IMATINIB

1. First-line treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) (NICE approved 2004)
2. Adjuvant treatment of completely resected Kit +ve GIST at high risk of relapse (NICE approved Nov 2014)

Drug/Dosage: **Imatinib** initiate at 400mg po od continuous

Doses above 400mg daily for patients whose disease progresses on the 400mg dose are not funded and not recommended by NICE

Administration: Imatinib available as 400mg and 100mg tablets, which are not scored or divisible.
The daily dose should be taken once daily with a large glass of water, with or after food.
Patients unable to swallow the tablets may disperse each dose in water or apple juice (about 200ml for a 400mg tablet). Advise patient to stir with a spoon and drink the suspension immediately after disintegration.

Frequency:

Unresectable / advanced disease:	If no response seen within 12 weeks of starting treatment, imatinib should be discontinued. Responders to receive continuous therapy until progression.
Adjuvant setting:	continuous treatment for a maximum of 3 years

Main Toxicities: myelosuppression; fluid retention, commonly presenting as periorbital oedema; rash; muscle cramps; diarrhoea; GI bleed; cardiotoxicity (rare - see Comments)

Anti- emetics: none usually needed, but some patients may have mild nausea

Regular Investigations:

FBC	monthly*
LFTs	monthly*
U&Es	monthly*

*may reduce monitoring to up to a maximum of 3 monthly intervals in stable patients, whether in adjuvant setting or advanced disease
(however, maximum of 1 month supply at a time will be issued in the advanced setting)

Comments: Elimination of imatinib is mainly through hepatic metabolism. Concomitant use of enzyme inducers (e.g. dexamethasone, phenytoin, carbamazepine, St Johns wort) and imatinib should be avoided, as this may increase the risk of therapeutic failure.

Co-administration of imatinib with enzyme inhibitors (eg itraconazole, erythromycin, clarithromycin) should also be avoided. If this is not possible, the dose of imatinib may need to be reduced according to tolerability.

Because of risks of bleeding with imatinib, patients who require anti-coagulation should be given LMWH instead of warfarin.

Reason for Update: review of frequency of bloods and monitoring in stable advanced patients	Approved by Consultant: Dr S Cummins
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In patients receiving levothyroxine, the plasma levels of levothyroxine may be decreased when imatinib is started, including cases of clinical hypothyroidism (mechanism unknown). Caution is therefore recommended, with TSH levels monitored closely.

Severe, symptomatic LV systolic dysfunction has occasionally been reported in patients taking imatinib[1]. In most cases, patients had other co-morbidities or cardiac risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully. There is no advice regarding withdrawal of imatinib in the event of declining cardiac function.

Dose Modifications

Haematological Toxicity:

If neutrophils < 1.0 $x10^9$/l and/or platelets < 50 $x10^9$/l, proceed as follows:

1. Stop imatinib until neutrophils ≥1.5 $x10^9$/l and platelets ≥ 75 $x10^9$/l
2. Resume treatment at 400mg dose
3. If recurrence of neutrophils < 1.0 $x10^9$/l and/or platelets < 50 $x10^9$/l, repeat step 1 and resume imatinib at reduced dose of 300 mg

Hepatic Impairment

Patients with mild, moderate or severe hepatic impairment should all be started at 400mg daily. The dose can be reduced if not tolerated.

For patients who develop raised LFTs as an adverse reaction after imatinib treatment has started, manage as follows:
If bilirubin > 3 x ULN or ALT/AST > 5 x ULN, withhold imatinib until bilirubin < 1.5 x ULN or ALT/AST < 2.5 x ULN, then continue treatment at a reduced dose of 300mg. Monitor peripheral blood counts and liver enzymes carefully.

Renal Impairment :

Patients with severe renal impairment or on dialysis should be started at 400 mg daily. Monitor closely and treat with caution - the dose can be reduced if not tolerated.

References:

Demetri, GD et al ; NEJM 2002; 347: 472 – 480
[1]Kerkela, R et al; Nature Medicine 2006; 12: 881 – 882
Joensuu, H et al; JAMA 2012; 307 (12): 1265 - 1272