Dasatinib

Indication

Newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
(NICE TA251)

Chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.
(NOT NICE approved funding via the CDF)

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

ICD-10 codes

C92.1, C91.0

Regimen details

Chronic phase CML

Days	Drug	Dose	Route
1-28 (ongoing)	Dasatinib	100 mg OD (dose escalation to 140mg OD*)	PO

Accelerated or blast phase CML or ALL

Days	Drug	Dose	Route
1-28 (ongoing)	Dasatinib	140mg OD (dose escalation to 180mg OD*)	PO

* Dose escalation may be considered for patients who have not achieved a haematological or cytogenetic response at the starting dose.

Cycle frequency

Continuous

Number of cycles

Continued until disease progression or unacceptable toxicity.

Administration

Dasatinib is available as 20mg, 50mg, 80mg, 100mg and 140mg tablets. Tablets should be swallowed whole. Dasatinib may be taken with or without food, but should be taken consistently at the same time of each day.

Patients should be advised to avoid grapefruit and grapefruit juice.

Pre-medication

Adequate hydration and allopurinol 300mg OD (100mg OD if CrCl <20mL/min) to prevent tumour lysis syndrome is recommended prior to initiation of dasatinib.

Emetogenicity

Dasatinib has low emetic potential.

Additional supportive medication

Allopurinol as above
Anti-emetics as per local policy, if required
Loperamide if required

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
Coagulation screen	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days

Prior to commencing treatment:
Confirm the presence of t (9;22) and/or BCR-ABL transcript (or other TKI sensitive target)
Consider initial hydroxyurea / leucopheresis in the event of hyperleucocytosis
Hepatitis B (HBV) serology testing – cases of reactivation of HBV have occurred in patients who are chronic carriers of HBV after they received BCR-ABL tyrosine kinase inhibitors

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Weekly for the first 2 months, then monthly
Coagulation screen	3 monthly
U+Es (including creatinine)	Monthly
LFTs	Monthly
Magnesium	Monthly

Marrow assessment (karyotype, FISH), peripheral blood BCR-ABL1/ABL1 or other relevant marker for disease monitoring.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	$\geq 0.5 \times 10^9$/L
Platelets	$\geq 50 \times 10^9$/L
Bilirubin	< 3 x ULN
AST/ALT	< 5 x ULN

Dose modifications

- **Haematological toxicity**

Chronic phase CML

Neutrophils ($\times 10^9$/L)		**Platelets** ($\times 10^9$/L)	**Action**
< 0.5	or	25-49	Withhold until counts have recovered (neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L) Resume treatment at the original starting dose.
2nd occurrence of neutrophils < 0.5 for > 7 days	or	< 25	Withhold until counts have recovered (neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L) Resume treatment at a reduced dose of 80mg OD.
3rd occurrence of neutrophils < 0.5 for > 7 days		2nd occurrence of platelets < 25	Withhold until counts have recovered (neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L) Resume treatment at a reduced dose of 50 mg OD (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy including imatinib).

Accelerated or blast phase CML or ALL

Neutrophils		**Platelets**	**Action**
< 0.5 x10^9/L	and/or	< 10 x 10^9/L	**If cytopenia unrelated to leukaemia**, withhold until counts have recovered (neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 20 x 10^9/L) then resume treatment as follows: 1st occurrence: original dose 2nd occurrence: 100mg OD 3rd occurrence: 80mg OD **If cytopenia is related to leukaemia** consider dose escalation to 180mg OD.

- **Renal impairment**

There is no data on dosing in renal impairment, however as there is minimal renal clearance of dasatinib and its metabolites, reduced clearance in patients with renal impairment is not expected.

- **Hepatic impairment**

Use with caution in hepatic impairment.

- **Other toxicities**

For any grade 2 toxicity: withhold treatment until resolved then resume with original dose if 1st occurrence or dose reduce as below if reoccurrence.

For any grade 3+ toxicity: withhold treatment until resolved, then resume with dose reduction.

Dose reduction	**Chronic phase**	**Accelerated or blast phase**
Full dose	100mg	140mg
1st reduction	80mg	100mg
2nd reduction	50mg	50mg

Pleural effusion
If a patient suffers a pleural effusion, withhold treatment until patient is asymptomatic or has returned to baseline. If the episode does not improve within approximately one week, consider diuretics or corticosteroids or both. Following resolution of the first episode, consider reintroduction of dasatinib at the same dose level. Following resolution of a subsequent episode, reintroduce dasatinib at one dose level reduction. Following resolution of a severe (grade 3 or 4) episode, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event (consultant decision).

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Pleural effusion
Cardiotoxicity, QT prolongation (has been reported)
Pulmonary arterial hypertension

- **Commonly occurring side effects**

Myelosuppression
Haemorrhage
Dyspnoea, cough
Diarrhoea
Nausea and vomiting
Fluid retention, periorbital oedema
Fatigue
Visual disturbances
Hypophosphatemia
Muscle cramps

- **Other side effects**

Rash
Headache

Significant drug interactions – for full details consult product literature/ reference texts

Potent CYP3A4 inhibitors (including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin) avoid concomitant treatment – increases dasatinib exposure.

Moderate CYP3A4 inhibitors: Consider switching to an alternative medicinal product with no or minimal CYP3A4 inhibition – may increase dasatinib exposure.

CYP3A4 inducers (including dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital and St John's Wort) avoid concomitant use - may induce dasatinib metabolism, potentially increasing the risk of therapeutic failure.

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided.

H_2 antagonists, proton pump inhibitors and aluminium hydroxide/magnesium hydroxide may reduce exposure to dasatinib. Avoid concomitant use. Aluminium hydroxide/magnesium hydroxide products should be administered up to 2 hours prior, or 2 hours following the administration of dasatinib.

Anticoagulants: caution should be exercised if patients are required to take medicinal products that inhibit platelet function or anticoagulants because of a risk of severe bleeding.

Dasatinib should be used with caution in patients who have or may develop prolongation of the QT interval,

including those patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicinal products that may lead to QT prolongation.

Domperidone: potential to increase QT interval prolongation and to induce "torsade de pointes"- arrhythmias; co-administration of domperidone should be avoided. It should only be used, if other medicinal products are not efficacious, with an individual benefit-risk assessment and patients monitoring for QT prolongation.

Additional comments

Women of childbearing potential must be advised to use effective contraception during treatment.

Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately.

References

- Dasatinib, nilotinib and high-dose imatinib for the treatment of chronic myeloid leukaemia (NICE TA241) accessed 8 April 2015 via www.nice.org.uk
- Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (NICE TA251) accessed 8 April 2015 via www.nice.org.uk
- European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Baccarani M, Deininger MW et al . Blood. 2013 Aug 8;122(6):872-84. doi: 10.1182/blood-2013-05-501569.
- Gotlib J. Am J Hematol. 2014 Mar;89(3):325-37. doi: 10.1002/ajh.23664.
- Summary of Product Characteristics Dasatinib (Pfizer), accessed 8 April 2015 via http://www.medicines.org.uk

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