

Imatinib Therapy - GIST

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).	C16	00335a	CDS
Adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST.	C16	00335b	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.

Unresectable/Metastatic GIST:

Imatinib 400mg is taken once daily until disease progression or unacceptable toxicity develops. The dose may be increased to 800mg daily in progressing disease.

Adjuvant:

Imatinib 400mg is taken once daily continuously for up to 3 years after resection or until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Imatinib	400mg once daily*	PO with food	Continuous
*For daily doses of 800mg, the dose should be administered as 400mg twice a day, in the morning and in the evening			

ELIGIBILITY:

- Indications as above
- ECOG status 0-3
- Adequate bone marrow, renal and liver function

EXCLUSIONS:

- Hypersensitivity to imatinib or any of the excipients
- Patients who have a low risk of recurrence are not eligible for adjuvant treatment

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile

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- ECG
- Virology screen -Hepatitis B (HBsAg, HBcoreAb)*

*(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

- Renal and liver profile monthly
- FBC every 2 weeks for first 12 weeks and then monthly or as clinically indicated.

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.

Haematological:

Table 1: Dose modification of imatinib in haematological toxicity

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose
1.5-1.99	or	<LLN* to 75	400mg daily
1-1.49	or	50-74	400mg daily
0.5-0.99	or	10-49	Hold until toxicity ≤ Grade 1, then resume at 300mg daily. For second occurrence, hold until toxicity ≤ Grade 1, then resume at 200mg daily.
<0.5	or	<10	
No dose reductions for Grade 3 or 4 anaemia. Patients can be transfused or treated with erythropoietin			
*LLN=Lower Limit Normal			

Renal and Hepatic Impairment:

Table 2: Dose modification of imatinib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
<ul style="list-style-type: none"> • Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. • However, in these patients caution is recommended. • The dose can be reduced if not tolerated. • If tolerated, the dose can be increased for lack of efficacy. 	<ul style="list-style-type: none"> • Imatinib is mainly metabolised through the liver. • Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. • The dose can be reduced if not tolerated.

Management of adverse events:

Table 3: Hepatotoxic Adverse Events

Bilirubin		Liver Transaminases	Dose
> 3 x ULN	or	> 5 x ULN	Hold until bilirubin < 1.5 x ULN and transaminase levels < 2.5 x ULN, then resume at 300 mg daily.

Table 4: Dose Modification for Non-Haematological Adverse Reactions

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Toxicity	Occurrence	Recommended dose modification and measures
Grade 2	1 st occurrence	Hold until toxicity ≤ Grade 1, then resume at the same daily dose.
	2 nd occurrence	Hold until toxicity ≤ Grade 1, then resume at 300mg daily
	3 rd occurrence	Hold until toxicity ≤ Grade 1, then resume at 200mg daily
Grade 3 or 4	1 st occurrence	Hold until toxicity ≤ Grade 1, then resume at 300mg daily
	2 nd occurrence	Hold until toxicity ≤ Grade 1, then resume at 200mg daily

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low (**Refer to local policy**).

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions

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

- **Hypothyroidism:** Hypothyroidism has been reported in thyroidectomy patients undergoing thyroxine replacement during treatment with imatinib.
- **Hepatotoxicity:** Metabolism of imatinib is mainly hepatic, and only 13% of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored. It should be noted that GIST patients may have hepatic metastases which could lead to hepatic impairment.
- **Fluid retention:** Monitor regularly for signs and symptoms of fluid retention caused by imatinib. Probability increases with higher doses, age greater than 65 years and patients with a prior history of cardiac disease. If severe fluid retention occurs treatment should be withheld until resolved.
- **Cardiac Disease:** Patients with cardiac disease, risk factors for cardiac failure or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.
- **Gastrointestinal haemorrhage:** In the study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoural haemorrhages were reported. Based on the available data, no predisposing factors (e.g. tumour size, tumour location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of haemorrhage. Since increased vascularity and propensity for bleeding is a part of the nature and clinical course of GIST, standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied
- **Reactivation of Hepatitis B Virus (HBV):** Cases of reactivation of HBV have occurred in patients who are chronic carriers of HBV after they received BCR-ABL tyrosine kinase inhibitors (TKIs). Some cases of HBV reactivation resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.
 - Patients should be tested for HBV infection before initiating treatment with BCR-ABL TKIs
 - 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.

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- Patients who are carriers of HBV requiring 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.

DRUG INTERACTIONS:

- CYP3A4 inhibitors may cause increased toxicity of imatinib due to reduced clearance. Caution should be taken when administering imatinib with inhibitors of the CYP3A4 family.
- CYP3A4 inducers may significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure. Concomitant use of strong CYP3A4 inducers and imatinib should be avoided.
- Caution is recommended when administering imatinib with CYP3A4 substrates. Imatinib may increase plasma concentrations of other CYP3A4 metabolised drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.) leading to increased effect/toxicity of these drugs.
- Because of known increased risks of bleeding in conjunction with the use of imatinib (e.g. haemorrhage), patients who require anticoagulation should receive low-molecular-weight or standard heparin, instead of coumarin derivatives such as warfarin.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Imatinib L01XE01

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Version	Date	Amendment	Approved By
1	20/06/2016		Prof Maccon Keane
2	20/06/2018	Updated with new NCCP template	Prof Maccon Keane
3	15/07/2020	Updated treatment table Updated emetogenic potential Updated adverse events Updated references	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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