Imatinib (GIST)

Indication

First-line management of KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumours (GISTs).
Continuation with imatinib therapy is recommended only if a response to initial treatment is achieved within 12 weeks.

(NICE TA86)

ICD-10 codes

Codes with a prefix C49

Regimen details

Day	Drug	Dose	Route
1-28*	Imatinib	400mg* OD	PO

*Doses above 400mg daily for patients whose disease progresses on the 400mg dose are **NOT recommended** by NICE (TA209)

Cycle frequency

Continuous

Number of cycles

Continued until disease progression or unacceptable toxicity.
Continuation with imatinib therapy is recommended only if a response to initial treatment is achieved within 12 weeks.

Administration

Imatinib is available as 400mg and 100mg film-coated tablets.

Imatinib can cause gastrointestinal irritation therefore doses should be taken once daily with a large glass of water, with or after food.

For patients unable to swallow imatinib tablets, the tablets may be dispersed in a glass of water or apple juice (about 200ml for a 400mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Grapefruit and grapefruit juice should be **avoided** whilst taking imatinib.

Pre-medication

Nil

Emetogenicity

This regimen has low emetic potential (no routine antiemetics required)

Additional supportive medication

Nil

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

Baseline evaluation of Left Ventricular Ejection Fraction (LVEF) is recommended in patients with underlying heart disease and in elderly patients.

Investigations – pre subsequent cycles

Patients should be reviewed every 3 months

Investigation	**Validity period** (or as per local policy)
FBC	3 monthly
U+E (including creatinine)	3 monthly
LFTs	3 monthly

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	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	≥ 20mL/min
Bilirubin	≤ 3 x ULN
AST/ALT	≤ 5 x ULN

Dose modifications

- **Haematological toxicity**

Neutrophils	**Platelets**	**Imatinib dose**
< 1.0 x 10^9/L	< 50 x 10^9/L	Stop imatinib until neutrophils ≥ 1.5 x 10^9/L and platelets ≥75 x 10^9/L. Resume at previous dose. In the event of recurrence of neutrophils < 1.0 x 10^9/L and platelets < 50 x 10^9/L withhold imatinib until recovery as above and resume with reduced dose of 300mg.

- **Renal impairment**

The renal clearance of imatinib is negligible so no dose reductions are required in mild-to-moderate renal impairment.

Although very limited information is available, patients with severe renal dysfunction (creatinine clearance < 20 mL/min) or on dialysis could also start at the same dose of 400 mg. However, caution is recommended in these patients.

- **Hepatic impairment**

Bilirubin		**ALT/AST**	**Imatinib dose**
>3 x ULN	or	> 5 x ULN	Withhold imatinib until bilirubin < 1.5 x ULN and ALT/AST < 2.5 x ULN Resume with reduced dose of 300mg.

- **Other toxicities**

Non-haematological adverse reactions

If a severe non-haematological adverse reaction develops with imatinib, treatment should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

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

- **Serious side effects**

Myelosuppression; neutropenia, thrombocytopenia, anaemia
Cardiotoxicity
Stomatitis, mucositis
Pleural effusion*
Infections (bacterial, viral and fungal)
Pulmonary fibrosis
Haemorrhage**

- **Frequently occurring side effects**

Diarrhoea
Nausea and vomiting
Headache
Periorbital oedema*
Oedema*
PPE, dermatitis, rash, eczema
Fatigue
Muscle cramps, musculoskeletal pain

*Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial oedema) have been reported in patients taking imatinib. Therefore, it is highly recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.

**Intra-tumoral haemorrhage or tumour-related intra-abdominal bleeding has been reported in an estimated 5% of cases and may be life-threatening. This may not be manifested as obvious gastro-intestinal bleeding as blood may be confined to the tumour, within the hepatic capsule, peritoneum or otherwise sequestered. Signs and symptoms of such an event may include hypotension, signs of hypovolaemia, fall in haematocrit, localised pain, apparent rapid increase in size of mass, and CT suggestive of bleeding. CT results should be evaluated carefully in light of this so that this syndrome is not mistaken for progressive disease.

- **Other side effects**

Anorexia
Insomnia

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

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, erythromycin ritonavir): avoid co-administration these may increase plasma concentrations of imatinib, increasing the risk of toxicity.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of imatinib.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these

may reduce exposure to imatinib.

Coumarin anticoagulants, e.g. Warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.

CYP3A4 substrates (e.g. statins, triazolo-benzodiazepines, dihydropyridine calcium channel blockers). Special caution is required when co-administering imatinib with substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide).

Paracetamol: Imatinib inhibits paracetamol O-glucuronidation *in vitro*. Caution should be exercised when using imatinib and paracetamol concomitantly.

Levothyroxine: Imatinib may reduce exposure to levothyroxine. TSH levels should be closely monitored in patients requiring both drugs.

Additional comments

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

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 86 - Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours. Accessed 21 May 2014 via www.nice.org.uk
- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 196 - Imatinib for the adjuvant treatment of gastro-intestinal stromal tumours. Accessed 21 May 2014 via www.nice.org.uk
- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 209 - Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours. Accessed via www.nice.org.uk
- Summary of Product Characteristics Imatinib (BMS) accessed 21 May 2014 via http://www.medicines.org.uk

Written/reviewed by: Dr S Falk (Consultant Oncologist, UHBristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

Date: 11 December 2014