

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MATINIB MESYLATE TABLETS safely and effectively. See full prescribing information for MATINIB MESYLATE TABLETS.

MATINIB MESYLATE TABLETS, for oral use
Initial U.S. Approval: 2001

Warnings and Precautions (5)
12015

INDICATIONS AND USAGE
imatnib mesylate is a kinase inhibitor indicated for the treatment of:

- Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (1.1)
Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon- α therapy (1.2)
Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.3)
Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements (1.5)
Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-KIT mutation or with c-KIT mutational status unknown (1.6)
Adult patients with hyperesophophic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFR α fusion kinase (mutational analysis or FISH demonstration of CHC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFR α fusion kinase negative or unknown (1.7)
Adult patients with inoperable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8)

- Adults with Ph+ CML CP (2.1): 400 mg/day
Adults with Ph+ CML AP or BC (2.1): 600 mg/day
Pediatric with Ph+ CML CP (2.2): 340 mg/m²/day
Adults with Ph+ ALL (2.3): 600 mg/day
Adults with MDS/MPD (2.5): 400 mg/day
Adults with ASM (2.6): 100 mg/day or 400 mg/day
Adults with HES/CEL (2.7): 100 mg/day or 400 mg/day
Adults with DFSP (2.8): 800 mg/day
Patients with mild to moderate hepatic impairment (2.11): 400 mg/day
Patients with severe hepatic impairment (2.11): 300 mg/day

All doses of imatinib mesylate tablets should be taken 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. Imatinib mesylate tablets can be dissolved in water or apple juice for patients having difficulty swallowing. Daily dosing of 800 mg and above should be accomplished using the 400 mg tablet to reduce exposure to iron.

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics (5.1, 6.1, 6.9)

- Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter (5.2)
Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Patients with cardiac disease or risk factors for cardiac failure should be monitored and treated (5.3)
Severe hepatotoxicity including fatalities may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction (5.4)
Grade 3/4 hemorrhage has been reported in clinical studies of patients with newly diagnosed CML (5.5)
Gastrointestinal perforations, some fatal, have been reported (5.6)
Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of imatinib mesylate in patients with conditions associated with high eosinophil levels (e.g., HES, MDS/MPD and ASM) (5.7)
Bullous dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of imatinib mesylate (5.8)
Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor TSH levels in such patients (5.9)
Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus (5.10, 8.1)
Growth retardation occurring in children and pre-adolescents receiving imatinib mesylate has been reported. Close monitoring of growth in children under imatinib mesylate treatment is recommended (5.11, 6.11)
Tumor lysis syndrome. Close monitoring is recommended (5.12)
Reports of motor vehicle accidents have been received in patients receiving imatinib mesylate. Caution patients about driving a car or operating machinery (5.13)

ADVERSE REACTIONS
The most frequently reported adverse reactions (>30%) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain (6.1, 6.9)

To report SUSPECTED ADVERSE REACTIONS, contact Ranbaxy Pharmaceuticals Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- CYP3A4 inducers may decrease imatinib mesylate C_{max} and AUC (2.11, 7.1)
CYP3A4 inhibitors may increase imatinib mesylate C_{max} and AUC (7.2)
Imatinib mesylate is an inhibitor of CYP3A4 and CYP2D6 which may increase the C_{max} and AUC of other drugs (7.3, 7.4)
Patients who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin (7.3)

- USE IN SPECIFIC POPULATIONS
There is no experience in children less than 1 year of age (8.4)
Pregnancy: Sexually active female patients should use highly effective contraception during treatment (5.10)

See 17 for PATIENT COUNSELING INFORMATION
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Skin and Subcutaneous Tissue Disorders: Ichthyoid keratosis, lichen planus, toxic epidermal necrolysis, palmar-plantar erythrodysesthesia syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and Connective Tissue Disorders: avascular necrosis/hip osteonecrosis, rhabdomyolysis/myopathy, growth retardation in children

Reproduction Disorders: hemorrhagic corpus luteum/hemorrhagic ovarian cyst

DRUG INTERACTIONS

7.1 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.

Similar findings were observed in patients receiving 400 to 1,200 mg/day imatinib mesylate concomitantly with enzyme-inducing anti-epileptic drugs (EEDs) (e.g., carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone). The mean dose normalized AUC for imatinib in the patients receiving EEDs decreased by 73% compared to patients not receiving EAD.

Concomitant administration of imatinib mesylate 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 mesylate is used up to 1,200 mg/day (600 mg BID) have been given to patients receiving concomitant strong CYP3A4 inducers [see *Dosage and Administration* (2.1)].

7.2 Agents Inhibiting CYP3A4 Metabolism
There was a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) in healthy subjects when imatinib mesylate was administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution is recommended when administering imatinib mesylate with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telmiflonyl, and voriconazole). Grapefruit juice may also decrease imatinib mesylate AUC. Avoidance of the above mentioned substances is recommended. The cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolite and increase imatinib concentrations.

7.3 Interactions with Drugs Metabolized by CYP3A4
Imatinib mesylate increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate 2- and 3.5-fold, respectively), 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, cyclosporin, cyclosporin, ergotamine, fenflurine, fenproporex, quinidine, sirolimus or tacrolimus).

Imatinib mesylate may increase plasma concentration of other CYP3A4 metabolized drugs (e.g., trizolam, benzodiazepines, hydroxyflutamide 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.

7.4 Interactions with Drugs Metabolized by CYP2D6
Imatinib mesylate increased the mean C_{max} and AUC of metoprolol by approximately 23% suggesting that imatinib mesylate has a weak inhibitory effect on CYP2D6-mediated metabolism. No dose adjustment is necessary, however, caution is recommended when administering imatinib mesylate with CYP2D6 substrates that have a narrow therapeutic window.

7.5 Interaction with Acetaminophen
In vitro, imatinib mesylate inhibits the acetaminophen O-glucuronidate pathway (10, 58.5 μ M), respectively in healthy subjects when imatinib mesylate was administered with a single dose of acetaminophen (4 mg/kg) in patients with CML. *In vivo*, imatinib mesylate did not result in any changes in the pharmacokinetics of acetaminophen. Imatinib mesylate pharmacokinetics were not altered in the presence of single-dose acetaminophen. There is no pharmacokinetic or safety data on the concomitant use of imatinib mesylate at doses >400 mg/day or the chronic use of concomitant acetaminophen and imatinib mesylate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category D [see *Warnings and Precautions* (5.10)].

Risk Summary
Imatinib mesylate can cause fetal harm when administered to a pregnant woman. There have been postmarket reports of spontaneous abortions and infant congenital anomalies from women who have taken imatinib mesylate. Imatinib was teratogenic in animals. 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 fetus.

Animal Data
Imatinib mesylate was teratogenic in rats when administered orally during organogenesis at doses ≥ 100 mg/kg (approximately equal to the maximum human dose of 800 mg/day based on body surface area). Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. Female rats administered doses ≥ 45 mg/kg (approximately one-half the maximum human dose of 800 mg/day) based on body surface area also experienced significant post-implantation loss as evidenced by early fetal resorption or stillbirths, nonviable pups and early pup mortality between postpartum days 0 and 4. At doses ≥ 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses ≤ 30 mg/kg (one-third the maximum human dose of 800 mg/day).

8.3 Nursing Mothers
Imatinib and its active metabolite are excreted into human milk. Based on data from three breastfeeding women taking imatinib mesylate, the milk:plasma ratio is about 0.5 to imatinib and about 0.9 for the active metabolite. 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.

8.4 Pediatric Use
Imatinib mesylate safety and efficacy have been demonstrated in children with newly diagnosed Ph+ chronic phase CML. There are no data in children under 1 year of age.

As in adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients, with a C_{max} of 2 to 4 hours. Apparent oral clearance was similar to adult values (11 L/h/m² in children vs. 10 L/h/m² in adults), as was the half-life (14.8 hours in children vs. 17.1 hours in adults). Following in children at both 260 mg/m² and 340 mg/m² achieved an AUC similar to the 400 mg dose in adults. The comparison of AUC on Day 8 vs. Day 1 at 260 mg/m² and 340 mg/m² doses revealed a 1.5- and 2.2-fold drug accumulation, respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase proportionally with increasing dose.

Based on pooled population pharmacokinetic analysis in pediatric patients with hematological disorders (CML, or other hematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that pediatric patients receiving 260 mg/m² once-daily (not exceeding 400 mg once-daily) or 340 mg/m² once-daily (not exceeding 600 mg once-daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once-daily.

8.5 Geriatric Use
In the CML clinical studies, approximately 20% of patients were older than 65 years. In the study of patients with newly diagnosed CML, 6% of patients were older than 65 years. 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 edema [see *Warnings and Precautions* (5.1)]. The efficacy of imatinib mesylate was similar in older and younger patients.

8.6 Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 84 cancer patients with varying degrees of hepatic impairment (Table 11) at imatinib doses ranging from 100 mg to 800 mg. Exposure to both imatinib and CGP74588 was comparable between the mildly and moderately hepatically-impaired groups and to the normal group. Patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean C_{max} (dose and AUC/dose for imatinib increased by about 53% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean C_{max} (dose and AUC/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function [see *Dosage and Administration* (2.1)].

Liver Function Test	Normal (n=20)	Mild (n=20)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	\leq ULN	> 1 to 1.5 times the ULN	> 1.5 to 3 times the ULN	> 3 to 10 times the ULN
SGOT	\leq ULN	>ULN (can be normal to 3x ULN)	Any	Any

ULN=upper limit of normal for the institution

8.7 Renal Impairment
The effect of renal impairment on the pharmacokinetics of imatinib was assessed in 59 cancer patients with varying degrees of renal impairment (Table 12) at single and steady state imatinib doses ranging from 100 to 800 mg/day. The mean exposure to imatinib (dose normalized AUC) in patients with mild and moderate renal impairment increased 1.5- to 2-fold compared to patients with normal renal function. The AUCs did not increase for doses greater than 400 mg in patients with mild renal impairment. The AUCs did not increase for doses greater than 400 mg in patients with moderate renal impairment. Two patients with severe renal impairment were dosed with 100 mg/day and their exposures were similar to those seen in patients with normal renal function receiving 400 mg/day. Dose reductions are necessary for patients with moderate and severe renal impairment [see *Dosage and Administration* (2.1)].

Renal Dysfunction	Renal Function Tests
Mild	CrCl \geq 40 to 59 mL/min
Moderate	CrCl \geq 20 to 39 mL/min
Severe	CrCl \leq 20 mL/min

CrCl = Creatinine Clearance

10 OVERDOSE
Experience with doses greater than 800 mg is limited. Isolated cases of imatinib mesylate overdose have been reported. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

Adult Overdose
1,200 to 1,800 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash, myalgia, edema, swelling, headache, 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 mesylate 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 mesylate daily for 6 days. Complete resolution of muscle cramps occurred following interruption of therapy and treatment was subsequently resumed. Another patient who was prescribed 400 mg daily, took 800 mg of imatinib mesylate 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 400 mg 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.

11 DESCRIPTION
Imatinib is a small molecule kinase inhibitor. Imatinib mesylate 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)pyrrolo[2,1-f]imidazo[5,4-d]phenyl]benzamide methanesulfonate and its structural formula is:

Inactive Ingredients: silicified microcrystalline cellulose, mannitol, croscollon, crospovidone, magnesium stearate, hypromellose, iron oxide yellow, polyethylene glycol, titanium dioxide, FD&G yellow #6 aluminum lake and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 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 inhibitory formation in assays using ex vivo peripheral blood and bone marrow samples from CML patients.

In vivo, imatinib inhibits tumor growth of BCR-ABL transduced 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.

12.3 Pharmacokinetics
The pharmacokinetics of imatinib mesylate have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with C_{max} achieved within 2 to 4 hours post-dose. Mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-life of imatinib and its major active metabolite, the N-demethylated derivative (CGP74588), are approximately 18 and 40 hours, respectively. Mean terminal AUC increases proportionally with increasing doses ranging from 25 mg to 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 mesylate is dosed once-daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vivo* experiments is approximately 95%, mostly to albumin and n-1'-acid glycoprotein.

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP2A2, CYP2D6, CYP2C9, and CYP2C19, have been shown to be involved in the metabolism of circulating active metabolite in humans is the N-demethylated epoxide 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 imatinib. Human liver microsomal studies demonstrated that imatinib mesylate is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4 with K_i values of 27, 7.5, and 8 μ M, respectively.

Imatinib elimination is predominantly 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 1.8 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 clearance does not appear to be related to body weight and/or age but indicates the need for close monitoring for treatment-related toxicity.

13 NONCLINICAL TOXICOLOGY

13.1 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 \geq 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, small intestine, parathyroid glands, adrenal glands and non-glandular stomach, and 15 mg/kg/day for the preputial and clitoral gland. The papilloma/carcinomas of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day, representing approximately 0.5 to 4 or 0.3 to 2.1 times the human daily exposure (based on AUC) at 60 mg/day or 800 mg/day, respectively, and 0.4 to 3 times the daily exposure in children (based on AUC) at 340 mg/day based on body surface area. The incidence of 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 effects were observed 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 positive for mutagenesis in the Ames assay. Imatinib was not genotoxic when tested in an *in vivo* bacterial cell assay (Ames test), an *in vivo* mammalian cell assay (mouse lymphoma) and an *in vivo* 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 \leq 20 mg/kg (one-fourth the maximum human dose of 800 mg/day). The fertility of male and female rats was not affected.

In a pre- and postnatal developmental 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 1 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 weights and epididymal weights as well as a reduced number of 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 mesylate.

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.

13.2 Animal Toxicology and/or Pharmacology
Toxicities from Long-Term Use
It is important to consider potential toxicities suggested by animal studies, specifically, early kidney, and cardiac toxicity and immunosuppression. Severe effects were observed in dogs treated for 2 weeks with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct dysplasia. 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 in this study revealed testicular atrophy, chronic progressive nephropathy (females) and preputial gland papillomas 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: hypertrophy and dilatation, leading to signs of cardiac insufficiency in some animals.

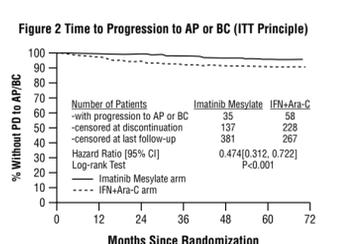
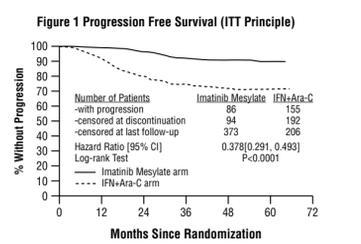
14 CLINICAL STUDIES

14.1 Chronic Myeloid Leukemia
14.1.1 Chronic Phase, Newly Diagnosed:
An open-label, multicenter, international randomized Phase 3 study (imatinib mesylate versus IFN- α) has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. This study compared treatment with either single-agent imatinib mesylate or a combination of interferon- α (IFN) plus cytarabine (Ara-C). Patients were allowed to cross over to the alternative treatment arm if they failed to show a complete hematologic response (CHR) at 6 months, a major cytogenetic response (MCR) at 12 months, or if they did a CHR or MCR. Patients with increasing WBC or severe intolerance to treatment were also allowed to cross over to the alternative treatment arm with the permission of the study monitoring committee (SMC). In the imatinib mesylate arm, patients were treated initially at 400 mg once daily. Dose escalations were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800 mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m² (day subcutaneously) in combination with subcutaneous Ara-C 20 mg/m²/day for 10 days/month.

A total of 1,106 patients were randomized from 177 centers in 16 countries, 553 to each arm. Baseline characteristics were well balanced between the two arms. Median age was 51 years (range 18 to 79 years), with 21% of patients \geq 60 years of age. There were 59% males and 41% females; 89.9% Caucasian and 1.7% black patients. The criteria for the analysis (7 years after start of treatment) were: (a) chronic myeloid leukemia (CML) in chronic phase. This study compared treatment with either single-agent imatinib mesylate or a combination of interferon- α (IFN) plus cytarabine (Ara-C). Patients were allowed to cross over to the alternative treatment arm if they failed to show a complete hematologic response (CHR) at 6 months, a major cytogenetic response (MCR) at 12 months, or if they did a CHR or MCR. Patients with increasing WBC or severe intolerance to treatment were also allowed to cross over to the alternative treatment arm with the permission of the study monitoring committee (SMC). In the imatinib mesylate arm, patients were treated initially at 400 mg once daily. Dose escalations were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800 mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m² (day subcutaneously) in combination with subcutaneous Ara-C 20 mg/m²/day for 10 days/month.

The primary efficacy endpoint of the study was progression-free survival (PFS). Progression was defined as any of the following events: progression to accelerated phase or blast crisis (AP/BC), death, loss of CHR or MCR, or in patients not achieving a CHR an increasing WBC despite appropriate therapeutic management. The protocol specified that the progression analysis would compare the intent to treat (ITT) population: patients randomized to receive imatinib mesylate versus imatinib mesylate plus interferon- α who received IFN. Patients that crossed over prior to progression were not censored at the time of cross-over and events that occurred in these patients following cross-over were attributed to the original randomized treatment. The estimated rate of progression-free survival at 84 months in the ITT population was 81.2% (95% CI: 78-85) in the imatinib mesylate arm and 60.6% (56-65) in the IFN arm ($p < 0.001$, log-rank test). (Figure 1). With 7 years follow up there were 33 (16.8%) progression events in the imatinib mesylate arm; 37 (7%) progression to AP/BC, 31 (5.6%) loss of MCR, 15 (2.7%) loss of CHR or increasing WBC and 10 (1.8%) MCL, unrelated deaths. In contrast, there were 195 (29.8%) events in the IFN-Ara-C arm of which 130 occurred during first-line treatment and 65 during second-line treatment. Patients free of progression to accelerated phase (AP) or blast crisis (BC) at 84 months was 92.5% (90, 95) in the imatinib mesylate arm compared to the 85.1%, (82, 89) ($p < 0.001$) in the IFN arm. (Figure 2). The annual rates of any progression events have decreased with time on therapy. The probability of remaining progression free for 60 months was 85% for patients who were in complete cytogenetic response (CoCR) with molecular response (\geq 3-log reduction in BCR-ABL transcripts as measured by quantitative reverse transcriptase polymerase chain reaction) at 12 months, compared to 85% for patients in complete cytogenetic response but without a major cytogenetic response and 70% in patients who were not in complete cytogenetic response at this time point ($p < 0.001$).

14.2 Pediatric CML
A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase were enrolled in an open-label, multicenter, single arm phase 2 trial. Patients were treated with imatinib mesylate 340 mg/m²/day, with no interruptions in the absence of dose limiting toxicity. Complete hematologic response (CHR) was observed in 78% of patients after 8 weeks of therapy. The complete cytogenetic response rate (CoCR) was 65%, comparable to the results observed in adults. Additionally, a partial cytogenetic response (PoCR) was observed in 16%. The majority of patients achieved a CoCR following 2 years after achieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC, and estimated overall survival was 90.8% (88.3-93.2). In accelerated phase, median duration of hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5 months for 400 mg). An estimated 63.8% of patients who achieved MoCR were still in complete cytogenetic response at 2 years. The median survival was 21.1 (11-34.4) months for the 400 mg group and was not yet reached for the 600 mg group ($p = 0.0097$). An estimated 46.2% (34.7-57.7) vs. 65.8% (58.4-73.3) of patients were still alive after 2 years of treatment in the 400 mg vs. 600 mg dosing groups, respectively. Blast crisis and estimated overall survival in the imatinib mesylate group was higher in untreated patients than in treated patients (26% vs. 22%, respectively) and in the group receiving an initial dose of 600 mg rather than 400 mg (33% vs. 16%). The confirmed and unconfirmed major cytogenetic response rate was also higher for the 600 mg dose group than for the 400 mg dose group (17% vs. 8%).



A total of 17 (12.8%) and 85 (15.4%) patients died in the imatinib mesylate and IFN-Ara-C group, respectively. The median time to death was 12.4 months (95% CI: 10.1-14.7) in the imatinib mesylate arm and 10.1 months (95% CI: 8.7-11.5) in the IFN-Ara-C group, respectively ($p = 0.073$ log-rank test). The hazard ratio is 0.75 with 95% CI 0.54 to 1.028. This time-to-event endpoint may be affected by the high crossover rate from IFN-Ara-C to imatinib mesylate. Other major cytogenetic response, hematologic response, resolution of minimal residual disease (MRD), time to accelerated phase or blast crisis and survival were main secondary endpoints. Response data are shown in Table 11. Complete hematologic response, major cytogenetic response and complete cytogenetic response were also statistically significantly higher in the imatinib mesylate arm compared to the IFN-Ara-C arm (no crossover data considered for evaluation of responses). Median time to CoCR in the 654 responders was 6 months (range 2 to 64 months, 25th to 75th percentiles= \geq 11 months) with 10% of responses seen only after 22 months of therapy).

Table 13 Response in Newly Diagnosed CML Study (84-Month Data)

(Best Response Rate)	Imatinib Mesylate n=553	IFN-Ara-C n=553
Hematologic Response¹		
CHR Rate n (%)	534 (96.6%)*	313 (56.6%)*
[95% CI]	[94.7%, 97.9%]	[52.4%, 60.8%]
Major Cytogenetic Response²		
n (%)	472 (85.4%)*	93 (16.8%)*
[95% CI]	[82.1%, 88.2%]	[13.8%, 20.2%]
Unconfirmed ³	88.6%	23.3%*
Complete Cytogenetic Response⁴		
n (%)	413 (74.7%)*	36 (6.5%)*
[95% CI]	[70.3, 79.1]	[4.6, 8.9]
Unconfirmed ³	82.5%	11.6%*

* $p < 0.001$, Fisher's exact test

¹Hematologic response criteria (all responses to be confirmed after 2-4 weeks): WBC $< 10 \times 10^9/L$, platelet $< 50 \times 10^9/L$, myelocyte + metamyelocyte $< 5\%$ in blood, no blasts and promyelocytes in blood, no extramedullary involvement.

²Cytogenetic response criteria (confirmed after 2-4 weeks): complete (0% Ph+ metaphases) or partial (1% to 35%). A major response (0% to 35%) combines both complete and partial responses.

³Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic response on a subsequent bone marrow evaluation.

Molecular response was defined as follows: In the peripheral blood, after 12 months of therapy, reduction of 2.3 log₁₀ in the amount of BCR-ABL transcripts (measured by real-time quantitative reverse transcriptase-PCR assay) over a standardized baseline. Molecular response was only evaluated in a subset of patients who had a complete cytogenetic response by 12 months or later (N=433). The molecular response rate in patients who had a complete cytogenetic response in the imatinib mesylate arm was 59% at 12 months and 72% at 24 months.

Physical, functional, and treatment-specific biological response modifier scales from the FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifier) instrument were used to assess patient-reported general effects of interferon therapy in 1,067 patients with CML in chronic phase. After one month of therapy to 6 months of therapy, there was a 1.3% to 1.2% decrease in mean index from baseline in patients treated with IFN, consistent with increased symptoms of IFN toxicity. There was no apparent change from baseline in mean index for patients treated with imatinib mesylate.

An open-label, multicenter, randomized trial (imatinib mesylate versus nilotinib) was conducted to determine the efficacy of imatinib mesylate versus nilotinib in adult patients with cytogenetically confirmed, newly diagnosed Ph+ CML-CoP. Patients were treated within 6 months of diagnosis and were previously untreated Ph+ CML-CoP except for hydroxyurea and/or aragadine therapy was based on a total of 846 patients: 293 patients in the imatinib mesylate 400 mg once-daily group, 292 patients in the nilotinib 300 mg twice-daily group, 281 patients in the nilotinib 400 mg twice-daily group.

Median age was 46 years in the imatinib mesylate group and 47 years in both nilotinib groups, with 12%, 13%, and 10% of patients \leq 65 years of age in imatinib mesylate 400 mg once-daily, nilotinib 300 mg twice-daily and nilotinib 400 mg twice-daily treatment groups, respectively. There were slightly more male than female patients in all groups (56%, 56%, and 62% in imatinib mesylate 400 mg once-daily, nilotinib 300 mg twice-daily and nilotinib 400 mg twice-daily treatment groups, respectively). More than 60% of all patients were Caucasian, and 25% were Asian.

The primary data analysis was performed when all 846 patients completed 12 months of treatment or discontinued earlier. Subsequent analyses were done when patients completed 36, 48 and 60 months of treatment or discontinued earlier. The median time on treatment was approximately 61 months in all three treatment groups.

The primary efficacy endpoint was major molecular response (MMR) at 12 months after the start of study medication. MMR was defined as $\geq 10^4$ BCR-ABL/ABL % (international scale measured by RT-PCR, which corresponds to a ≥ 3 log reduction of BCR-ABL transcript from standardized baseline). Efficacy endpoints are summarized in Table 14.

Twelve patients in the imatinib mesylate arm progressed to either accelerated phase or blast crisis (7 patients within first 6 months, 2 patients within 6 to 12 months, 2 patients within 12 to 18 months and 1 patient within 18 to 24 months) while two patients in the nilotinib arm progressed to either accelerated phase or blast