

For the use of a Registered Medical Practitioner or a Hospital only

Matinib mesylate tablets

100mg and 400mg

ImatiRel™

Composition

ImatiRel™ 100	
Each film coated tablet contains:	
Matinib mesylate equivalent to Imatinib	100 mg
Excipients	q.s.
ImatiRel™ 400	
Each film coated tablet contains:	
Matinib mesylate equivalent to Imatinib	400 mg
Excipients	q.s.

Colours used (in coating): Red oxide of Iron & Yellow oxide of Iron.

Description

Imatinib is a small molecule kinase inhibitor. ImatiRel film-coated tablets contain imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[[4-Methyl-1-piperazinyl)methyl]-N-[4-(4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate. Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{40}N_6O_3S$, and its molecular weight is 589.7.

Inactive Ingredients: Microcrystalline Cellulose, Hydroxypropylcellulose, Colloidal silicon dioxide, Magnesium Stearate, Croscopolvidone.

Pharmacology

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Imatinib inhibits proliferation and induces apoptosis in bcr-abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive chronic myeloid leukaemia. Imatinib inhibits colony formation in assays using ex vivo peripheral blood and bone marrow samples from CML patients.

In vivo, imatinib inhibits tumour growth of bcr-abl transfected murine myeloid cells as well as bcr-abl positive leukaemia lines derived from CML patients in blast crisis.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation.

Pharmacokinetics

Imatinib is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose.

Mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-demethyl derivative (CGP74588), are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases proportionally with increasing doses ranging from 25 mg-1,000 mg.

At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and α1-acid glycoprotein.

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows in vitro potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib. The plasma protein binding of N-demethylated metabolite CGP74588 is similar to that of the parent compound.

Imatinib elimination is predominantly in the faeces, mostly as

metabolites. Unchanged imatinib accounted for 25% of the dose (5% urine, 20% faeces), the remainder being metabolites. The inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment-related toxicity.

Indications

Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukaemia (Ph+ CML)

Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase.

Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-α (IFN) Therapy

Patients with Philadelphia chromosome positive chronic myeloid leukaemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-α therapy.

Paediatric Patients with Ph+ CML in Chronic Phase

Paediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-α therapy. There are no controlled trials in paediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Ph+ Acute Lymphoblastic Leukaemia (ALL)

Adult patients with relapsed or a refractory Philadelphia chromosome positive acute lymphoblastic leukaemia.

Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

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

Aggressive Systemic Mastocytosis (ASM)

Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown.

Hyperesoinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukaemia (CEL)

Adult patients with hyperesoinophilic syndrome and/or chronic eosinophilic leukaemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.

Dermatofibrosarcoma Protuberans (DFSP)

Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.

Kit+ Gastrointestinal Stromal Tumours (GIST)

Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours.

Adjuvant Treatment of GIST

Adjuvant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

Dosage and Administration

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In children, Imatinib mesylate treatment can be given as a once-daily dose or alternatively the daily dose may be split into two - once in the morning and once in the evening. There is no experience with Imatinib mesylate treatment in children under 2 years of age.

For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron.

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

Adult Patients with Ph+ CML CP, AP and BC

The recommended dose of Imatinib (as mesylate) is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe

neutropaenia related neutropaenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory haematological response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6-12 months of treatment, or loss of a previously achieved haematologic or cytogenetic response.

Paediatric Patients with Ph+ CML

The recommended dose of Imatinib (as mesylate) for children with newly diagnosed Ph+ CML is 340 mg/m²/day (not to exceed 600 mg). The recommended Imatinib (as mesylate) dose is 260 mg/m²/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-α therapy.

Ph+ ALL

The recommended dose of Imatinib (as mesylate) is 600 mg/day for adult patients with relapsed/refractory Ph+ ALL.

MDS/MPD

The recommended dose of Imatinib (as mesylate) is 400 mg/day for adult patients with MDS/MPD.

ASM

The recommended dose of Imatinib (as mesylate) is 400 mg/day for adult patients with ASM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Imatinib (as mesylate) 400 mg/day may be considered for patients with ASM not responding satisfactorily to other therapies.

For patients with ASM associated with eosinophilia, a clonal haematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

HES/CEL

The recommended dose of Imatinib (as mesylate) is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg/day is recommended. Dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

DFSP

The recommended dose of Imatinib (as mesylate) is 800 mg/day for adult patients with DFSP.

GIST

The recommended dose of Imatinib (as mesylate) is 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically indicated, in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of severe adverse drug reactions.

The recommended dose of Imatinib (as mesylate) is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST.

Dose Modification Guidelines

Concomitant Strong CYP3A4 Inhibitors

The use of concomitant strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampicin, phenobarbital). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dosage of Imatinib mesylate should be increased by at least 50%, and clinical response should be carefully monitored.

Hepatic Impairment

Patients with mild and moderate hepatic impairment do not require a dose adjustment and should be treated as per the recommended dose. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

Renal Impairment

Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment doses greater than 400 mg are not recommended.

Imatinib should be used with caution in patients with severe renal

impairment.

Dose Adjustment for Hepatotoxicity and Non-Haematologic Adverse Reactions

If elevations in bilirubin > 3 x institutional upper limit of normal (IULN) or liver transaminases > 5 x IULN occur, Imatinib mesylate should be withheld until bilirubin levels have returned to a < 1.5 x IULN and transaminase levels to < 2.5 x IULN. In adults, treatment with Imatinib (as mesylate) may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg, 600 mg to 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same circumstances from 340 mg/m²/day to 260 mg/m²/day or from 260 mg/m²/day to 200 mg/m²/day, respectively.

If a severe non-haematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), Imatinib mesylate should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

Dose Adjustment for Haematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropaenia and thrombocytopenia are recommended as indicated in Table 1.

Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia

ASM associated with eosinophilia (starting dose 100 mg)	ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L	1. Stop Imatinib mesylate until ANC 1.5 x 10 ⁹ /L and platelets 75 x 10 ⁹ /L	2. Resume treatment with Imatinib (as mesylate) at previous dose (i.e., dose before severe adverse reaction)		
HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L	1. Stop Imatinib mesylate until ANC 1.5 x 10 ⁹ /L and platelets 75 x 10 ⁹ /L	2. Resume treatment with Imatinib (as mesylate) at previous dose (i.e., dose before severe adverse reaction)		
Chronic Phase CML (starting dose 400 mg)	ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L	1. Stop Imatinib mesylate until ANC 1.5 x 10 ⁹ /L and platelets 75 x 10 ⁹ /L	2. Resume treatment with Imatinib (as mesylate) at the original starting dose of 400 mg	3. If recurrence of ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L, repeat step 1 and resume Imatinib (as mesylate) at a reduced dose of 300 mg	
MDS/MPD, ASM and HES/CEL (starting dose 400 mg)	ANC < 0.5 x 10 ⁹ /L and/or platelets < 10 x 10 ⁹ /L	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy)	2. If cytopenia is unrelated to leukaemia, reduce dose of Imatinib (as mesylate) to 400 mg	3. If cytopenia persists 2 weeks, reduce further to 300mg	4. If cytopenia persists 4 weeks and is still unrelated to leukaemia, stop Imatinib mesylate until ANC 1.1 x 10 ⁹ /L and platelets 20 x 10 ⁹ /L and then resume treatment at 300 mg
DFSP (starting dose 800 mg)	ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L	1. Stop Imatinib mesylate until ANC 1.5 x 10 ⁹ /L and platelets 75 x 10 ⁹ /L	2. Resume treatment with Imatinib (as mesylate) at 600 mg	3. In the event of recurrence of ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L, repeat step 1 and resume Imatinib (as mesylate) at reduced dose of 400 mg	
Paediatric newly diagnosed chronic phase	ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L	1. Stop Imatinib mesylate until ANC 1.5 x 10 ⁹ /L and platelets 75 x 10 ⁹ /L	2. Resume treatment with Imatinib (as mesylate) at previous dose (i.e., dose before severe adverse reaction)	3. In the event of recurrence of ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L, repeat step 1 and resume Imatinib (as mesylate) at reduced dose of 260 mg/m ²	
CML (starting dose 340 mg/m ²)	ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L	1. Stop Imatinib mesylate until ANC 1.5 x 10 ⁹ /L and platelets 75 x 10 ⁹ /L	2. Resume treatment with Imatinib (as mesylate) at previous dose (i.e., dose before severe adverse reaction)	3. In the event of recurrence of ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L, repeat step 1 and resume Imatinib (as mesylate) at reduced dose of 200 mg/m ²	
Paediatric patients with chronic phase CML recurring after transplant or resistant to Interferon (starting dose 260 mg/m ²)	ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L	1. Stop Imatinib mesylate until ANC 1.5 x 10 ⁹ /L and platelets 75 x 10 ⁹ /L	2. Resume treatment with Imatinib (as mesylate) at previous dose (i.e., dose before severe adverse reaction)	3. In the event of recurrence of ANC < 1.0 x 10 ⁹ /L and/or platelets < 50 x 10 ⁹ /L, repeat step 1 and resume Imatinib (as mesylate) at reduced dose of 200 mg/m ²	

Side Effects & Drug Interactions

Chronic Myeloid Leukaemia

The most frequently reported drug-related adverse reactions were Oedema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhoea and rash. Oedema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of Imatinib mesylate.

A variety of adverse reactions represent local or general fluid retention including pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema.

These reactions were usually managed by interrupting Imatinib mesylate treatment and using diuretics or other appropriate supportive care measures.

Haematologic Toxicity

In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients.

The frequency of Grade 3 or 4 neutropenia and thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase compared to chronic phase. The median duration of the neutropenic and thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively.

These reactions can usually be managed with either a reduction of the dose or an interruption of treatment with Imatinib mesylate, but in rare cases require permanent discontinuation of treatment.

Hepatotoxicity

Severe elevation of transaminases or bilirubin occurred in approximately 5% of CML patients and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately 1 week).

Adverse Reactions in Paediatric Population

Nausea and vomiting were the most commonly reported individual adverse reactions with an incidence similar to that seen in adult patients.

Adverse Reactions in Other Sub-populations

In older patients (≥ 65 years old), with the exception of oedema, where it was more frequent, there was no evidence of an increase in the incidence or severity of adverse reactions. In women there was an increase in the frequency of neutropenia, as well as Grade 3/4: superficial oedema, headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen that were related to race.

Acute Lymphoblastic Leukaemia

The most frequently reported drug-related adverse reactions reported in the Ph+ ALL were mild nausea and vomiting, diarrhoea, myalgia, muscle cramps and rash, which were easily manageable. Superficial oedema was a common finding and were described primarily as periorbital or lower limb oedemas. These oedemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Imatinib mesylate.

Myelodysplastic/Myeloproliferative Diseases

Adverse reactions viz: nausea, diarrhoea, anaemia, fatigue, muscle cramp, arthralgia, periorbital oedema were reported in at least 10% of the patients treated with Imatinib mesylate for MDS/MPD.

Aggressive Systemic Mastocytosis

All ASM patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were diarrhoea, nausea, muscle cramps, dyspnoea, fatigue, peripheral oedema, anaemia, pruritus, rash and lower respiratory tract infection.

Hyperesoinophilic Syndrome and Chronic Eosinophilic Leukaemia

The safety profile in the HES/CEL patient population does not appear to be different from the safety profile of Imatinib mesylate observed in other haematologic malignancy populations, such as Ph+ CML. All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders.

Haematological abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia and anaemia.

Dermatofibrosarcoma Protuberans

Adverse reactions viz: nausea, diarrhoea, vomiting, anaemia, fatigue, rash, periorbital oedema were reported in at least 10% of patients treated with Imatinib mesylate for DFSP.

Gastrointestinal Stromal Tumours

Unresectable and/or Malignant Metastatic GIST

The most frequently reported adverse reactions were oedema, fatigue,

nausea, abdominal pain, diarrhoea, rash, vomiting and myalgia, anaemia and anorexia. Superficial oedema, most frequently periorbital or lower extremity oedema was managed with diuretics, other supportive measures, or by reducing the dose of Imatinib mesylate.

Adjuvant Treatment of GIST

The most frequently reported adverse reactions include diarrhoea, fatigue, nausea, oedema, decreased haemoglobin, rash, vomiting and abdominal pain.

Drug Interactions

Agents Inducing CYP3A4 Metabolism

Pre-treatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Imatinib mesylate, increased Imatinib mesylate oral-dose clearance by 3.8-fold, which significantly ($p < 0.05$) decreased mean C_{max} and AUC. If alternative treatment cannot be administered, a dose adjustment should be considered.

Agents Inhibiting CYP3A4 Metabolism

Caution is recommended when administering Imatinib mesylate with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, neflavinir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of imatinib and should be avoided. Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations.

Interactions with Drugs Metabolized by CYP3A4

Imatinib mesylate increases the mean C_{max} and AUC of simvastatin, suggesting an inhibition of the CYP3A4 by Imatinib mesylate. Particular caution is recommended when administering Imatinib mesylate with CYP3A4 substrates that have a narrow therapeutic window (e.g., alfentanil, cyclosporine, diltiazem, ergotamine, fentanyl, pimozide, quinidine, sirolimus or tacrolimus).

Imatinib mesylate will increase plasma concentrations of other CYP3A4 metabolized drugs (e.g., trazolam, benzodiazepines, diltiazem, dydrogeline calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.). Because warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin instead of warfarin.

Interactions with Drugs Metabolized by CYP2D6

In vitro, Imatinib mesylate inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when co-administered with Imatinib mesylate. Caution is recommended.

Interaction with Acetaminophen

In vitro, Imatinib mesylate inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μ M) at therapeutic levels.

Systemic exposure to acetaminophen is expected to be increased when co-administered with Imatinib mesylate. No specific studies in humans have been performed and caution is recommended.

Warnings and Precautions

Fluid Retention and Oedema

Imatinib mesylate is often associated with oedema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided.

Haematologic Toxicity

Treatment with Imatinib mesylate is associated with anaemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. In Paediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

Severe Congestive Heart Failure and Left Ventricular Dysfunction

Severe congestive heart failure and left ventricular dysfunction have

occasionally been reported in patients taking Imatinib mesylate. Most of the patients with reported cardiac reactions have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease.

Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur with Imatinib mesylate. Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly, or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with Imatinib mesylate.

Gastrointestinal Disorders

Imatinib mesylate is sometimes associated with GI irritation. Imatinib mesylate should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

Hyperesoinophilic Cardiac Toxicity

In patients with hyperesoinophilic syndrome and cardiac involvement, cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of Imatinib mesylate therapy.

The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Imatinib mesylate. Myelodysplastic/myeloproliferative disease and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with Imatinib mesylate should be considered at the initiation of therapy.

Dermatologic Toxicities

Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with use of Imatinib mesylate.

Hypothyroidism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Imatinib mesylate. TSH levels should be closely monitored in such patients.

Use in Pregnancy

Pregnancy Category D

Women of childbearing potential should be advised to avoid becoming pregnant while taking Imatinib mesylate. Sexually active female patients taking Imatinib mesylate should use adequate contraception. Imatinib (as mesylate) was teratogenic in rats when administered during organogenesis at doses approximately equal to the maximum human dose of 800 mg/day based on body surface area. Significant post-implantation loss was seen in female rats administered imatinib (as mesylate) at doses approximately one-half the maximum human dose of 800 mg/day based on body surface area.

Non-clinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Positive genotoxic effects were obtained for imatinib in an in vitro mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Imatinib was not genotoxic when tested in an in vitro bacterial cell assay (Ames test), an in vitro mammalian cell assay (mouse lymphoma) and an in vivo rat micronucleus assay.

Human studies on male patients receiving Imatinib mesylate and its effect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on Imatinib mesylate treatment should consult with their physician.

Use in Specific Populations

Pregnancy

Pregnancy Category D

Imatinib (as mesylate) can cause foetal harm when administered to a pregnant woman.

There are no adequate and well-controlled studies with Imatinib mesylate in pregnant women. Women should be advised not to become pregnant when taking Imatinib mesylate. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus.

Nursing Mothers

Imatinib and its active metabolite are excreted into human milk. Considering the combined concentration of imatinib and active metabolite, a breastfed infant could receive up to 10 % of the maternal therapeutic dose based on body weight. Because of the potential for serious adverse reactions in nursing infants from Imatinib mesylate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use

Imatinib mesylate safety and efficacy have been demonstrated in children with newly diagnosed Ph+ chronic phase CML and in children with Ph+ chronic phase CML with recurrence after stem cell transplantation or resistance to interferon- α therapy. There are no data in children under 2 years of age. Follow-up in children with newly diagnosed Ph+ chronic phase CML is limited.

Geriatric Use

No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of oedema. The efficacy of Imatinib mesylate was similar in older and younger patients.

Hepatic Impairment

Patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function.

Renal Impairment

Dose reductions are necessary for patients with moderate and severe renal impairment.

Overdosage and Contraindications

Experience with doses greater than 800 mg is limited. Isolated cases of Imatinib (as mesylate) overdose have been reported. In the event of overdosage, the patient should be observed and appropriate supportive treatment given.

Contraindications

Hypersensitivity to Imatinib mesylate or to any other ingredients used in the formulation.

Storage

Store in a cool, dry place, protected from light. Keep out of reach of children.

Shelf life

24 months from the date of manufacturing.

Presentation

Imatinib (as mesylate) is supplied as 100 mg and 400 mg film coated tablets for oral consumption.

