HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Tyronib safely and effectively. See full prescribing information for Tyronib.

TYRONIB (imatinib mesylate) tablets for oral use
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------

Indications and Usage, Newly Diagnosed Pediatric Ph+ ALL (1.4) 01/2013

----------INDICATIONS AND USAGE----------

Tyronib 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-alpha therapy (1.2)
- Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) (1.3)
- Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy (1.4)
- 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 hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) 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 (1.7)
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (1.8)
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) (1.9)
- Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST (1.10)

DOSAGE AND ADMINISTRATION----------

- Adults with Ph+ CML CP (2.1): 400 mg/day
- Adults with Ph+ CML AP or BC (2.1): 600 mg/day
- Pediatrics with Ph+ CML CP (2.2): 340 mg/m^2/day
- Adults with Ph+ ALL (2.3): 600 mg/day
- Pediatrics with Ph+ ALL (2.4): 340 mg/m^2/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
- Adults with metastatic and/or unresectable GIST (2.9): 400 mg/day
- Adjuvant treatment of adults with GIST (2.10): 400 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 Tyronib 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. Tyronib 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.

----------DOSAGE FORMS AND STRENGTHS----------

Tablets (scored): 100 mg and 400 mg (3)

----------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, 6.11)
- 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 in patients with newly diagnosed CML and with GIST. GI tumor sites may be the source of GI bleeds in GIST (5.5)
- Gastrointestinal perforations, some fatal, have been reported (5.6)
- Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of Tyronib 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 Tyronib (5.8)
- Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor TSH levels in such patients (5.9)
- Consider potential toxicities, specifically, liver, kidney, and cardiac toxicity, and immunosuppression from long-term use (5.10)
- Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus (5.11, 8.1)
- Growth retardation occurring in children and pre-adolescents receiving Tyronib has been reported. Close monitoring of growth in children under Tyronib treatment is recommended (5.12, 6.13)
- Tumor lysis syndrome. Close monitoring is recommended (5.13)
- Reports of motor vehicle accidents have been received in patients receiving Tyronib. Caution patients about driving a car or operating machinery (5.14)

----------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, 6.11)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers may decrease Tyronib C_{max} and AUC (2.11, 7.1)
- CYP3A4 inhibitors may increase Tyronib C_{max} and AUC (7.2)
- Tyronib 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 (5.11)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 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.

1.2 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.

1.3 Adult patients with Ph+ Acute Lymphoblastic Leukemia (ALL)

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

1.4 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.

1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

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

1.6 Aggressive Systemic Mastocytosis (ASM)

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

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

Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia 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.

1.8 Dermatofibrosarcoma Protuberans (DFSP)

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

1.9 Kit+ Gastrointestinal Stromal Tumors (GIST)

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

1.10 Adjuvant Treatment of GIST

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

2 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, Tyronib 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 Tyronib 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.

2.1 Adult Patients with Ph+ CML CP, AP, and BC

The recommended dose of Tyronib 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.

2.2 Pediatric Patients with Ph+ CML CP

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

2.3 Adults Patients with Ph+ ALL

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

2.4 Pediatric Patients with Ph+ ALL

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

2.5 MDS/MPD

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

2.6 ASM

The recommended dose of Tyronib 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 Tyronib 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-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.

2.7 HES/CEL

The recommended dose of Tyronib 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.

2.8 DFSP

The recommended dose of Tyronib is 800 mg/day for adult patients with DFSP.

2.9 Metastatic or Unresectable GIST

The recommended dose of Tyronib 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.

2.10 Adjuvant GIST

The recommended dose of Tyronib is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In clinical trials one year of Tyronib and three years of Tyronib were studied. In the patient population defined in Study 2, three years of Tyronib is recommended [*see Clinical Studies (14.8)*]. The optimal treatment duration with Tyronib is not known.

2.11 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 co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dosage of Tyronib should be increased by at least 50%, and clinical response should be carefully monitored [*see Drug Interactions (7.1)*].

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 [*See Warnings and Precautions (5.3), Use in Specific Populations (8.7)*].

2.12 Dose Adjustment for Hepatotoxicity and Non-Hematologic Adverse Reactions

If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, Tyronib 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 Tyronib 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), Tyronib should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

2.13 Dose Adjustment for Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia 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 Tyronib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L 2. Resume treatment with Tyronib 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 Tyronib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L 2. Resume treatment with Tyronib at previous dose (i.e., dose before severe adverse reaction)
Chronic Phase CML (starting dose 400 mg) MDS/MPD, ASM and HES/CEL (starting dose 400 mg) GIST (starting dose 400 mg)	ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L	1. Stop Tyronib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L 2. Resume treatment with Tyronib 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 Tyronib at a reduced dose of 300 mg
Ph+ CML : Accelerated Phase and Blast Crisis (starting dose 600 mg) Ph+ ALL (starting dose 600 mg)	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 Tyronib to 400 mg 3. If cytopenia persists 2 weeks, reduce further to 300 mg 4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop Tyronib until ANC ≥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 Tyronib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L 2. Resume treatment with Tyronib 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 Tyronib at reduced dose of 400 mg
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 Tyronib until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L 2. Resume treatment with Tyronib 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 Tyronib at reduced dose of 260 mg/m^2

3 DOSAGE FORMS AND STRENGTHS

100 mg film coated tablets

Very dark yellow to brownish orange, film-coated tablets, round, biconvex with bevelled edges, debossed with
"NVR" on one side, and "SA" with score on the other side

400 mg film coated tablets

Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with
"400" on one side with score on the other side, and "SL" on each side of the score

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Fluid Retention and Edema

Tyronib is often associated with edema and occasionally serious fluid retention [*see Adverse Reactions (6.1)*]. 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 Tyronib dose and age >65 years in the CML studies. Severe superficial edema was reported in 1.5% of newly diagnosed CML patients taking Tyronib, and in 2%-6% of other adult CML patients taking Tyronib. 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 Tyronib, and in 2%-6% of other adult CML patients taking Tyronib. Severe fluid retention was reported in 9% to 13.1% of patients taking Tyronib for GIST *[see Adverse Reactions (6.11)]*.

5.2 Hematologic Toxicity

Treatment with Tyronib 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 [*see Dosage and Administration (2.12)*].

5.3 Severe Congestive Heart Failure and Left Ventricular Dysfunction

Severe congestive heart failure and left ventricular dysfunction have been reported in patients taking Tyronib. 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 Tyronib compared to 0.9% of patients taking IFN + Ara-C. 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.

5.4 Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur with Tyronib [*see Adverse Reactions (6.3)*]. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of Tyronib. 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 Tyronib interruption and/or dose reduction [*see Dosage and Administration (2.12)*].

When Tyronib 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.

5.5 Hemorrhage

In the newly diagnosed CML trial, 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 been the source of GI hemorrhages. Patients should therefore be monitored for gastrointestinal symptoms at the start of therapy.

5.6 Gastrointestinal Disorders

Tyronib is sometimes associated with GI irritation. Tyronib 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.

5.7 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 Tyronib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Tyronib. 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 Tyronib should be considered at the initiation of therapy.

5.8 Dermatologic Toxicities

Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with use of Tyronib. 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 re-challenge. Several foreign post-marketing reports have described cases in which patients tolerated the reintroduction of Tyronib therapy after resolution or improvement of the bullous reaction. In these instances, Tyronib was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

5.9 Hypothyroidism

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

5.10 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.

5.11 Embryo-fetal Toxicity

Tyronib 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 Tyronib 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 [*see Use in Specific Populations (8.1)*].

5.12 Children and Adolescents

Growth retardation has been reported in children and pre-adolescents receiving Tyronib. The long term effects of prolonged treatment with Tyronib on growth in children are unknown. Therefore, close monitoring of growth in children under Tyronib treatment is recommended [*see Adverse Reactions (6.13)*].

5.13 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 Tyronib. 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 Tyronib.

5.14 Driving and Using Machinery

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

6 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.

6.1 Chronic Myeloid Leukemia

The majority of Tyronib-treated patients experienced adverse reactions at some time. Most reactions were of mild-to-moderate grade, but drug was discontinued for drug-related adverse reactions in 2.4% of newly diagnosed patients, 4% of patients in chronic phase after failure of interferon-alpha therapy, 4% in accelerated phase and 5% 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 for newly diagnosed CML, Table 3 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 Tyronib [*see Dosage and Administration (2.12)*]. 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 Tyronib 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.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the Tyronib treated patients are shown in Tables 2 and 3.

Table 2 Adverse Reactions Regardless of Relationship to Study Drug Reported in Newly Diagnosed CML

Clinical Trial (≥10% of Tyronib Treated Patients)[1]

	All Grades		CTC Grades 3/4	
	Tyronib	IFN+Ara−C	Tyronib	IFN+Ara−C
Preferred Term	**N=551 (%)**	**N=533 (%)**	**N=551 (%)**	**N=533 (%)**
Fluid Retention	61.7	11.1	2.5	0.9
− Superficial Edema	59.9	9.6	1.5	0.4
− Other Fluid Retention Reactions[2]	6.9	1.9	1.3	0.6
Nausea	49.5	61.5	1.3	5.1
Muscle Cramps	49.2	11.8	2.2	0.2
Musculoskeletal Pain	47.0	44.8	5.4	8.6
Diarrhea	45.4	43.3	3.3	3.2
Rash and Related Terms	40.1	26.1	2.9	2.4
Fatigue	38.8	67.0	1.8	25.1
Headache	37.0	43.3	0.5	3.8
Joint Pain	31.4	38.1	2.5	7.7
Abdominal Pain	36.5	25.9	4.2	3.9
Nasopharyngitis	30.5	8.8	0	0.4
Hemorrhage	28.9	21.2	1.8	1.7
- GI Hemorrhage	1.6	1.1	0.5	0.2
- CNS Hemorrhage	0.2	0.4	0	0.4
Myalgia	24.1	38.8	1.5	8.3
Vomiting	22.5	27.8	2.0	3.4
Dyspepsia	18.9	8.3	0	0.8
Cough	20.0	23.1	0.2	0.6
Pharyngolaryngeal Pain	18.1	11.4	0.2	0
Upper Respiratory Tract Infection	21.2	8.4	0.2	0.4
Dizziness	19.4	24.4	0.9	3.8
Pyrexia	17.8	42.6	0.9	3.0
Weight Increased	15.6	2.6	2.0	0.4
Insomnia	14.7	18.6	0	2.3
Depression	14.9	35.8	0.5	13.1
Influenza	13.8	6.2	0.2	0.2
Bone Pain	11.3	15.6	1.6	3.4
Constipation	11.4	14.4	0.7	0.2
Sinusitis	11.4	6.0	0.2	0.2

(1)All adverse reactions occurring in ≥10% of Tyronib treated patients are listed regardless of suspected relationship to treatment.

(2)Other fluid retention reactions include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

Table 3 Adverse Reactions Regardless of Relationship to Study Drug Reported in Other CML Clinical Trials (≥10% of All Patients in any Trial)(1)

	Myeloid Blast Crisis (n=260)		Accelerated Phase (n=235)		Chronic Phase, IFN Failure (n=532)	
	%		%		%	
Preferred Term	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Fluid Retention	72	11	76	6	69	4
-Superficial Edema	66	6	74	3	67	2
-Other Fluid Retention Reactions (2)	22	6	15	4	7	2
Nausea	71	5	73	5	63	3
Muscle Cramps	28	1	47	0.4	62	2
Vomiting	54	4	58	3	36	2
Diarrhea	43	4	57	5	48	3
Hemorrhage	53	19	49	11	30	2
- CNS Hemorrhage	9	7	3	3	2	1
- GI Hemorrhage	8	4	6	5	2	0.4
Musculoskeletal Pain	42	9	49	9	38	2
Fatigue	30	4	46	4	48	1
Skin Rash	36	5	47	5	47	3
Pyrexia	41	7	41	8	21	2
Arthralgia	25	5	34	6	40	1
Headache	27	5	32	2	36	0.6
Abdominal Pain	30	6	33	4	32	1
Weight Increased	5	1	17	5	32	7
Cough	14	0.8	27	0.9	20	0
Dyspepsia	12	0	22	0	27	0
Myalgia	9	0	24	2	27	0.2
Nasopharyngitis	10	0	17	0	22	0.2
Asthenia	18	5	21	5	15	0.2
Dyspnea	15	4	21	7	12	0.9
Upper Respiratory Tract Infection	3	0	12	0.4	19	0
Anorexia	14	2	17	2	7	0
Night Sweats	13	0.8	17	1	14	0.2
Constipation	16	2	16	0.9	9	0.4
Dizziness	12	0.4	13	0	16	0.2
Pharyngitis	10	0	12	0	15	0
Insomnia	10	0	14	0	14	0.2
Pruritus	8	1	14	0.9	14	0.8
Hypokalemia	13	4	9	2	6	0.8

Pneumonia	13	7	10	7	4	1
Anxiety	8	0.8	12	0	8	0.4
Liver Toxicity	10	5	12	6	6	3
Rigors	10	0	12	0.4	10	0
Chest Pain	7	2	10	0.4	11	0.8
Influenza	0.8	0.4	6	0	11	0.2
Sinusitis	4	0.4	11	0.4	9	0.4

(1) All adverse reactions occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

(2) Other fluid retention reactions include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

6.2 Hematologic Toxicity

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 4 and 5). 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 Tyronib, but in rare cases require permanent discontinuation of treatment.

Table 4 Lab Abnormalities in Newly Diagnosed CML Clinical Trial

	Tyronib N=551 %		**IFN+Ara−C N=533 %**	
CTC Grades	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology Parameters*				
− Neutropenia*	13.1	3.6	20.8	4.5
− Thrombocytopenia*	8.5	0.4	15.9	0.6
− Anemia	3.3	1.1	4.1	0.2
Biochemistry Parameters				
− Elevated Creatinine	0	0	0.4	0
− Elevated Bilirubin	0.9	0.2	0.2	0
− Elevated Alkaline Phosphatase	0.2	0	0.8	0
− Elevated SGOT /SGPT	4.7	0.5	7.1	0.4

*p<0.001 (difference in Grade 3 plus 4 abnormalities between the two treatment groups)

Table 5 Lab Abnormalities in Other CML Clinical Trials

	Myeloid Blast Crisis (n=260)	**Accelerated Phase (n=235)**	**Chronic Phase, IFN Failure (n=532)**

	600 mg n=223 400 mg n=37 %		600 mg n=158 400 mg n=77 %		400 mg %	
CTC Grades[1]	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology Parameters						
− Neutropenia	16	48	23	36	27	9
− Thrombocytopenia	30	33	31	13	21	<1
− Anemia	42	11	34	7	6	1
Biochemistry Parameters						
− Elevated Creatinine	1.5	0	1.3	0	0.2	0
− Elevated Bilirubin	3.8	0	2.1	0	0.6	0
− Elevated Alkaline Phosphatase	4.6	0	5.5	0.4	0.2	0
− Elevated SGOT (AST)	1.9	0	3.0	0	2.3	0
− Elevated SGPT (ALT)	2.3	0.4	4.3	0	2.1	0

[1]CTC Grades: neutropenia (Grade 3 ≥0.5-1.0 x 10^9/L, Grade 4 <0.5 x 10^9/L), thrombocytopenia (Grade 3 ≥10-50 x 10^9/L, Grade 4 <10 x 10^9/L), anemia (hemoglobin ≥65-80 g/L, Grade 4 <65 g/L), elevated creatinine (Grade 3 >3-6 x upper limit normal range [ULN], Grade 4 >6 x ULN), elevated bilirubin (Grade 3 >3-10 x ULN, Grade 4 >10 x ULN), elevated alkaline phosphatase (Grade 3 >5-20 x ULN, Grade 4 >20 x ULN), elevated SGOT or SGPT (Grade 3 >5-20 x ULN, Grade 4 >20 x ULN)

6.3 Hepatotoxicity

Severe elevation of transaminases or bilirubin occurred in approximately 5% of CML patients (see Tables 4 and 5) 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.

6.4 Adverse Reactions in Pediatric Population Single agent therapy

The overall safety profile of pediatric patients treated with Tyronib in 93 children studied was similar to that found in studies with adult patients, except that musculoskeletal pain was less frequent (20.5%) and peripheral edema was not reported. Nausea and vomiting were the most commonly reported individual adverse reactions with an incidence similar to that seen in adult patients. Although most patients experienced adverse reactions at some time during the study, the incidence of Grade 3/4 adverse reactions was low.

In combination with multi-agent chemotherapy

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 Tyronib and treated in 5 successive cohorts. Tyronib exposure was systematically increased in successive cohorts by earlier introduction and more prolonged duration.

The safety of Tyronib given in combination with intensive chemotherapy was evaluated by comparing the incidence of grade 3 and 4 adverse events, neutropenia (<750/µL) and thrombocytopenia (<75,000/ µL) in the 92 patients with Ph+ ALL compared to 65 patients with Ph- ALL enrolled on the trial who did not

receive Tyronib. The safety was also evaluated comparing the incidence of adverse events in cycles of therapy administered with or without Tyronib. The protocol included up to 18 cycles of therapy. Patients were exposed to a cumulative total of 1425 cycles of therapy, 778 with Tyronib and 647 without Tyronib. The adverse events that were reported with a 5% or greater incidence in patients with Ph+ ALL compared to Ph- ALL or with a 1% or greater incidence in cycles of therapy that included Tyronib are presented in Table 6.

Table 6 Adverse Reactions Reported More Frequently in Patients Treated with Study Drug (>5%) or in Cycles with Study Drug (>1%)

Adverse Event	Per Patient Incidence Ph+ALL With Tyronib N = 92	Per Patient Incidence Ph- ALL No Tyronib N = 65	Per Patient Per Cycle Incidence With Tyronib* N = 778	Per Patient Per Cycle Incidence No Tyronib** N = 647
Grade 3 and 4 Adverse Events				
Nausea and/or Vomiting	15(16%)	6 (9%)	28(4%)	8 (1%)
Hypokalemia	31(34%)	16 (25%)	72(9%)	32(5%)
Pneumonitis	7(8%)	1 (1%)	7(1%)	1(<1%)
Pleural effusion	6(7%)	0	6 (1%)	0
Abdominal Pain	8(9%)	2 (3%)	9 (1%)	3(<1%)
Anorexia	10(11%)	3 (5%)	19(2%)	4 (1%)
Hemorrhage	11(12%)	4 (6%)	17(2%)	8 (1%)
Hypoxia	8(9%)	2 (3%)	12(2%)	2 (<1%)
Myalgia	5(5%)	0	4 (1%)	1 (<1%)
Stomatitis	15(16%)	8 (12%)	22(3%)	14 (2%)
Diarrhea	8(9%)	3 (5%)	12(2%)	3 (<1%)
Rash / Skin Disorder	4(4%)	0	5 (1%)	0
Infection	49(53%)	32 (49%)	131(17%)	92(14%)
Hepatic (transaminase and/or bilirubin)	52(57%)	38 (58%)	172(22%)	113 (17%)
Hypotension	10(11%)	5 (8%)	16(2%)	6 (1%)
Myelosuppression				
Neutropenia (<750/µL)	92 (100%)	63 (97%)	556 (71%)	218 (34%)
Thrombocytopenia (<75,000/µL)	90 (92%)	63 (97%)	431 (55%)	329 (51%)

* Defined as the frequency of AEs per patient per treatment cycles that included Tyronib (includes patients with Ph+ ALL that received cycles with Tyronib

** Defined as the frequency of AEs per patient per treatment cycles that did not include Tyronib (includes patients with Ph+ALL that received cycles without Tyronib as well as all patients with Ph- ALL who did not receive Tyronib in any treatment cycle)

6.5 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.

6.6 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 Tyronib.

6.7 Myelodysplastic/Myeloproliferative Diseases

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Tyronib for MDS/MPD in the phase 2 study, are shown in Table 7.

Table 7 Adverse Reactions Regardless of Relationship to Study Drug Reported (More than One Patient) in MPD Patients in the Phase 2 Study (≥10% All Patients) All Grades

Preferred Term	N=7 n (%)
Nausea	4 (57.1)
Diarrhea	3 (42.9)
Anemia	2 (28.6)
Fatigue	2 (28.6)
Muscle Cramp	3 (42.9)
Arthralgia	2 (28.6)
Periorbital Edema	2 (28.6)

6.8 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 Tyronib due to drug-related adverse reactions or abnormal laboratory values.

6.9 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 Tyronib 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.

6.10 Dermatofibrosarcoma Protuberans

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the 12 patients treated with Tyronib for DFSP in the phase 2 study are shown in Table 8.

Table 8 Adverse Reactions Regardless of Relationship to Study Drug Reported in DFSP Patients in the Phase 2 Study (≥10% All Patients) All Grades

Preferred term	N=12 n (%)
Nausea	5 (41.7)
Diarrhea	3 (25.0)

Vomiting	3 (25.0)
Periorbital Edema	4 (33.3)
Face Edema	2 (16.7)
Rash	3 (25.0)
Fatigue	5 (41.7)
Edema Peripheral	4 (33.3)
Pyrexia	2 (16.7)
Eye Edema	4 (33.3)
Lacrimation Increased	3 (25.0)
Dyspnea Exertional	2 (16.7)
Anemia	3 (25.0)
Rhinitis	2 (16.7)
Anorexia	2 (16.7)

Clinically relevant or severe laboratory abnormalities in the 12 patients treated with Tyronib for DFSP in the phase 2 study are presented in Table 9.

Table 9 Laboratory Abnormalities Reported in DFSP Patients in the Phase 2 Study

	N=12	
CTC Grades[1]	**Grade 3**	**Grade 4**
Hematology Parameters		
- Anemia	17%	0%
- Thrombocytopenia	17%	0%
- Neutropenia	0%	8%
Biochemistry Parameters		
- Elevated Creatinine	0%	8%

[1]CTC Grades: neutropenia (Grade 3 ≥0.5-1.0 x 10^9/L, Grade 4 <0.5 x 10^9/L), thrombocytopenia (Grade 3 ≥10 - 50 x 10^9/L, Grade 4 <10 x 10^9/L), anemia (Grade 3 ≥65-80 g/L, Grade 4 <65 g/L), elevated creatinine (Grade 3 >3-6 x upper limit normal range [ULN], Grade 4 >6 x ULN),

6.11 Gastrointestinal Stromal Tumors

Unresectable and/or Malignant Metastatic GIST

In the Phase 3 trials the majority of Tyronib-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 Tyronib [*see Dosage and Administration (2.12)*]. Severe (CTC Grade 3/4) edema was observed in 182 patients (11.1%).

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Tyronib are shown in Table 10.

Overall the incidence of all grades of adverse reactions and the incidence of severe adverse reactions (CTC Grade 3 and above) were similar between the two treatment arms except for edema, which was reported more frequently in the 800 mg group.

Table 10 Number (%) of Patients with Adverse Reactions Regardless of Relationship to Study

Drug where Frequency is ≥10% in any One Group (Full Analysis Set) in the Phase 3 Unresectable and/or Malignant Metastatic GIST Clinical Trials

	Imatinib 400 mg N=818		Imatinib 800 mg N=822	
Reported or Specified Term	**All Grades %**	**Grades 3/4/5 %**	**All Grades %**	**Grades 3/4/5 %**
Edema	76.7	9.0	86.1	13.1
Fatigue/lethargy, malaise, asthenia	69.3	11.7	74.9	12.2
Nausea	58.1	9.0	64.5	7.8
Abdominal pain/cramping	57.2	13.8	55.2	11.8
Diarrhea	56.2	8.1	58.2	8.6
Rash/desquamation	38.1	7.6	49.8	8.9
Vomiting	37.4	9.2	40.6	7.5
Myalgia	32.2	5.6	30.2	3.8
Anemia	32.0	4.9	34.8	6.4
Anorexia	31.1	6.6	35.8	4.7
Other GI toxicity	25.2	8.1	28.1	6.6
Headache	22.0	5.7	19.7	3.6
Other pain (excluding tumor related pain)	20.4	5.9	20.8	5.0
Other dermatology /skin toxicity	17.6	5.9	20.1	5.7
Leukopenia	17.0	0.7	19.6	1.6
Other constitutional symptoms	16.7	6.4	15.2	4.4
Cough	16.1	4.5	14.5	3.2
Infection (without neutropenia)	15.5	6.6	16.5	5.6
Pruritus	15.4	5.4	18.9	4.3
Other neurological toxicity	15.0	6.4	15.2	4.9
Constipation	14.8	5.1	14.4	4.1
Other renal/genitourinary toxicity	14.2	6.5	13.6	5.2
Arthralgia (joint pain)	13.6	4.8	12.3	3.0
Dyspnea (shortness of breath)	13.6	6.8	14.2	5.6
Fever in absence of neutropenia (ANC<1.0 x 10^9/L)	13.2	4.9	12.9	3.4
Sweating	12.7	4.6	8.5	2.8
Other hemorrhage	12.3	6.7	13.3	6.1
Weight gain	12.0	1.0	10.6	0.6
Alopecia	11.9	4.3	14.8	3.2
Dyspepsia/heartburn	11.5	0.6	10.9	0.5
Neutropenia/ granulocytopenia	11.5	3.1	16.1	4.1
Rigors/chills	11.0	4.6	10.2	3.0
Dizziness/ lightheadedness	11.0	4.8	10.0	2.8
Creatinine increase	10.8	0.4	10.1	0.6
Flatulence	10.0	0.2	10.1	0.1
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	9.2	5.4	10.0	4.3
Lymphopenia	6.0	0.7	10.1	1.9

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values were not reported or evaluated in the Phase 3 GIST trials. Severe abnormal laboratory values reported in the Phase 2 GIST trial are presented in Table 11.

Table 11 Laboratory Abnormalities in the Phase 2 Unresectable and/or Malignant Metastatic GIST Trial

	400 mg (n=73)	600 mg (n=74)

CTC Grades[1]	% Grade 3	% Grade 4	% Grade 3	% Grade 4
Hematology Parameters				
− Anemia	3	0	8	1
− Thrombocytopenia	0	0	1	0
− Neutropenia	7	3	8	3
Biochemistry Parameters				
− Elevated Creatinine	0	0	3	0
− Reduced Albumin	3	0	4	0
− Elevated Bilirubin	1	0	1	3
− Elevated Alkaline Phosphatase	0	0	3	0
− Elevated SGOT (AST)	4	0	3	3
− Elevated SGPT (ALT)	6	0	7	1

[1]CTC Grades: neutropenia (Grade 3 ≥0.5-1.0 x 10^9/L, Grade 4 <0.5 x 10^9/L), thrombocytopenia (Grade 3 ≥10 - 50 x 10^9/L, Grade 4 <10 x 10^9/L), anemia (Grade 3 ≥65-80 g/L, Grade 4 <65 g/L), elevated creatinine (Grade 3 >3-6 x upper limit normal range [ULN], Grade 4 >6 x ULN), elevated bilirubin (Grade 3 >3-10 x ULN, Grade 4 >10 x ULN), elevated alkaline phosphatase, SGOT or SGPT (Grade 3 >5-20 x ULN, Grade 4 >20 x ULN), albumin (Grade 3 <20 g/L)

Adjuvant Treatment of GIST

In Study 1, the majority of both Tyronib 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 Tyronib 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 Tyronib 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.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 5% of the patients treated with Tyronib are shown in Table 12 (Study 1) and Table 13 (Study 2). There were no deaths attributable to Tyronib treatment in either trial.

Table 12: Adverse Reactions Regardless of Relationship to Study Drug Reported in Study 1 (≥5% of Tyronib Treated Patients)(1)

	All CTC Grades		CTC Grade 3 and above	
	Tyronib (n=337)	Placebo (n=345)	Tyronib (n=337)	Placebo (n=345)
Preferred Term	%	%	%	%
Diarrhea	59.3	29.3	3.0	1.4
Fatigue	57.0	40.9	2.1	1.2
Nausea	53.1	27.8	2.4	1.2
Periorbital Edema	47.2	14.5	1.2	0

Hemoglobin Decreased	46.9	27.0	0.6	0
Peripheral Edema	26.7	14.8	0.3	0
Rash (Exfoliative)	26.1	12.8	2.7	0
Vomiting	25.5	13.9	2.4	0.6
Abdominal Pain	21.1	22.3	3.0	1.4
Headache	19.3	20.3	0.6	0
Dyspepsia	17.2	13.0	0.9	0
Anorexia	16.9	8.7	0.3	0
Weight Increased	16.9	11.6	0.3	0
Liver enzymes (ALT) Increased	16.6	13.0	2.7	0
Muscle spasms	16.3	3.3	0	0
Neutrophil Count Decreased	16.0	6.1	3.3	0.9
Arthralgia	15.1	14.5	0	0.3
White Blood Cell Count Decreased	14.5	4.3	0.6	0.3
Constipation	12.8	17.7	0	0.3
Dizziness	12.5	10.7	0	0.3
Liver Enzymes (AST) Increased	12.2	7.5	2.1	0
Myalgia	12.2	11.6	0	0.3
Blood Creatinine Increased	11.6	5.8	0	0.3
Cough	11.0	11.3	0	0
Pruritus	11.0	7.8	0.9	0
Weight Decreased	10.1	5.2	0	0
Hyperglycemia	9.8	11.3	0.6	1.7
Insomnia	9.8	7.2	0.9	0
Lacrimation Increased	9.8	3.8	0	0
Alopecia	9.5	6.7	0	0
Flatulence	8.9	9.6	0	0
Rash	8.9	5.2	0.9	0
Abdominal Distension	7.4	6.4	0.3	0.3
Back Pain	7.4	8.1	0.6	0
Pain in Extremity	7.4	7.2	0.3	0
Hypokalemia	7.1	2.0	0.9	0.6
Depression	6.8	6.4	0.9	0.6
Facial Edema	6.8	1.2	0.3	0
Blood Alkaline Phosphatase Increased	6.5	7.5	0	0
Dry skin	6.5	5.2	0	0
Dysgeusia	6.5	2.9	0	0
Abdominal Pain Upper	6.2	6.4	0.3	0
Neuropathy Peripheral	5.9	6.4	0	0
Hypocalcemia	5.6	1.7	0.3	0
Leukopenia	5.0	2.6	0.3	0
Platelet Count Decreased	5.0	3.5	0	0
Stomatitis	5.0	1.7	0.6	0
Upper Respiratory Tract Infection	5.0	3.5	0	0
Vision Blurred	5.0	2.3	0	0

(1) All adverse reactions occurring in ≥5% of patients are listed regardless of suspected relationship to treatment.
A patient with multiple occurrences of an adverse reaction is counted only once in the adverse reaction category.

Table 13: Adverse Reactions Regardless of Relationship to Study Drug by Preferred Term All

Grades and 3/4 Grades (≥5% of Tyronib Treated Patients) Study 2[(1)]

Preferred Term	All CTC Grades		CTC Grades 3 and above	
	Tyronib 12 Months (N=194) %	Tyronib 36 Months (N=198) %	Tyronib 12 Months (N=194) %	Tyronib 36 Months (N=198) %
Patients with at least one AE	99.0	100.0	20.1	32.8
Hemoglobin decreased	72.2	80.3	0.5	0.5
Periorbital edema	59.3	74.2	0.5	1.0
Blood lactate dehydrogenase increased	43.3	60.1	0	0
Diarrhea	43.8	54.0	0.5	2.0
Nausea	44.8	51.0	1.5	0.5
Muscle spasms	30.9	49.0	0.5	1.0
Fatigue	48.5	48.5	1.0	0.5
White blood cell count decreased	34.5	47.0	2.1	3.0
Pain	25.8	45.5	1.0	3.0
Blood creatinine increased	30.4	44.4	0	0
Edema peripheral	33.0	40.9	0.5	1.0
Dermatitis	29.4	38.9	2.1	1.5
Aspartate aminotransferase increased	30.9	37.9	1.5	3.0
Alanine aminotransferase increased	28.9	34.3	2.1	3.0
Neutrophil count decreased	24.2	33.3	4.6	5.1
Hypoproteinemia	23.7	31.8	0	0
Infection	13.9	27.8	1.5	2.5
Weight increased	13.4	26.8	0	0.5
Pruritus	12.9	25.8	0	0
Flatulence	19.1	24.7	1.0	0.5
Vomiting	10.8	22.2	0.5	1.0
Dyspepsia	17.5	21.7	0.5	1.0
Hypoalbuminemia	11.9	21.2	0	0
Edema	10.8	19.7	0	0.5
Abdominal distension	11.9	19.2	0.5	0
Headache	8.2	18.2	0	0
Lacrimation increased	18.0	17.7	0	0
Arthralgia	8.8	17.2	0	1.0
Blood alkaline phosphatase increased	10.8	16.7	0	0.5
Dyspnea	6.2	16.2	0.5	1.5
Myalgia	9.3	15.2	0	1.0
Platelet count decreased	11.3	14.1	0	0
Blood bilirubin increased	11.3	13.1	0	0
Dysgeusia	9.3	12.6	0	0

Paresthesia	5.2	12.1	0	0.5
Vision blurred	10.8	11.1	1.0	0.5
Alopecia	11.3	10.6	0	0
Decreased appetite	9.8	10.1	0	0
Constipation	8.8	9.6	0	0
Pyrexia	6.2	9.6	0	0
Depression	3.1	8.1	0	0
Abdominal pain	2.6	7.6	0	0
Conjunctivitis	5.2	7.6	0	0
Photosensitivity reaction	3.6	7.1	0	0
Dizziness	4.6	6.6	0.5	0
Hemorrhage	3.1	6.6	0	0
Dry skin	6.7	6.1	0.5	0
Nasopharyngitis	1.0	6.1	0	0.5
Palpitations	5.2	5.1	0	0

(1)All adverse reactions occurring in ≥5% of patients are listed regardless of suspected relationship to treatment.
A patient with multiple occurrences of an adverse reaction is counted only once in the adverse reaction category.

6.12 Additional Data from Multiple Clinical Trials

The following adverse reactions have been reported during clinical trials of Tyronib.

Cardiac Disorders:

Estimated 0.1%-1%: congestive cardiac failure, tachycardia, palpitations, pulmonary edema

Estimated 0.01%-0.1%: arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion

Vascular Disorders:

Estimated 1%-10%: flushing, hemorrhage

Estimated 0.1%-1%: hypertension, hypotension, peripheral coldness, Raynauds phenomenon, hematoma, subdural hematoma

Clinical Laboratory Tests:

Estimated 0.1%-1%: blood CPK increased, blood LDH increased

Estimated 0.01%-0.1%: blood amylase increased

Dermatologic:

Estimated 1%-10%: dry skin, alopecia, face edema, erythema, photosensitivity reaction

Estimated 0.1%-1%: exfoliative dermatitis, bullous eruption, nail disorder, purpura, psoriasis, rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, skin hyperpigmentation, onychoclasis, folliculitis, petechiae

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, erythema multiforme, leucocytoclastic vasculitis

Digestive:

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

Hematologic:

Estimated 1%-10%: pancytopenia, febrile neutropenia

Estimated 0.1%-1%: thrombocythemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy

Estimated 0.01%-0.1%: hemolytic anemia, aplastic anemia

Hepatobiliary:

Estimated 0.1%-1%: hepatitis, jaundice

Estimated 0.01%-0.1%: hepatic failure and hepatic necrosis[1]

Hypersensitivity:

Estimated 0.01%-0.1%: angioedema

Infections:

Estimated 0.1%-1%: sepsis, herpes simplex, herpes zoster, cellulitis, urinary tract infection, gastroenteritis

Estimated 0.01%-0.1%: fungal infection

Metabolic and Nutritional:

Estimated 1%-10%: weight decreased

Estimated 0.1%-1%: hypophosphatemia, dehydration, gout, increased appetite, decreased appetite, hyperuricemia, hypercalcemia, hyperglycemia, hyponatremia

Estimated 0.01%-0.1%: hyperkalemia, hypomagnesemia

Musculoskeletal:

Estimated 1%-10%: joint swelling

Estimated 0.1%-1%: joint and muscle stiffness

Estimated 0.01%-0.1%: muscular weakness, arthritis

Nervous System/Psychiatric:

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 pressure[1], confusional state, convulsions, optic neuritis

Renal:

Estimated 0.1%-1%: renal failure acute, urinary frequency increased, hematuria, renal pain

Reproductive:

Estimated 0.1%-1%: breast enlargement, menorrhagia, sexual dysfunction, gynecomastia, erectile dysfunction, menstruation irregular, nipple pain, scrotal edema

Respiratory:

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

Special Senses:

Estimated 1%-10%: conjunctivitis, vision blurred, eyelid edema, conjunctival hemorrhage, dry eye

Estimated 0.1%-1%: vertigo, tinnitus, eye irritation, eye pain, orbital edema, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema, hearing loss

Estimated 0.01%-0.1%: papilledema[1], glaucoma, cataract

[1]Including some fatalities

6.13 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of Tyronib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system disorders: cerebral edema[1]

Eye disorders: vitreous hemorrhage

Cardiac disorders: pericarditis, cardiac tamponade[1]

Vascular disorders: thrombosis/embolism, anaphylactic shock

Respiratory, thoracic and mediastinal disorders: acute respiratory failure[1], interstitial lung disease

Gastrointestinal disorders: ileus/intestinal obstruction, tumor hemorrhage/tumor necrosis, gastrointestinal perforation[1] [*see Warnings and Precautions (5.6)*], diverticulitis

Skin and subcutaneous tissue disorders: lichenoid keratosis, lichen planus, toxic epidermal necrolysis, palmar-plantar erythrodysesthesia syndrome

Musculoskeletal and connective tissue disorders: avascular necrosis/hip osteonecrosis, rhabdomyolysis/myopathy, growth retardation in children

Reproduction disorders: hemorrhagic corpus luteum/hemorrhagic ovarian cyst

[1]Including some fatalities

7 DRUG INTERACTIONS

7.1 Agents Inducing CYP3A Metabolism

Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Tyronib, increased Tyronib 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 400-1200 mg/day Tyronib 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 Tyronib 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. Tyronib doses up to 1200 mg/day (600 mg BID) have been given to patients receiving concomitant strong CYP3A4 inducers [*see Dosage and Administration (2.11)*].

7.2 Agents Inhibiting CYP3A 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 Tyronib was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution is recommended when administering Tyronib 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.

7.3 Interactions with Drugs Metabolized by CYP3A4

Tyronib increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Tyronib. Particular caution is recommended when administering Tyronib with CYP3A4 substrates that have a narrow therapeutic window (e.g., alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus or tacrolimus).

Tyronib 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.

7.4 Interactions with Drugs Metabolized by CYP2D6

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

7.5 Interaction with Acetaminophen

In vitro, Tyronib inhibits the acetaminophen O-glucuronidate pathway (K_i 58.5 µM). Co-administration of Tyronib (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. Tyronib pharmacokinetics were not altered in the presence of single-dose acetaminophen. There is no pharmacokinetic or safety data on the concomitant use of Tyronib at doses >400 mg/day or the chronic use of concomitant acetaminophen and Tyronib.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.11)*].

Risk Summary

Tyronib can cause fetal harm when administered to a pregnant woman. There have been post-market reports of spontaneous abortions and infant congenital anomalies from women who have taken Tyronib. Imatinib was teratogenic in animals. Women should be advised not to become pregnant when taking Tyronib. 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 higher than 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).

8.3 Nursing Mothers

Imatinib and its active metabolite are excreted into human milk. Based on data from three breastfeeding women taking Tyronib, the milk:plasma ratio is about 0.5 for 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 Tyronib, 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

Tyronib safety and efficacy have been demonstrated in children with newly diagnosed Ph+ chronic phase CML and Ph+ ALL. 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 2-4 hours. Apparent oral clearance was similar to adult values (11.0 L/hr/m^2 in children vs. 10.0 L/hr/m^2 in adults), as was the half-life (14.8 hours in children vs. 17.1 hours in adults). Dosing in children at both 260 mg/m^2 and 340 mg/m^2 achieved an AUC similar to the 400 mg dose in adults. The comparison of AUC on Day 8 vs. Day 1 at 260 mg/m^2 and 340 mg/m^2 dose levels 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, Ph+ ALL, 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 exposure of imatinib in pediatric patients receiving 260 mg/m^2 once daily (not exceeding 400 mg once daily) or 340 mg/m^2 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 Tyronib was similar in older and younger patients.

In the unresectable or metastatic GIST study, 16% of patients were older than 65 years. No obvious differences in the safety or efficacy profile were noted in patients older than 65 years as compared to younger patients, but the small number of patients does not allow a formal analysis.In the adjuvant GIST study, 221 patients (31%) 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. The efficacy of Tyronib was similar in patients older than 65 years 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 14) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and 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 63% 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 (2.11)*].

Table 14 Liver Function Classification

Liver Function Test	Normal (n=14)	Mild (n=30)	Moderate (n=20)	Severe (n=20)
Total Bilirubin	≤ULN	>1.0-1.5x ULN	>1.5-3x ULN	>3-10x ULN
SGOT	≤ULN	>ULN (can be normal if Total Bilirubin is >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 15) 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 600 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 (2.11)*].

Table 15 Renal Function Classification

Renal Dysfunction	Renal Function Tests

Mild	CrCL = 40-59 mL/min
Moderate	CrCL = 20-39 mL/min
Severe	CrCL = <20 mL/min

CrCL = Creatinine Clearance

10 OVERDOSAGE

Experience with doses greater than 800 mg is limited. Isolated cases of Tyronib 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.

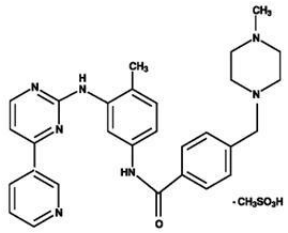
A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after inadvertently taking 1,200 mg of Tyronib daily for 6 days. Therapy was temporarily interrupted and complete reversal 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 Tyronib 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 Tyronib 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. Tyronib 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.

Inactive Ingredients: colloidal silicon dioxide (NF); crospovidone (NF); hydroxypropyl methylcellulose (USP); magnesium stearate (NF); and microcrystalline cellulose (NF). Tablet coating: ferric oxide, red (NF); ferric oxide, yellow (NF); hydroxypropyl methylcellulose (USP); polyethylene glycol (NF) and talc (USP).

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 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.

12.3 Pharmacokinetics

The pharmacokinetics of Tyronib have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. The pharmacokinetics of Tyronib are similar in CML and GIST patients. 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. 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 Tyronib 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 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. Human liver microsome studies demonstrated that Tyronib 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 ^{14}C-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.

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 ≥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 post-natal 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 Tyronib.

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

14 CLINICAL STUDIES

14.1 Chronic Myeloid Leukemia

Chronic Phase, Newly Diagnosed: An open-label, multicenter, international randomized Phase 3 study 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 Tyronib or a combination of interferon-alpha (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 (MCyR) at 12 months, or if they lost a CHR or MCyR. 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 Tyronib arm, patients were treated initially with 400 mg 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/m^2/day subcutaneously in combination with subcutaneous Ara-C 20 mg/m^2/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 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males and 41% females; 89.9% Caucasian and 4.7% Black patients. At the cut-off for this analysis (7 years after last patient had been recruited), the median duration of first-line treatment was 82 and 8 months in the Tyronib and IFN arm, respectively. The median duration of second-line treatment with Tyronib was 64 months. Sixty percent of patients randomized to Tyronib are still receiving first-line treatment. In these patients, the average dose of Tyronib was 403 mg ± 57 mg. Overall, in patients receiving first line Tyronib, the average daily dose delivered was 406 mg ± 76 mg. Due to discontinuations and cross-overs, only 2% of patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of consent (14%) was the most frequent reason for discontinuation of first-line therapy, and the most frequent reason for cross over to the Tyronib arm was severe intolerance to treatment (26%) and progression (14%).

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 MCyR, 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 Tyronib were compared with patients randomized to receive 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 Tyronib arm and 60.6 % [56, 65] in the IFN arm ($p<0.0001$, log-rank test), (Figure 1). With 7 years follow up there were 93 (16.8%) progression events in the Tyronib arm: 37(6.7%) progression to AP/BC, 31(5.6%) loss of MCyR, 15 (2.7%) loss of CHR or increase in WBC and 10 (1.8%) CML unrelated deaths. In contrast, there were 165 (29.8%) events in the IFN+Ara-C arm of which 130 occurred during first-line treatment with IFN-Ara-C. The estimated rate of patients free of progression to accelerated phase (AP) or blast crisis (BC) at 84 months was 92.5%[90, 95] in the Tyronib arm compared to the 85.1%, [82, 89] ($p\leq0.001$) 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 at 60 months was 95% for patients who were in complete cytogenetic response (CCyR) with molecular response (≥3 log reduction in Bcr-Abl transcripts as measured by quantitative reverse transcriptase polymerase chain reaction) at 12 months, compared to 89% for patients in complete cytogenetic response but without a major molecular response and 70% in patients who were not in complete cytogenetic response at this time point ($p<0.001$).

Figure 1 Progression Free Survival (ITT Principle

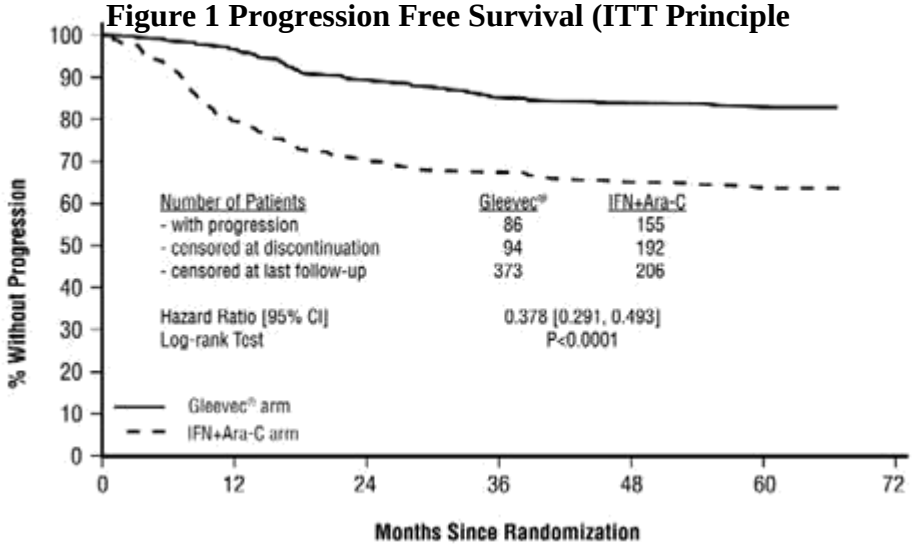
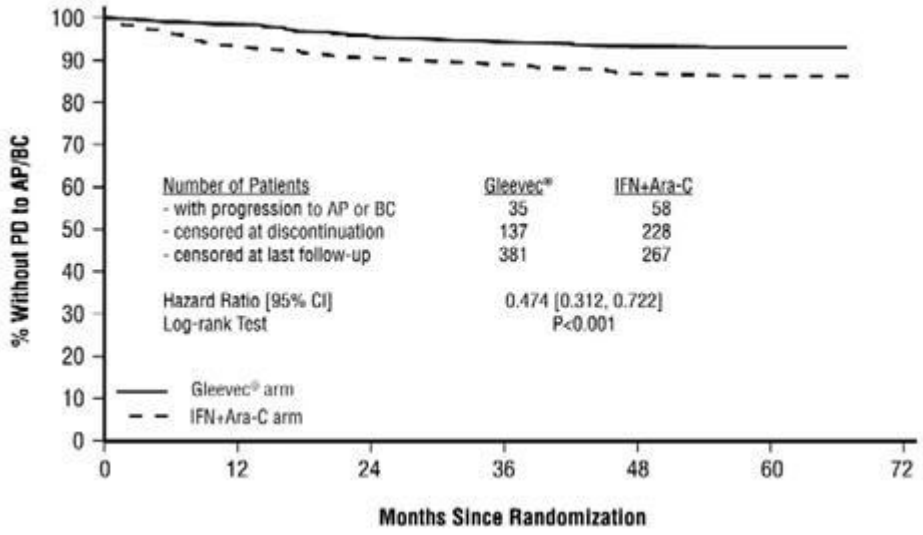


Figure 2 Time to Progression to AP or BC (ITT Principle)



A total of 71 (12.8%) and 85 (15.4%) patients died in the Tyronib and IFN+Ara-C group, respectively. At 84 months the estimated overall survival is 86.4% (83, 90) vs. 83.3% (80, 87) in the randomized Tyronib and the IFN+Ara-C group, respectively (p=0.073 log-rank test). The hazard ratio is 0.750 with 95% CI 0.547–1.028.

This time-to-event endpoint may be affected by the high crossover rate from IFN+Ara-C to Tyronib. Major

cytogenetic response, hematologic response, evaluation of minimal residual disease (molecular response), time to accelerated phase or blast crisis and survival were main secondary endpoints. Response data are shown in Table 16. Complete hematologic response, major cytogenetic response and complete cytogenetic response were also statistically significantly higher in the Tyronib arm compared to the IFN + Ara-C arm (no cross-over data considered for evaluation of responses). Median time to CCyR in the 454 responders was 6 months (range 2-64 months, 25th to 75th percentiles=3 to 11 months) with 10% of responses seen only after 22 months of therapy).

Table 16 Response in Newly Diagnosed CML Study (84-Month Data)

(Best Response Rate)	Tyronib n=553	IFN+Ara−C n=553
Hematologic Response[1]		
CHR Rate n (%)	534 (96.6%)*	313 (56.6%)*
[95% CI]	[94.7%, 97.9%]	[52.4%, 60.8%]
Cytogenetic Response[2]		
Major Cytogenetic Response 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 Response n (%)	413 (74.7%)*	36 (6.5%)*
[95% CI]	[70.8, 78.3]	[4.6, 8.9]
Unconfirmed[3]	82.5%*	11.6%*

*p<0.001, Fischer's exact test

[1]**Hematologic response criteria** (all responses to be confirmed after ≥4 weeks):
WBC<10 x 10^9/L, platelet <450 x 10^9/L, myelocyte + metamyelocyte <5% in blood, no blasts and promyelocytes in blood, no extramedullary involvement.

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

[3]**Unconfirmed 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 ≥3 logarithms 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=333). The molecular response rate in patients who had a complete cytogenetic response in the Tyronib arm was 59% at 12 months and 72% at 24 months.

Physical, functional, and treatment-specific biologic 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 toxicity in 1,067 patients with CML in chronic phase. After one month of therapy to six months of therapy, there was a 13%-21% decrease in median index from baseline in patients treated with IFN, consistent with increased symptoms of IFN toxicity. There was no apparent change from baseline in median index for patients treated with Tyronib.

Late Chronic Phase CML and Advanced Stage CML: Three international, open-label, single-arm phase 2 studies were conducted to determine the safety and efficacy of Tyronib in patients with Ph+ CML: 1) in the chronic phase after failure of IFN therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. About 45% of patients were women and 6% were Black. In clinical studies 38%-40% of patients were ≥60 years of age and 10%-12% of patients were ≥70 years of age.

Chronic Phase, Prior Interferon-Alpha Treatment: 532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three main categories according to

their response to prior interferon: failure to achieve (within 6 months), or loss of a complete hematologic response (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥25 x 10^6 IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). Median duration of treatment was 29 months with 81% of patients treated for ≥24 months (maximum = 31.5 months). Efficacy results are reported in Table 16. Confirmed major cytogenetic response rates were higher in patients with IFN intolerance (66%) and cytogenetic failure (64%), than in patients with hematologic failure (47%). Hematologic response was achieved in 98% of patients with cytogenetic failure, 94% of patients with hematologic failure, and 92% of IFN-intolerant patients.

Accelerated Phase: 235 patients with accelerated phase disease were enrolled. These patients met one or more of the following criteria: ≥15%-<30% blasts in PB or BM; ≥30% blasts + promyelocytes in PB or BM; ≥20% basophils in PB; and <100 x 10^9/L platelets. The first 77 patients were started at 400 mg, with the remaining 158 patients starting at 600 mg.

Effectiveness was evaluated primarily on the basis of the rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of blasts from the marrow and the blood, but without a full peripheral blood recovery as for complete responses), or return to chronic phase CML. Cytogenetic responses were also evaluated. Median duration of treatment was 18 months with 45% of patients treated for ≥24 months (maximum=35 months). Efficacy results are reported in Table 17. Response rates in accelerated phase CML were higher for the 600 mg dose group than for the 400 mg group: hematologic response (75% vs. 64%), confirmed and unconfirmed major cytogenetic response (31% vs. 19%).

Myeloid Blast Crisis: 260 patients with myeloid blast crisis were enrolled. These patients had ≥30% blasts in PB or BM and/or extramedullary involvement other than spleen or liver; 95 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pretreated patients") whereas 165 (63%) had not ("untreated patients"). The first 37 patients were started at 400 mg; the remaining 223 patients were started at 600 mg.

Effectiveness was evaluated primarily on the basis of rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia, or return to chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic responses were also assessed. Median duration of treatment was 4 months with 21% of patients treated for ≥12 months and 10% for ≥24 months (maximum=35 months). Efficacy results are reported in Table 17. The hematologic response rate was higher in untreated patients than in treated patients (36% 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%).

Table 17 Response in CML Studies

	Chronic Phase IFN Failure (n=532)	**Accelerated Phase (n=235)**	**Myeloid Blast Crisis (n=260)**
		600 mg n=158	**600 mg n=223**
	400 mg	**400 mg n=77**	**400 mg n=37**
		% of patients [CI 95%]	
Hematologic Response[1]	95% [92.3−96.3]	71%[64.8-76.8]	31% [25.2−36.8]
Complete Hematologic Response (CHR)	95%	38%	7%
No Evidence of Leukemia (NEL)	Not applicable	13%	5%

Return to Chronic Phase (RTC)	Not applicable	20%	18%
Major Cytogenetic Response[2]	60% [55.3−63.8]	21% [16.2−27.1]	7% [4.5−11.2]
(Unconfirmed[3])	(65%)	(27%)	(15%)
Complete[4] (Unconfirmed[3])	39% (47%)	16% (20%)	2% (7%)

[1] **Hematologic response criteria** (all responses to be confirmed after ≥4 weeks):

CHR:Chronic phase study [WBC <10 x 10^9/L, platelet <450 x 10^9/L, myelocytes + metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, no blood blasts, BM blasts <5% and no extramedullary disease]

NEL: Same criteria as for CHR but ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L (accelerated and blast crisis studies)

RTC: <15% blasts BM and PB, <30% blasts + promyelocytes in BM and PB, <20% basophils in PB, no extramedullary disease other than spleen and liver (accelerated and blast crisis studies).

BM=bone marrow, PB=peripheral blood

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

[3] **Unconfirmed 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.

[4] **Complete cytogenetic response** confirmed by a second bone marrow cytogenetic evaluation performed at least 1 month after the initial bone marrow study.

The median time to hematologic response was 1 month. In late chronic phase CML, with a median time from diagnosis of 32 months, an estimated 87.8% of patients who achieved MCyR maintained their response 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 MCyR were still in response 2 years after achieving initial response. The median survival was 20.9 [13.1, 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 dose groups, respectively. In blast crisis, the estimated median duration of hematologic response is 10 months. An estimated 27.2% [16.8, 37.7] of hematologic responders maintained their response 2 years after achieving their initial response. Median survival was 6.9 [5.8, 8.6] months, and an estimated 18.3% [13.4, 23.3] of all patients with blast crisis were alive 2 years after start of study.

Efficacy results were similar in men and women and in patients younger and older than age 65. Responses were seen in Black patients, but there were too few Black patients to allow a quantitative comparison.

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 Tyronib 340 mg/m^2/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 (CCyR) was 65%, comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16%. The majority of patients who achieved a CCyR developed the CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier estimate of 6.74 months. Patients were allowed to be removed from protocol therapy to undergo alternative therapy including hematopoietic stem cell transplantation. Thirty one children received stem cell transplantation. Of the 31 children, 5 were transplanted after disease progression on study and 1 withdrew from study during first week treatment and received transplant approximately 4 months after withdrawal. Twenty five children withdrew from protocol therapy to undergo stem cell transplant after receiving a median of 9 twenty-eight day courses (range 4 to 24). Of the 25

patients 13 (52%) had CCyR and 5 (20%) had PCyR at the end of protocol therapy.

One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to interferon-alpha therapy. These patients had not previously received Tyronib and ranged in age from 3-20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years old. Patients were treated at doses of 260 mg/m^2/day (n=3), 340 mg/m^2/day (n=4), 440 mg/m^2/day (n=5) and 570 mg/m^2/day (n=2). In the 13 patients for whom cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic response, and 2 had a minimal cytogenetic response.

In a second study, 2 of 3 patients with Ph+ chronic phase CML resistant to interferon-alpha therapy achieved a complete cytogenetic response at doses of 242 and 257 mg/m^2/day.

14.3 Acute Lymphoblastic Leukemia

A total of 48 Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients with relapsed/refractory disease were studied, 43 of whom received the recommended Tyronib dose of 600 mg/day. In addition 2 patients with relapsed/refractory Ph+ ALL received Tyronib 600 mg/day in a phase 1 study.

Confirmed and unconfirmed hematologic and cytogenetic response rates for the 43 relapsed/refractory Ph+ALL phase 2 study patients and for the 2 phase 1 patients are shown in Table 18. The median duration of hematologic response was 3.4 months and the median duration of MCyR was 2.3 months.

Table 18 Effect of Tyronib on Relapsed/Refractory Ph+ ALL.

	Phase 2 Study (N=43)	Phase 1 Study (N=2)
CHR	8 (19%)	2 (100%)
NEL	5 (12%)	
RTC/PHR	11 (26%)	
MCyR	15 (35%)	
CCyR	9 (21%)	
PCyR	6 (14%)	

14.4 Pediatric ALL

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 safety and effectiveness of Tyronib (340 mg/m^2/day) in combination with intensive chemotherapy was evaluated in a subgroup of patients with Ph+ ALL. The protocol included intensive chemotherapy and hematopoietic stem cell transplant after 2 courses of chemotherapy for patients with an appropriate HLA-matched family donor. There were 92 eligible patients with Ph+ ALL enrolled. The median age was 9.5 years (1 to 21 years), 64% were male, 75% were white, 9% were Asian/Pacific Islander, and 5% were black. In 5 successive cohorts of patients, Tyronib exposure was systematically increased by earlier introduction and prolonged duration. Cohort 1 received the lowest intensity and cohort 5 received the highest intensity of Tyronib exposure.

There were 50 patients with Ph+ ALL assigned to cohort 5 all of whom received Tyronib plus chemotherapy; 30 were treated exclusively with chemotherapy and Tyronib and 20 received chemotherapy plus Tyronib and then underwent hematopoietic stem cell transplant, followed by further Tyronib treatment. Patients in cohort 5 treated with chemotherapy received continuous daily exposure to Tyronib beginning in the first course of post induction chemotherapy continuing through maintenance cycles 1 through 4 chemotherapy. During

maintenance cycles 5 through 12 Tyronib was administered 28 days out of the 56 day cycle. Patients who underwent hematopoietic stem cell transplant received 42 days of Tyronib prior to HSCT, and 28 weeks (196 days) of Tyronib after the immediate post transplant period. The estimated 4-year EFS of patients in cohort 5 was 70% (95% CI: 54, 81). The median follow-up time for EFS at data cutoff in cohort 5 was 40.5 months.

14.5 Myelodysplastic/Myeloproliferative Diseases

An open label, multicenter, phase 2 clinical trial was conducted testing Tyronib in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 7 patients with MDS/MPD. These patients were treated with Tyronib 400 mg daily. The ages of the enrolled patients ranged from 20 to 86 years. A further 24 patients with MDS/MPD aged 2 to 79 years were reported in 12 published case reports and a clinical study. These patients also received Tyronib at a dose of 400 mg daily with the exception of three patients who received lower doses. Of the total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a complete hematological response and 12 (39%) a major cytogenetic response (including 10 with a complete cytogenetic response). Sixteen patients had a translocation, involving chromosome 5q33 or 4q12, resulting in a PDGFR gene re-arrangement. All of these patients responded hematologically (13 completely). Cytogenetic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1(7%) out of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8-26.7) in the 7 patients treated within the phase 2 study and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in Table 19. Response durations of phase 2 study patients ranged from 141+ days to 457+ days.

Table 19 Response in MDS/MPD

		Complete Hematologic Response	Major Cytogenetic Response
	N	**N (%)**	**N (%)**
Overall Population	31	14 (45)	12 (39)
Chromosome 5 Translocation	14	11 (79)	11 (79)
Chromosome 4 Translocation	2	2 (100)	1 (50)
Others / no Translocation	14	1 (7)	0 (0)
Molecular Relapse	1	NE[1]	NE[1]

[1] NE: Not Evaluable

14.6 Aggressive Systemic Mastocytosis

One open-label, multicenter, phase 2 study was conducted testing Tyronib in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 5 patients with aggressive systemic mastocytosis (ASM) treated with 100 mg to 400 mg of Tyronib daily. These 5 patients ranged from 49 to 74 years of age. In addition to these 5 patients, 10 published case reports and case

series describe the use of Tyronib in 23 additional patients with ASM aged 26 to 85 years who also received 100 mg to 400 mg of Tyronib daily.

Cytogenetic abnormalities were evaluated in 20 of the 28 ASM patients treated with Tyronib from the published reports and in the phase 2 study. Seven of these 20 patients had the FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion). Patients with this cytogenetic abnormality were predominantly males and had eosinophilia associated with their systemic mast cell disease. Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I) and four patients had a D816V c-Kit mutation (not considered sensitive to Tyronib), one with concomitant CML.

Of the 28 patients treated for ASM, 8 (29%) achieved a complete hematologic response and 9 (32%) a partial hematologic response (61% overall response rate). Median duration of Tyronib therapy for the 5 ASM patients in the phase 2 study was 13 months (range 1.4-22.3 months) and between 1 month and more than 30 months in the responding patients described in the published medical literature. A summary of the response rates to Tyronib in ASM is provided in Table 20. Response durations of literature patients ranged from 1+ to 30+ months.

Table 20 Response in ASM

Cytogenetic Abnormality	Number of Patients	Complete Hematologic Response N (%)	Partial Hematologic Response N (%)
FIP1L1-PDGFRα Fusion Kinase (or CHIC2 Deletion)	7	7(100%)	0%
Juxtamembrane Mutation	2	0 (0%)	2 (100%)
Unknown or No Cytogenetic Abnormality Detected	15	0(0%)	7 (44%)
D816V Mutation	4	1* (25%)	0%
Total	28	8 (29%)	9 (32%)

* Patient had concomitant CML and ASM

Tyronib has not been shown to be effective in patients with less aggressive forms of systemic mastocytosis (SM). Tyronib is therefore not recommended for use in patients with cutaneous mastocytosis, indolent systemic mastocytosis (smoldering SM or isolated bone marrow mastocytosis), SM with an associated clonal hematological non-mast cell lineage disease, mast cell leukemia, mast cell sarcoma or extracutaneous mastocytoma. Patients that harbor the D816V mutation of c-Kit are not sensitive to Tyronib and should not receive Tyronib.

14.7 Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia

One open-label, multicenter, phase 2 study was conducted testing Tyronib in diverse populations of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 14 patients with Hypereosinophilic Syndrome/Chronic Eosinophilic Leukemia (HES/CEL). HES patients were treated with 100 mg to 1000 mg of Tyronib daily. The ages of these patients ranged from 16 to 64 years. A further 162 patients with HES/CEL aged 11 to 78 years were reported in 35 published case reports and case series. These patients received Tyronib at doses of 75 mg to 800 mg daily. Hematologic response rates are summarized in Table 21. Response durations for literature patients ranged from 6+ weeks to 44 months.

Table 21 Response in HES/CEL

Cytogenetic Abnormality	Number of Patients	Complete Hematological Response N (%)	Partial Hematological Response N (%)

Positive FIP1L1-PDGFRα Fusion Kinase	61	61 (100%)	0%
Negative FIP1L1-PDGFRα Fusion Kinase	56	12 (21%)	9 (16%)
Unknown Cytogenetic Abnormality	59	34 (58%)	7 (12%)
Total	176	107 (61%)	23 (13%)

14.8 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma Protuberans (DFSP) is a cutaneous soft tissue sarcoma. It is characterized by a translocation of chromosomes 17 and 22 that results in the fusion of the collagen type 1 alpha 1 gene and the PDGF B gene.

An open-label, multicenter, phase 2 study was conducted testing Tyronib in a diverse population of patients with life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 12 patients with DFSP who were treated with Tyronib 800 mg daily (age range 23 to 75 years). DFSP was metastatic, locally recurrent following initial surgical resection and not considered amenable to further surgery at the time of study entry. A further 6 DFSP patients treated with Tyronib are reported in 5 published case reports, their ages ranging from 18 months to 49 years. The total population treated for DFSP therefore comprises 18 patients, 8 of them with metastatic disease. The adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) Tyronib daily. A single pediatric patient received 400 mg/m^2/daily, subsequently increased to 520 mg/m^2/daily. Ten patients had the PDGF B gene rearrangement, 5 had no available cytogenetics and 3 had complex cytogenetic abnormalities. Responses to treatment are described in Table 22.

Table 22 Response in DFSP

	Number of Patients (n=18)	%
Complete Response	7	39
Partial Response *	8	44
Total Responders	15	83

* 5 patients made disease free by surgery

Twelve of these 18 patients either achieved a complete response (7 patients) or were made disease free by surgery after a partial response (5 patients, including one child) for a total complete response rate of 67%. A further 3 patients achieved a partial response, for an overall response rate of 83%. Of the 8 patients with metastatic disease, five responded (62%), three of them completely (37%). For the 10 study patients with the PDGF B gene rearrangement there were 4 complete and 6 partial responses. The median duration of response in the phase 2 study was 6.2 months, with a maximum duration of 24.3 months, while in the published literature it ranged between 4 weeks and more than 20 months.

14.9 Gastrointestinal Stromal Tumors

Unresectable and/or Malignant Metastatic GIST

Two open-label, randomized, multinational Phase 3 studies were conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). The two study designs were similar allowing a predefined combined analysis of safety and efficacy. A total of 1640 patients were enrolled into the two studies and randomized 1:1 to receive either 400 mg or 800 mg orally daily continuously until disease progression or unacceptable toxicity. Patients in the 400 mg daily treatment group who experienced disease progression were permitted to crossover to receive treatment with 800 mg daily. The studies were designed to compare response rates, progression-free survival and overall survival between the dose groups. Median age at patient entry was 60 years. Males comprised 58% of the patients enrolled. All patients had a

pathologic diagnosis of CD117 positive unresectable and/or metastatic malignant GIST.

The primary objective of the two studies was to evaluate either progression-free survival (PFS) with a secondary objective of overall survival (OS) in one study or overall survival with a secondary objective of PFS in the other study. A planned analysis of both OS and PFS from the combined datasets from these two studies was conducted. Results from this combined analysis are shown in Table 23.

Table 23 Overall Survival, Progression-Free Survival and Tumor Response Rates in the Phase 3 GIST Trials

	Tyronib 400 mg N=818	**Tyronib 800 mg N=822**
Progression-Free Survival (months)		
Median	18.9	23.2
95% CI	17.4-21.2	20.8-24.9
Overall Survival (months)	49.0	48.7
95% CI	45.3-60.0	45.3-51.6
Best Overall Tumor Response		
Complete Response (CR)	43 (5.3%)	41 (5.0%)
Partial Response (PR)	377 (46.1%)	402 (48.9%)

Median follow up for the combined studies was 37.5 months. There were no observed differences in overall survival between the treatment groups (p=0.98). Patients who crossed over following disease progression from the 400 mg/day treatment group to the 800 mg/day treatment group (n=347) had a 3.4 month median and a 7.7 month mean exposure to Tyronib following crossover.

One open-label, multinational Phase 2 study was conducted in patients with Kit (CD117) positive unresectable or metastatic malignant GIST. In this study, 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally q.d. for up to 36 months. The primary outcome of the study was objective response rate. Tumors were required to be measurable at entry in at least one site of disease, and response characterization was based on Southwestern Oncology Group (SWOG) criteria. There were no differences in response rates between the 2 dose groups. The response rate was 68.5% for the 400 mg group and 67.6% for the 600 mg group. The median time to response was 12 weeks (range was 3-98 weeks) and the estimated median duration of response is 118 weeks (95% CI: 86, not reached).

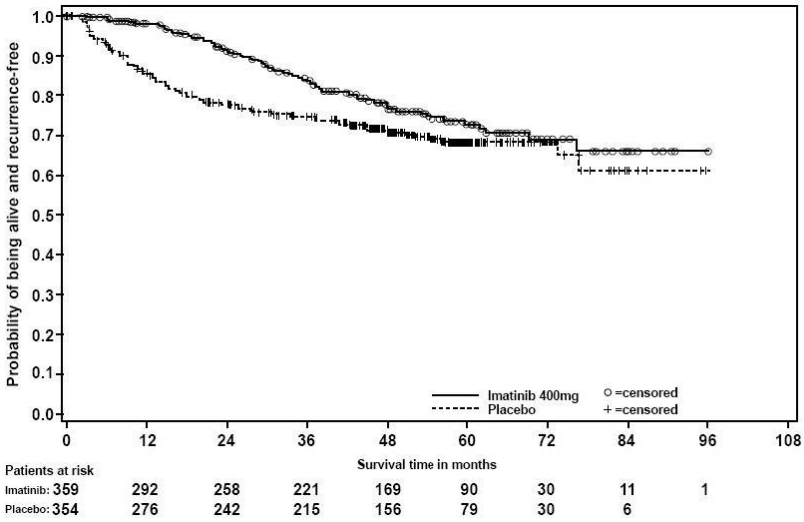
Adjuvant Treatment of GIST

In the adjuvant setting, Tyronib was investigated in a multicenter, double-blind, placebo-controlled, randomized trial involving 713 patients (Study 1). Patients were randomized one to one to Tyronib at 400 mg/day or matching placebo for 12 months. The ages of these patients ranged from 18 to 91 years. Patients were included who had a histologic diagnosis of primary GIST, expressing KIT protein by immunochemistry and a tumor size ≥3 cm in maximum dimension with complete gross resection of primary GIST within 14 to 70 days prior to registration.

Recurrence-free survival (RFS) was defined as the time from date of randomization to the date of recurrence or death from any cause. In a planned interim analysis, the median follow up was 15 months in patients without a RFS event; there were 30 RFS events in the 12-month Tyronib arm compared to 70 RFS events in the placebo arm with a hazard ratio of 0.398 (95% CI: 0.259, 0.610), p<0.0001. After the interim analysis of RFS, 79 of the 354 patients initially randomized to the placebo arm were eligible to cross over to the 12-month Tyronib arm. Seventy-two of these 79 patients subsequently crossed over to Tyronib therapy. In an updated analysis, the median follow-up for patients without a RFS event was 50 months. There were 74

(21%) RFS events in the 12-month Tyronib arm compared to 98 (28%) events in the placebo arm with a hazard ratio of 0.718 (95% CI: 0.531-0.971) (Figure 3). The median follow-up for OS in patients still living was 61 months. There were 26 (7%) and 33 (9%) deaths in the 12-month Tyronib and placebo arms, respectively with a hazard ratio of 0.816 (95% CI: 0.488-1.365).

Figure 3 Study 1 Recurrence-Free Survival (ITT Population)



A second randomized, multicenter, open label, phase 3 trial in the adjuvant setting (Study 2) compared 12 months of Tyronib treatment to 36 months of Tyronib treatment at 400 mg/day in adult patients with KIT (CD117) positive GIST after surgical resection with one of the following: tumor diameter >5 cm and mitotic count >5/50 high power fields (HPF), or tumor diameter >10 cm and any mitotic count, or tumor of any size with mitotic count >10/50 HPF, or tumors ruptured into the peritoneal cavity. There were a total of 397 patients randomized in the trial with 199 patients on the 12-month treatment arm and 198 patients on the 36-month treatment arm. The median age was 61 years (range 22 to 84 years).

RFS was defined as the time from date of randomization to the date of recurrence or death from any cause. The median follow-up for patients without a RFS event was 42 months. There were 84 (42%) RFS events in the 12-month treatment arm and 50 (25%) RFS events in the 36-month treatment arm. Thirty-six months of Tyronib treatment significantly prolonged RFS compared to 12 months of Tyronib treatment with a hazard ratio of 0.46 (95% CI: 0.32, 0.65), p<0.0001 (Figure 4).

The median follow-up for overall survival (OS) in patients still living was 48 months. There were 25 (13%) deaths in the 12-month treatment arm and 12 (6%) deaths in the 36-month treatment arm. Thirty-six months of Tyronib treatment significantly prolonged OS compared to 12 months of Tyronib treatment with a hazard ratio of 0.45 (95% CI: 0.22, 0.89), p=0.0187 (Figure 5).

Figure 4 Study 2 Recurrence-Free Survival (ITT Population)

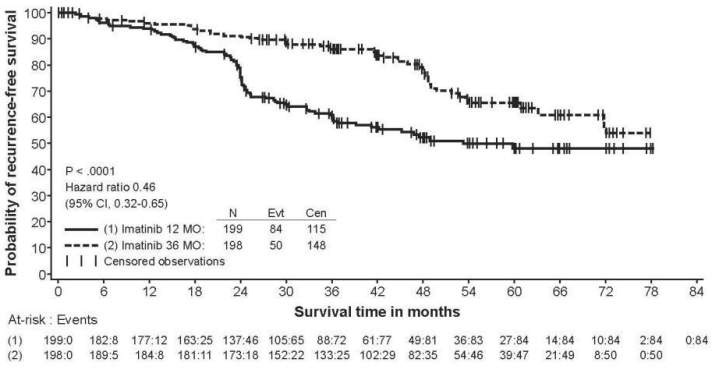
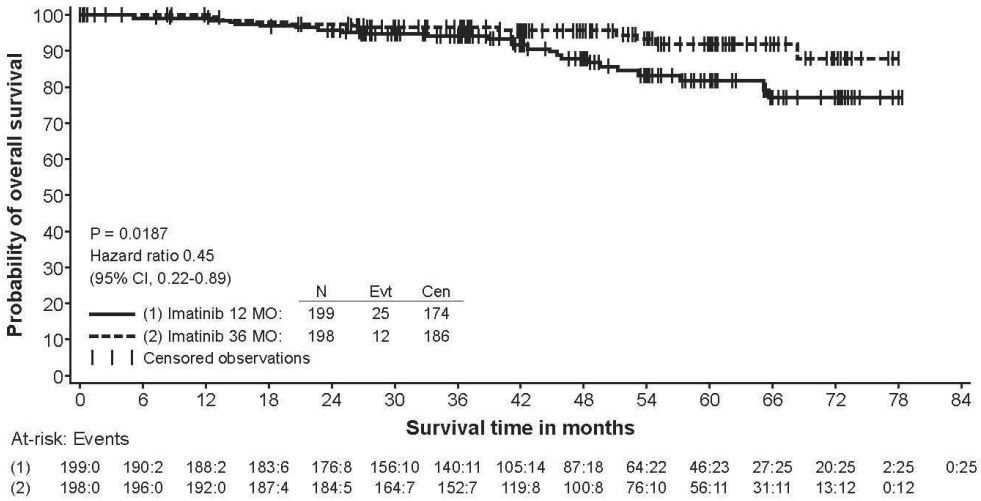


Figure 5 Study 2 Overall Survival (ITT Population)



15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA.* [Accessed on 20-September- 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

Each film-coated tablet contains 100 mg or 400 mg of imatinib free

base. 100 mg Tablets

Very dark yellow to brownish orange, film-coated tablets, round, biconvex with bevelled edges, debossed with "NVR" on one side, and "SA" with score on the other side.

Bottles of 90 tablets…….NDC 0078-0401-

34 400 mg Tablets

Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with

"400" on one side with score on the other side, and "SL" on each side of the

score. Bottles of 30 tablets……NDC 0078-0438-15

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture.

Dispense in a tight container, USP.

Tyronib is an antineoplastic product. Follow special handling and disposal procedures[1]

Tyronib tablets should not be crushed. Direct contact of crushed tablets with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed tablets.

17 PATIENT COUNSELING INFORMATION

17.1 Dosing and Administration

Patients should be informed to take Tyronib exactly as prescribed, not to change their dose or to stop taking Tyronib unless they are told to do so by their doctor. If patients miss a dose they should be advised to take their dose as soon as possible unless it is almost time for their next dose in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose. Patients should be advised to take Tyronib with a meal and a large glass of water.

17.2 Pregnancy and Breast-Feeding

Patients should be advised to inform their doctor if they are or think they may be pregnant. Women of reproductive potential should be advised to avoid becoming pregnant while taking Tyronib. Sexually active female patients taking Tyronib should use highly effective contraception. Patients should also be advised not to breast feed while taking Tyronib.

17.3 Adverse Reactions

Patients should be advised to tell their doctor if they experience side effects during Tyronib therapy including fever, shortness of breath, blood in their stools, jaundice, sudden weight gain, symptoms of cardiac failure, or if they have a history of cardiac disease or risk factors for cardiac failure.

17.4 Drug Interactions

Patients should be advised not to take any other medications, including over-the-counter medications such as herbal products without talking to their doctor or pharmacist first. Examples of other medications that should not be taken with Tyronib are warfarin, erythromycin, and phenytoin. Patients should also be advised to tell their doctor if they are taking or plan to take iron supplements. Patients should also avoid grapefruit juice and other foods known to inhibit CYP3A4 while taking Tyronib.

17.5 Pediatric

Patients should be advised that growth retardation has been reported in children and pre-adolescents receiving Tyronib. The long term effects of prolonged treatment with Tyronib on growth in children are unknown. Therefore, close monitoring of growth in children under Tyronib treatment is recommended.

17.6 Driving and Using Machines

Patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with Tyronib. Therefore, caution patients about driving a car or operating machinery.

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