MATNIB™, but in rare cases require permanent discontinuation of treatment.

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

Acute Lymphoblastic Leukemia
The adverse reactions were similar for Ph+ ALL as for 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.

Gastrointestinal Stromal Tumors
The majority of MATNIB™ treated patients experienced adverse reactions at some time. The most frequently reported adverse reactions were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue, and rash. Most reactions were of mild to moderate severity. Drug was discontinued for adverse reactions in patients (5 %) in both dose levels studied. Superficial edema, most frequently periorbital or lower extremity edema, was managed with diuretics, other supportive measures, or by reducing the dose of MATNIB™. Severe (CTC Grade 3/4) superficial edema was observed in 3 patients (2 %), including facial edema in one patient. Grade 3/4 pleural effusion or ascites was observed in 3 patients (2 %).
The following less common (estimated 1-10 %), infrequent (estimated 0.1-1 %), and rare (estimated less than 0.1%) adverse reactions have been reported during clinical trials of MATNIB™. These reactions are included based on clinical relevance.

Cardiovascular: Infrequent: cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness
Rare: pericarditis
Clinical Laboratory Tests: Infrequent: blood CPK increased, blood LDH increased
Dermatologic: Less common: dry skin, alopecia
Infrequent: exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura, psoriasis
Rare: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, acute febrile neutrophilic dermatosis (Sweet's syndrome)
Digestive: Less common: abdominal distention, gastroesophageal reflux, mouth ulceration Infrequent: gastric ulcer, gastroenteritis, gastritis
Rare: colitis, ileus/intestinal obstruction, pancreatitis, diverticulitis, tumor hemorrhage/tumor necrosis, gastrointestinal perforation.
General Disorders and Administration Site Conditions: Rare: tumor necrosis
Hematologic: Infrequent: pancytopenia
Rare: aplastic anemia
Hepatobiliary: Infrequent: hepatitis
rare: hepatic failure
Hypersensitivity: Rare: angioedema
Infections: Infrequent: sepsis, herpes simplex, herpes zoster
Metabolic and Nutritional: Infrequent: hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased
Rare: hyperkalemia, hyponatremia
Musculoskeletal: Less common: joint swelling
Infrequent: sciatica, joint and muscle stiffness
Rare: avascular necrosis/hip osteonecrosis
Nervous System/Psychiatric: Less common: paresthesia
Infrequent: depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment
Rare: increased intracranial pressure, cerebral edema (including fatalities), confusion, convulsions
Renal: Infrequent: renal failure, urinary frequency, hematuria
Reproductive: Infrequent: breast enlargement, menorrhagia, sexual dysfunction
Respiratory: Rare: interstitial pneumonitis, pulmonary fibrosis
Special Senses: Less common: conjunctivitis, vision blurred
Infrequent: conjunctival hemorrhage, dry eye, vertigo, tinnitus
Rare: macular edema, papilledema, retinal hemorrhage, glaucoma, vitreous hemorrhage
Vascular Disorders: Rare: thrombosis/embolism

DRUG INTERACTIONS
Agents Inducing CYP3A Metabolism
Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of MATNIB™, increased MATNIB™ oral-dose clearance by 3.8 fold, which significantly ($p < 0.05$) decreased mean Cmax and AUC. If alternative treatment cannot be administered, a dose adjustment should be considered.
Agents Inhibiting CYP3A Metabolism
There was a significant increase in exposure to imatinib (mean Cmax and AUC increased by 26 % and 40 %, respectively) in healthy subjects when MATNIB™ was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution is recommended when administering MATNIB™ 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 P_{450} isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations.
Interactions with Drugs Metabolized by CYP3A4
MATNIB™ increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2 and 3.5 fold, respectively, suggesting an inhibition of the CYP3A4 by MATNIB. Particular caution is recommended when administering MATNIB™ with CYP3A4 substrates that have a narrow therapeutic window (e.g., alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus,). MATNIB™ will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., Triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.). Because warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin instead of warfarin.
Interactions with Drugs Metabolized by CYP2D6
In vitro, MATNIB™ inhibits the cytochrome P_{450} isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when coadministered with MATNIB™. No specific studies have been performed and caution is recommended.
Interaction with Acetaminophen
In vitro, MATNIB™ inhibits acetaminophen O-glucuronidation (Ki value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when co-administered with MATNIB™. No specific studies in humans have been performed and caution is recommended.

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

PRESENTATION
MATNIB™ Imatinib tablets 100 & 400 mg are available in blister pack of 10 tablets.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V,
Gurgaon - 122 016, Haryana, India.

Manufactured by:
Getwell Pharmaceuticals
Vastrapur, Ahmedabad - 380015,
Gujarat, INDIA.
At 357, GIDC, Sachin,Surat Gujarat, INDIA

L-0700/MTDM1116-00

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

Imatinib Tablets IP
MATNIB™

COMPOSITION

MATNIB™ 100
Each film coated tablet contains:

Imatinib mesylate IP equivalent to Imatinib	100 mg
Excipients	q.s.

Colour : Iron oxide red and Titanium dioxide

MATNIB™ 400
Each film coated tablet contains:

Imatinib mesylate IP equivalent to Imatinib	400 mg
Excipients	q.s.

Colour : Iron oxide red and Titanium dioxide

DESCRIPTION
Imatinib is a small molecule kinase inhibitor. 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. Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7OCH_4SO_3$ and its molecular weight is 589.7.

CLINICAL PHARMACOLOGY
Mechanism of Action
Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the **Philadelphia chromosome** abnormality in CML. Imatinib inhibits proliferation and induces apoptosis in bcr-abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive **chronic myeloid leukemia**. Imatinib inhibits colony formation in assays using *ex vivo* peripheral blood and bone marrow samples from CML patients.
In vivo, imatinib inhibits tumor growth of bcr-abl transfected murine myeloid cells as well as bcr-abl positive leukemia lines derived from CML patients in blast crisis.
Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation.

Pharmacokinetics
The pharmacokinetics of Imatinib 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 Imatinib is dosed once daily. At clinically relevant concentrations of Imatinib, binding to plasma proteins in in vitro experiments is approximately 95%, mostly to albumin and a1-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 MATNIB™ 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.

INDICATIONS

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

Pediatric Patients with Ph+ CML in Chronic Phase

Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia.(Ph+ Acute Lymphoblastic Leukemia (ALL)

Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors(Kit+Gastrointestinal Stromal Tumors (GIST).

DOSAGE AND ADMINISTRATION

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

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

Adult Patients with Ph+ CML CP, AP and BC

The recommended dose of MATNIB™ is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

Pediatric Patients with Ph+ CML

The recommended dose of MATNIB™ for children with newly diagnosed Ph+ CML is 340 mg/m^2/day (not to exceed 600 mg). The recommended MATNIB™ dose is 260 mg/m^2/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy.

Ph+ ALL

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

Kit+ Gastrointestinal Stromal Tumors (GIST).

The recommended dose of MATNIB™ is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

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 MATNIB should be increased by at least 50 %, and clinical response should be carefully monitored.

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

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, MATNIB™ 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 MATNIB™ 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 or from 260 mg/m^2/day to 200 mg/m^2/day, respectively.

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

OVERDOSE

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

CONTRAINDICATIONS

Use of Imatinib mesylate is contraindicated in patients with hypersensitivity to Imatinib or to other components of Imatinib Mesylate.

PRECAUTIONS

Pregnancy : Pregnancy Category D

Women of childbearing potential should be advised to avoid becoming pregnant while taking MATNIB. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Fluid Retention and Edema

MATNIB™ is often associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher MATNIB™ dose and age > 65 years in the CML patients. Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1-6 % of patients taking MATNIB™ for GIST.

Hematologic Toxicity

Treatment with MATNIB™ 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.

Severe Congestive Heart failure and Left Ventricular Dysfunction

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported in patients taking MATNIB™. 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.

Hepatotoxicity

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

Hemorrhage

In CML Patients 1.8 % of patients had Grade 3/4 hemorrhage. In GIST patients, seven patients (5 %), four in the 600 mg dose group and three in the 400 mg dose group, had a total of eight reactions of CTC Grade 3/4 - gastrointestinal (GI) bleeds (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient). Gastrointestinal tumor sites may have been the source of GI bleeds.

Gastrointestinal Disorders

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

Hypereosinophilic Cardiac Toxicity

In patients with hypereosinophilic syndrome and cardiac involvement, cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib.

Dermatologic Toxicities

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Nursing Mothers

It is not known whether imatinib mesylate or its metabolites are excreted in human milk, 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.

Pediatric Use

MATNIB™ safety and efficacy have been demonstrated in children with newly diagnosed Ph+ chronic phase CML and in children with Ph+ chronic phase CML with recurrence after stem cell transplantation or resistance to interferon-alpha therapy.

Geriatric Use

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

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 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.

Renal Impairment

No clinical studies were conducted with MATNIB™ in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range).

SIDE EFFECTS

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice.

Chronic Myeloid Leukemia

The majority of MATNIB™ 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. Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of MATNIB™. 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 MATNIB™ treatment and using diuretics or other appropriate supportive care measures.

Hematologic Toxicity

In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients. The frequency of grade 3 or 4 neutropenia and thrombocytopenia was between 2 and 3 fold higher in blast crisis and accelerated phase compared to chronic phase. The median duration of the neutropenic and thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively.

These reactions can usually be managed with either a reduction of the dose or an interruption of treatment with