renal / Hepatic Impairment

Renal impairment	Hepatic impairment
Use with caution. Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400mg OD. Reduce dose if not tolerated or increase dose for lack of efficacy.	Start at 400mg OD minimum dose with any impairment. Reduce dose if not tolerated. **Dose adjustment for adverse reactions** If bilirubin > 3 x ULN (not Gilberts related) or liver transaminases > 5 x ULN, withhold until bilirubin < 1.5 x ULN and liver transaminase < 2.5 x ULN. Resume at reduced dose: 400mg to 300mg; 600mg to 400mg; 800mg daily to 600mg

INVESTIGATIONS & ON-TREATMENT MONITORING

Monitoring for Imatinib		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 (for CML patients only)	Baseline	N/A	Monthly	3 monthly *
Blood pressure	Baseline	N/A	Monthly	3 monthly
Lipid profile	Baseline	N/A	N/A	Annually
BNP	Baseline	N/A	N/A	As clinically indicated
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	N/A	N/A	N/A	As clinically indicated
Blood pressure	Baseline	N/A	As clinically	Annually

			indicated	
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 (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 restarted within 1 month
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.
Consider allopurinol 300mg OD for 7 days at diagnosis.
Consider GCSF support in patients with recurrent neutropenia.
Consider erythropoietin-stimulating agents (ESA) in anaemic 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 imatinib, potentially increasing the risk of therapeutic failure. Consider checking imatinib levels if suspected interaction.

- Caution should be taken when co-administering imatinib with CYP3A4 inhibitors (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin), as they could increase imatinib exposure.

- Caution should be taken when co-administering imatinib with a CYP3A4 substrate with narrow therapeutic index (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) as they could increase exposure to the CYP3A4 substrate.

- Imatinib may increase plasma concentration of other CYP3A4 substrates such as simvastatin. Consider alternative statins that do not have this effect.

- Paracetamol can be safely administered with imatinib in patients with normal liver function.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Very commonly reported:
Neutropenia, thrombocytopenia, anaemia, headache, nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, periorbital oedema, dermatitis/eczema/rash, muscle spasm and cramps,

musculoskeletal pain including myalgia, arthralgia, bone pain, fluid retention and oedema, fatigue, weight increase.

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.

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

Extremely rare (<1%).

REFERENCES

1. NICE (2018) 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 (2016) 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. Sandoz. Imatinib Film Coated Tablets Summary of Product Characteristics. Updated 24/5/2022. Accessed on 17/8/23 via http://www.medicines.org.uk.
4. Cipla EU Ltd. Imatinib Hard Capsules Summary of Product Characteristics. Updated 12/10/2022. Accessed on 17/8/23 via http://www.medicines.org.uk.
5. MHRA (2016) Drug Safety Update: BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation[Link]
6. 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
7. Hocchaus A et al (2020). European LeukemiaNet 2020 recommendations for treating chronic myeloid leukaemia. Leukemia 34: 966-984
8. Hochhaus et al (2017) Chronic Myeloid Leukaemia: ESMO Clinical Practice Guidelines. Ann Oncol 28(S4):iv41-51
9. 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

Name	Revision	Date	Version	Review date
Julia Wong	Protocol has been re-drafted	Mar 2017	4.0	
Cheuk-kie Cheung	General formatting	May 2017	4.1	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting	Oct 2019	4.2	Oct 2021
Dr Oni Chowdhury, Prof Adam Mead, Dr Connor Sweeney, Consultant Haematologists. Yen Lim, Zishaan Ramzan, Haematology Pharmacists. NSSG Myeloid Group.	Updated as per BSH/ELN guidelines and SPC. Addition of monitoring table, treatment-free period and reinitiation guidance. Annual protocol meeting.	Aug 2023	5.0	Nov 2025