# Relisylate™


RELIC
Biotechnology Pvt. Ltd.
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For the use only of a Registered Medical Practitioner / Oncologist or a Cancer Hospital or a Laboratory

# Imatinib Capsules IP 100mg & Imatinib Tablets IP 100mg/400mg

## Relisylate™

Rx only

COMPOSITION:

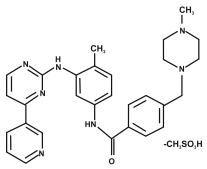
**Relisylate™**
Imatinib Tablets IP 100mg
Each film coated tablets contains
Imatinib Mesylate IP
Equivalent to Imatinib 100mg
Excipients q.s.
Colours: Iron Oxide of Yellow, Iron Oxide of Red & Titanium Dioxide IP

**Relisylate™**
Imatinib Tablets IP 400mg
Each film coated tablets contains
Imatinib Mesylate IP
Equivalent to Imatinib 400mg
Excipients q.s.
Colours: Iron Oxide of Yellow, Iron Oxide of Red & Titanium Dioxide IP

**Relisylate™**
Imatinib Capsules IP 100mg
Each capsule contains
Imatinib Mesylate IP
Equivalent to Imatinib 100mg
Excipients q.s.
Colour: Approved colours used in capsule shell

Description

Imatinib is a small molecule kinase inhibitor. Imatinib 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-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate and its structural formula is:




Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O\cdot CH_4SO_3$ and its molecular weight is 589.7. Imatinib mesylate is soluble in aqueous buffers ≤pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol, and ethanol, but is insoluble in n-octanol, acetone, and acetonitrile.

Clinical particulars

Mechanism of Action

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 leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. Imatinib inhibits colony formation in assays using ex vivo peripheral blood and bone marrow samples from CML patients.

In vivo, imatinib inhibits tumor growth of BCR-ABL transfected murine myeloid cells as well as BCR-ABL positive leukemia 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

The pharmacokinetics of Imatinib have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. The pharmacokinetics of Imatinib are similar in CML and GIST patients. Imatinib is well absorbed after oral administration with Cmax 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. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5- to 2.5-fold at steady state when Imatinib is dosed once-daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in in vitro experiments is approximately 95%, mostly to albumin and 1-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. Human liver microsome studies demonstrated that Imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with Ki values of 27, 7.5, and 8 μM, respectively.

Imatinib elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral 14C-labeled dose of imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Typically, clearance of imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to 14 L/h. 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 AND USAGE

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

Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase.

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

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

Adult patients with Ph+ Acute Lymphoblastic Leukemia (ALL)

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

Pediatric patients with Ph+ Acute Lymphoblastic Leukemia (ALL)

Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.

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.

Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)

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

Dermatofibrosarcoma Protuberans (DFSP)

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

Kit+ Gastrointestinal Stromal Tumors (GIST)

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

Adjuvant Treatment of GIST

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

NON CLINICAL TOXICOLOGY

Carcinogenesis , Mutagenesis , Impairment of Fertility

In the 2-year rat carcinogenicity study administration of imatinib at 15, 30, and 60 mg/kg/day resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/day and females at ≥30 mg/kg/day. Target organs for neoplastic changes were the kidneys (renal tubule and renal pelvis), urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach. Neoplastic lesions were not seen at: 30 mg/kg/day for the kidneys, urinary bladder, urethra, small intestine, parathyroid glands, adrenal glands and non-glandular stomach, and 15 mg/kg/day for the preputial and clitoral gland. The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day, representing approximately 0.5 to 4 or 0.3 to 2.4 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 to 3.0 times the daily exposure in children (based on AUC) at 340 mg/m$^2$. The renal tubule adenoma/carcinoma, renal pelvis transitional cell neoplasms, the urinary bladder and urethra transitional cell papillomas, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumors of the adrenal glands and the non-glandular stomach papillomas/carcinomas were noted at 60 mg/kg/day. The relevance of these findings in the rat carcinogenicity study for humans is not known.

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. Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay, 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.

In a study of fertility, male rats were dosed for 70 days prior to mating and female rats were dosed 14 days prior to mating and through to gestational Day 6.

Testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately three-fourths the maximum clinical dose of 800 mg/day based on body surface area. This was not seen at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg). The fertility of male and female rats was not affected.

In a pre- and postnatal development study in female rats dosed with imatinib mesylate at 45 mg/kg (approximately one-half the maximum human dose of 800 mg/day, based on body surface area) from gestational Day 6 until the end of lactation, red vaginal discharge was noted on either gestational Day 14 or 15. In the first generation offspring at this same dose level, mean body weights were reduced from birth until terminal sacrifice. First generation offspring fertility was not affected but reproductive effects were noted at 45 mg/kg/day including an increased number of resorptions and a decreased number of viable fetuses.

Fertility was not affected in the preclinical fertility and early embryonic development study although lower testes and epididymal weights as well as a reduced number of motile sperm were observed in the high dose males rats. In the preclinical pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by Imatinib.

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

Animal Toxicology and/or Pharmacology

Toxicities from Long-Term Use

It is important to consider potential toxicities suggested by animal studies, specifically, liver, kidney, and cardiac toxicity and immunosuppression. Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia. Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these animals. An increased rate of opportunistic infections was observed with chronic imatinib treatment in laboratory animal studies. In a 39 week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans). Additional long-term toxicities were identified in a 2-year rat study. Histopathological examination of the treated rats that died on study revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Non-neoplastic lesions seen in this 2-year study which were not identified in earlier preclinical studies were the cardiovascular system, pancreas, endocrine organs and teeth. The most important changes included cardiac hypertrophy and dilatation, leading to signs of cardiac insufficiency in some animals.

CONTRAINDICATIONS

Contraindicated in patients having hypersensitivity to Imatinib or to other constituents of Imatinib Tablets/Capsules.

WARNINGS AND PRECAUTIONS

Fluid Retention and Edema

Imatinib is often associated with edema and occasionally serious fluid retention [see Adverse Reactions]. 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. The probability of edema was increased with higher Imatinib dose and age >65 years in the CML studies. Severe superficial edema was reported in 1.5% of newly diagnosed CML patients taking Imatinib, and in 2%–6% of other adult CML patients taking Imatinib. In addition, other severe fluid

retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) reactions were reported in 1.3% of newly diagnosed CML patients taking Imatinib, and in 2%–6% of other adult CML patients taking Imatinib. Severe fluid retention was reported in 9% to 13.1% of patients taking Imatinib for GIST [see Adverse Reactions (6.9)]. In a randomized trial in patients with newly diagnosed Ph+ CML in chronic phase comparing Imatinib and nilotinib, severe (Grade 3 or 4) fluid retention occurred in 2.5% of patients receiving Imatinib and in 3.9% of patients receiving nilotinib 300 mg bid. Effusions (including pleural effusion, pericardial effusion, ascites) or pulmonary edema were observed in 2.1% (none were Grade 3 or 4) of patients in the Imatinib arm and 2.2% (0.7% Grade 3 or 4) of patients in the nilotinib 300 mg bid arm.

Hematologic Toxicity

Treatment with Imatinib is associated with anemia, 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 pediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy.

Congestive Heart Failure and Left Ventricular Dysfunction

Congestive heart failure and left ventricular dysfunction have been reported in patients taking Imatinib. Most of the patients with reported cardiac reactions have had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Imatinib compared to 0.9% of patients taking IFN + Ara-C. In another randomized trial with newly diagnosed Ph+ CML patients in chronic phase that compared Imatinib and nilotinib, cardiac failure was observed in 1.1% of patient in the Imatinib arm and 2.2% of patients in the nilotinib 300 mg bid arm and severe (Grade 3 or 4) cardiac failure occurred in 0.7% of patients in each group. Patients with cardiac disease or risk factors for cardiac 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.

Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur with Imatinib. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of Imatinib. 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 Imatinib interruption and/or dose reduction.

When Imatinib is combined with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended.

Hemorrhage

In a trial of Imatinib versus IFN + Ara-C in patients with the newly diagnosed CML, 1.8% of patients had Grade 3/4 hemorrhage. In the Phase 3 unresectable or metastatic GIST studies, 211 patients (12.9%) reported Grade 3/4 hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 7 patients (5%) had a total of 8 CTC Grade 3/4 hemorrhages; gastrointestinal (GI) (3 patients), intra-tumoral (3 patients) or both (1 patient). Gastrointestinal tumor sites may have

Gastrointestinal Disorders

Imatinib is sometimes associated with GI irritation. Imatinib 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.

Hypereosinophilic Cardiac Toxicity

In patients with hypereosinophilic syndrome with occult infiltration of HES cells within the myocardium, cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of Imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Imatinib.

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 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. In some cases of bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome reported during postmarketing surveillance, a recurrent dermatologic reaction was observed upon rechallenge. Several foreign postmarketing reports have described cases in which patients tolerated the reintroduction of Imatinib therapy after resolution or improvement of the bullous reaction. In these instances, Imatinib was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

Hypothyroidism

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

Embryo-fetal Toxicity

Imatinib can cause fetal harm when administered to a pregnant woman. Imatinib 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 mesylate at doses approximately one-half the maximum human dose of 800 mg/day based on body surface area. Sexually active female patients of reproductive potential taking Imatinib should use highly effective contraception. 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 a fetus.

Children and Adolescents

Growth retardation has been reported in children and pre-adolescents receiving Imatinib. The long term effects of prolonged treatment with Imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under Imatinib treatment is recommended.

Tumor Lysis Syndrome

Cases of Tumor Lysis Syndrome (TLS), including fatal cases, have been reported in patients with CML, GIST, ALL and eosinophilic leukemia receiving Imatinib. The patients at risk of TLS are those with tumors having a high proliferative rate or high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Imatinib.

Driving and Using Machinery

Reports of motor vehicle accidents have been received in patients receiving Imatinib. While most of these reports are not suspected to be caused by Imatinib, patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with Imatinib. Therefore, caution should be recommended when driving a car or operating machinery.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies or malignant sarcomas, as appropriate. 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 treatment can be given as a once-daily dose in CML and Ph+ ALL. Alternatively, in children with CML the daily dose may be split into two-one portion dosed in the morning and one portion in the evening. There is no experience with Imatinib treatment in children under 1 year of age.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg tablet, and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

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 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 non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic 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 hematologic or cytogenetic response.

Pediatric Patients with Ph+ CML CP

The recommended dose of Imatinib for children with newly diagnosed Ph+ CML is 340 mg/m$^2$/day (not to exceed 600 mg).

Adults Patients with Ph+ ALL

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

Pediatric Patients with Ph+ ALL

The recommended dose of Imatinib to be given in combination with chemotherapy to children with newly diagnosed Ph+ ALL is 340 mg/m$^2$/day (not to exceed 600 mg).

MDS/MPD

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

ASM

The recommended dose of Imatinib 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 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 hematological disease related to the fusion kinase FIP1L1-PDGFR , 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 is 400 mg/day for adult patients with HES/CEL. For HES/CEL patients with demonstrated FIP1L1-PDGFR 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 is 800 mg/day for adult patients with DFSP.

Metastatic or Unresectable GIST

The recommended dose of Imatinib 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.

2Adjuvant GIST

The recommended dose of Imatinib is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In clinical trials, one year of Imatinib and three years of Imatinib were studied. In the patient population defined in Study 2, three years of Imatinib is recommended. The optimal treatment duration with Imatinib is not known.

Dose Modification Guidelines

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dosage of Imatinib 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 per the recommended dose. A 25% decrease in the

recommended dose should be used for patients with severe hepatic impairment [see Use in Specific Populations (8.6)].
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. A dose of 100 mg/day was tolerated in two patients with severe renal impairment.
Dose Adjustment for Hepatotoxicity and Non-Hematologic Adverse Reactions
If elevations in bilirubin greater than 3 times the institutional upper limit of normal (IULN) or in liver transaminases greater than 5 times the IULN occur, Imatinib should be withheld until bilirubin levels have returned to a less than 1.5 times the IULN and transaminase levels to less than 2.5 times the IULN. In adults, treatment with Imatinib 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/m$^2$/day to 260 mg/m$^2$/day.
If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), Imatinib 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 Hematologic Adverse Reactions
Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in the following Table
Dose Adjustments for Neutropenia and Thrombocytopenia

| | | |
|---|---|---|
| ASM associated with eosinophilia (starting dose 100mg) | ANC<1.0 x $10^9$/L and/or platelets <50 x $10^9$/L | Stop Imatinib until ANC ≥1.5 x $10^9$/L and platelets ≥75 x $10^9$/L Resume treatment with Imatinib at previous dose (i.e., dose before severe adverse reaction) |
| HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100mg) | ANC <1.0 x $10^9$/L and/or platelets <50 x $10^9$/L | 1.Stop Imatinib until ANC ≥1.5 x $10^9$/L and platelets ≥ 75 x $10^9$/L Resume treatment with Imatinib at previous dose (i.e., dose before severe adverse reaction) |
| Chronic Phase CML (starting dose 400mg) MDS/MPD, ASM and HES/CEL (starting dose 400mg) GIST (starting dose 400mg) | ANC <1.0 x $10^9$/L and/or platelets <50 x $10^9$/L | 1.Stop Imatinib until ANC ≥1.5 x 109/L and platelets ≥75 x $10^9$/L 2.Resume treatment with Imatinib at the original starting dose of 400mg if recurrence of ANC <1.0 x $10^9$/L and/or platelets <50 x $10^9$/L, repeat step 1 and resume Imatinib at a reduced dose of 300mg |
| Ph+ CML : Accelerated Phase and Blast Crisis (starting dose 600mg) Ph+ ALL (starting dose 600 g) | ANC <0.5 x $10^9$/L and/or platelets <10 x $10^9$/L | 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of Imatinib to 400mg 3. If cytopenia persists 2 weeks, reduce further to 300mg If cytopenia persists 4 weeks and is still unrelated to leukemia, stop Imatinib until ANC ≥1 x $10^9$/L and platelets ≥20 x $10^9$/L and then resume treatment at 300mg |
| DFSP (starting dose 800 mg) | ANC <1.0 x $10^9$/L and/or platelets <50 x $10^9$/L | 1.Stop Imatinib until ANC ≥1.5 x $10^9$/L and platelets ≥75 x $10^9$/L 2.Resume treatment with Imatinib at 600mg 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 at reduced dose of 400mg |
| Pediatric newly diagnosed chronic phase 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 until ANC ≥1.5 x $10^9$/L and platelets ≥75 x $10^9$/L 2.Resume treatment with Imatinib at previous dose (i.e., dose before severe adverse reaction)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 at reduced dose of 260 mg/m$^2$ |

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice.
Chronic Myeloid Leukemia
The majority of Imatinib-treated patients experienced adverse reactions at some time, most adverse reactions were of mild-to-moderate grade. Imatinib was discontinued due to drug-related adverse reactions in 2.4% of patients receiving Imatinib in the randomized trial of newly diagnosed patients with Ph+ CML in chronic phase comparing Imatinib versus INF+Ara-C, and in 12.5% of patients receiving Imatinib in the randomized trial of newly diagnosed patients with Ph+ CML in chronic phase comparing Imatinib and nilotinib. Imatinib was discontinued due to drug-related adverse reactions in 4% of patients in chronic phase after failure of interferon-alpha therapy, in 4% of patients in accelerated phase and in 5% of patients in blast crisis.
The most frequently reported drug-related adverse reactions were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (Table 2 and Table 3 for newly diagnosed CML, Table 4 for other CML patients). Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of Imatinib. The frequency of severe superficial edema was 1.5% - 6%.
A variety of adverse reactions represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These reactions appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day), and are more common in the elderly. These reactions were usually managed by interrupting Imatinib treatment and using diuretics or other appropriate supportive care measures. A few of these reactions may be serious or life threatening, and one patient with blast crisis died with pleural effusion, congestive heart failure, and renal failure.
Hematologic and Biochemistry Laboratory Abnormalities
Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in all studies, with a higher frequency at doses ≥750 mg (Phase 1 study). The occurrence of cytopenias in CML patients was also dependent on the stage of the disease.
In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients (see Tables 5, 6, and 7). 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 (see Tables 4 and 5). 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, but in rare cases require permanent discontinuation of treatment.
Hepatotoxicity
Severe elevation of transaminases or bilirubin occurred in approximately 5% of CML patients (see Tables 6 and 7) and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately 1 week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1.0% of CML patients. One patient, who was taking acetaminophen regularly for fever, died of acute liver failure. In the Phase 2 GIST trial, Grade 3 or 4 SGPT (ALT) elevations were observed in 6.8% of patients and Grade 3 or 4 SGOT (AST) elevations were observed in 4.8% of patients. Bilirubin elevation was observed in 2.7% of patients.
Adverse Reactions in Pediatric Population
Pediatric and young adult patients with very high risk ALL, defined as those with an expected 5 year event-free survival (EFS) less than 45%, were enrolled after induction therapy on a multicenter, non-randomized cooperative group pilot protocol. The study population included patients with a median age of 10 years (1 to 21 years), 61% of whom were male, 75% were white, 7% were black and 6% were Asian/Pacific Islander. Patients with Ph+ ALL (n=92) were assigned to receive Imatinib and treated in 5 successive cohorts. Imatinib exposure was systematically increased in successive cohorts by earlier introduction and more prolonged duration.
The safety of Imatinib given in combination with intensive chemotherapy was evaluated by comparing the incidence of grade 3 and 4 adverse events, neutropenia (<750/mcL) and thrombocytopenia (<75,000/mcL) in the 92 patients with Ph+ ALL compared to 65 patients with Ph- ALL enrolled on the trial who did not receive Imatinib. The safety was also evaluated comparing the incidence of adverse events in cycles of therapy administered with or without Imatinib. The protocol included up to 18 cycles of therapy. Patients were exposed to a cumulative total of 1425 cycles of therapy, 778 with Imatinib and 647 without Imatinib.
Adverse Reactions in Other Subpopulations
In older patients (≥65 years old), with the exception of edema, 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 1/2 superficial edema, headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen that were related to race but the subsets were too small for proper evaluation.
Acute Lymphoblastic Leukemia
The adverse reactions were similar for Ph+ ALL as for Ph+ CML. The most frequently reported drug-related adverse reactions reported in the Ph+ ALL studies were mild nausea and vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial edema was a common finding in all studies and were described primarily as periorbital or lower limb edemas. These edemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Imatinib.
Myelodysplastic/Myeloproliferative Diseases
Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Imatinib for MDS/MPD in the phase 2 study.
Aggressive Systemic Mastocytosis
All ASM patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritus, rash and lower respiratory tract infection. None of the 5 patients in the phase 2 study with ASM discontinued Imatinib due to drug-related adverse reactions or abnormal laboratory values.
Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia
The safety profile in the HES/CEL patient population does not appear to be different from the safety profile of Imatinib observed in other hematologic malignancy populations, such as Ph+ CML. All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia, and anemia.
Dermatofibrosarcoma Protuberans
Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the 12 patients treated with Imatinib for DFSP in the phase 2 study
Gastrointestinal Stromal Tumors
Unresectable and/or Malignant Metastatic GIST
In the Phase 3 trials, the majority of Imatinib-treated patients experienced adverse reactions at some time. The most frequently reported adverse reactions were edema, fatigue, nausea, abdominal pain, diarrhea, rash, vomiting, myalgia, anemia, and anorexia. Drug was discontinued for adverse reactions in a total of 89 patients (5.4%). Superficial edema, most frequently periorbital or lower extremity edema was managed with diuretics, other supportive measures, or by reducing the dose of Imatinib [see Dosage and Administration (2.12)]. Severe (CTC Grade 3/4) edema was observed in 182 patients (11.1%).
Adjuvant Treatment of GIST
In Study 1, the majority of both Imatinib and placebo treated patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting, and abdominal pain. No new adverse reactions were reported in the adjuvant GIST treatment setting that had not been previously reported in other patient populations including patients with unresectable and/or malignant metastatic GIST. Drug was discontinued for adverse reactions in 57 patients (17%) and 11 patients (3%) of the Imatinib and placebo treated patients respectively. Edema, gastrointestinal disturbances (nausea, vomiting, abdominal distention and diarrhea), fatigue, low hemoglobin, and rash were the most frequently reported adverse reactions at the time of discontinuation.
In Study 2, discontinuation of therapy due to adverse reactions occurred in 15 patients (8%) and 27 patients (14%) of the Imatinib 12-month and 36-month treatment arms, respectively. As in previous trials the most common adverse reactions were diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting, and abdominal pain.
Additional Data from Multiple Clinical Trials
The following adverse reactions have been reported during clinical trials of Imatinib.
Cardiac Disorders:
Estimated 1%–10%: palpitations, pericardial effusion
Estimated 0.1%-1%: congestive cardiac failure, tachycardia, pulmonary edema
Estimated 0.01%-0.1%: arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris
Vascular Disorders:
Estimated 1%-10%: flushing, hemorrhage
Estimated 0.1%-1%: hypertension, hypotension, peripheral coldness, Raynauds phenomenon, hematoma, subdural hematoma
Investigations:
Estimated 1%–10%: blood CPK increased, blood amylase increased
Estimated 0.1%–1%: blood LDH increased
Skin and Subcutaneous Tissue Disorders:
Estimated 1%–10%: dry skin, alopecia, face edema, erythema, photosensitivity reaction, nail disorder, purpura
Estimated 0.1%–1%: exfoliative dermatitis, bullous eruption, psoriasis, rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise,
hypotrichosis, skin hypopigmentation, skin hyperpigmentation, onychoclasis, folliculitis, petechiae, erythema multiforme
Estimated 0.01%–0.1%: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discoloration, angioneurotic edema, leucocytoclastic vasculitis
Gastrointestinal Disorders:
Estimated 1%-10%: abdominal distention, gastroesophageal reflux, dry mouth, gastritis
Estimated 0.1%-1%: gastric ulcer, stomatitis, mouth ulceration, eructation, melena, esophagitis, ascites, hematemesis, chelitis, dysphagia, pancreatitis
Estimated 0.01%-0.1%: colitis, ileus, inflammatory bowel disease
General Disorders and Administration Site Conditions:
Estimated 1%-10%: weakness, anasarca, chills
Estimated 0.1%-1%: malaise
Blood and Lymphatic System Disorders:
Estimated 1%-10%: pancytopenia, febrile neutropenia, lymphopenia, eosinophila
Estimated 0.1%-1%: thrombocythemia, bone marrow depression, lymphadenopathy
Estimated 0.01%-0.1%: hemolytic anemia, aplastic anemia
Hepatobiliary Disorders:
Estimated 0.1%-1%: hepatitis, jaundice
Estimated 0.01%-0.1%: hepatic failure and hepatic necrosis1
Immune System Disorders:
Estimated 0.01%-0.1%: angioedema
Infections and Infestations:
Estimated 0.1%-1%: sepsis, herpes simplex, herpes zoster, cellulitis, urinary tract infection, gastroenteritis
Estimated 0.01%-0.1%: fungal infection
Metabolism and Nutrition Disorders:
Estimated 1%-10%: weight decreased, decreased appetite
Estimated 0.1%–1%: dehydration, gout, increased appetite, hyperuricemia, hypercalcemia, hyperglycemia, hyponatremia, hyperkalemia, hypomagnesemia
Musculoskeletal and Connective Tissue Disorders:
Estimated 1%-10%: joint swelling
Estimated 0.1%–1%: joint and muscle stiffness, muscular weakness, arthritis
Nervous System/Psychiatric Disorders:
Estimated 1%-10%: paresthesia, hypesthesia
Estimated 0.1%-1%: syncope, peripheral neuropathy, somnolence, migraine, memory impairment, libido decreased, sciatica, restless leg syndrome, tremor
Estimated 0.01%-0.1%: Increased intracranial pressure1, confusional state, convulsions, optic neuritis
Renal and Urinary Disorders:
Estimated 0.1%-1%: renal failure acute, urinary frequency increased, hematuria, renal pain
Reproductive System and Breast Disorders:
Estimated 0.1%-1%: breast enlargement, menorrhagia, sexual dysfunction, gynecomastia, erectile dysfunction, menstruation irregular, nipple pain, scrotal edema
Respiratory, Thoracic and Mediastinal Disorders:
Estimated 1%-10%: epistaxis
Estimated 0.1%-1%: pleural effusion
Estimated 0.01%-0.1%: interstitial pneumonitis, pulmonary fibrosis, pleuritic pain, pulmonary hypertension, pulmonary hemorrhage
Eye, Ear and Labyrinth Disorders:
Estimated 1%–10%: conjunctivitis, vision blurred, orbital edema, conjunctival hemorrhage, dry eye
Estimated 0.1%–1%: vertigo, tinnitus, eye irritation, eye pain, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema, hearing loss, cataract
Estimated 0.01%-0.1%: papilledema, glaucoma

DRUG INTERACTIONS
Agents Inducing CYP3A Metabolism
Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Imatinib, increased Imatinib oral-dose clearance by 3.8-fold, which significantly ($p<0.05$) decreased mean Cmax and AUC.
Similar findings were observed in patients receiving 400-1200 mg/day Imatinib concomitantly with enzyme-inducing anti-epileptic drugs (EIAED) (e.g., carbamazepine, oxcarbamazepine, phenytoin, fosphenytoin, phenobarbital, and primidone). The mean dose normalized AUC for imatinib in the patients receiving EIAED's decreased by 73% compared to patients not receiving EIAED.
Concomitant administration of Imatinib and St. John's Wort led to a 30% reduction in the AUC of imatinib.
Consider alternative therapeutic agents with less enzyme induction potential in patients when rifampin or other CYP3A4 inducers are indicated. Imatinib doses up to 1200 mg/day (600 mg BID) have been given to patients receiving concomitant strong CYP3A4 inducers.
Agents Inhibiting CYP3A Metabolism
There was a significant increase in exposure to imatinib (mean Cmax and AUC increased by 26% and 40%, respectively) in healthy subjects when Imatinib was coadministered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution is recommended when administering Imatinib with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, 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 increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Imatinib. Particular caution is recommended when administering Imatinib with CYP3A4 substrates that have a narrow therapeutic window (e.g., alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus or tacrolimus).
Imatinib will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine 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
Imatinib increased the mean Cmax and AUC of metoprolol by approximately 23% suggesting that Imatinib has a weak inhibitor y effect on CYP2D6-mediated metabolism. No dose adjustment is necessary, however, caution is recommended when administering Imatinib with CYP2D6 substrates that have a narrow therapeutic window.
Interaction with Acetaminophen
In vitro, Imatinib inhibits the acetaminophen O-glucuronidate pathway (Ki 58.5 $\mu$M). Coadministration of Imatinib (400 mg/day for eight days) with acetaminophen (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of acetaminophen. Imatinib pharmacokinetics were not altered in the presence of single-dose acetaminophen. There is no pharmacokinetic or safety data on the concomitant use of Imatinib at doses >400 mg/day or the chronic use of concomitant acetaminophen and Imatinib.

OVERDOSAGE
Experience with doses greater than 800 mg is limited. Isolated cases of Imatinib overdose have been reported. In the event of overdosage, the patient should be observed and appropriate supportive treatment given.
Adult Overdose
1,200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash erythema, edema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.
1,800 to 3,200 mg (as high as 3,200 mg daily for 6 days): Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain.
6,400 mg (single dose): One case in the literature reported one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increase transaminases.
8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.
A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after inadvertently taking 1,200 mg of Imatinib daily for 6 days. Therapy was temporarily interrupted and complete reversal of all abnormalities occurred within 1 week. Treatment was resumed at a dose of 400 mg daily without recurrence of adverse reactions. Another patient developed severe muscle cramps after taking 1,600 mg of Imatinib daily for 6 days. Complete resolution of muscle cramps occurred following interruption of therapy and treatment was subsequently resumed. Another patient that was prescribed 400 mg daily, took 800 mg of Imatinib on Day 1 and 1,200 mg on Day 2. Therapy was interrupted, no adverse reactions occurred and the patient resumed therapy.
Pediatric Overdose
One 3-year-old male exposed to a single dose of 400mg experienced vomiting, diarrhea and anorexia and another 3-year-old male exposed to a single dose of 980 mg experienced decreased white blood cell count and diarrhea.

DOSAGE FORMS AND STRENGTHS
100mg & 400mg film coated tablets
100mg capsules

STORAGE
Store protected from moisture, at a temperature not exceeding 30°C.

HOW SUPPLIED
**Reli**sylate™
Imatinib Tablets IP 100mg
Blister pack of 10 Tablets.
**Reli**sylate™
Imatinib Tablets IP 400mg
Blister pack of 10 Tablets.
**Reli**sylate™
Imatinib Capsules IP 100mg
Blister pack of 10 Capsules.

SHELF LIFE
24 Months