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imatigliv Tablets

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[imatinib]

1. NAME OF THE MEDICINAL PRODUCT
Imatigliv 100mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Imatigliv 100mg Film Coated Tablets: Each tablet contains imatinib Mesylate Ph.Eur equivalent to 100mg Imatinib.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Imatigliv 100mg Film Coated Tablets: Dark Yellow to Brownish-orange tablets, round, biconvex with bevelled edges debossed with "100" on one side and plain on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
•Imatinib is indicated for the treatment of adult and pediatric patients with newly diagnosed chronic myeloid leukemia (CML) as well as for the treatment of adult and pediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
• Adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
• Adjuvant treatment of adult patients following resection of GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
• Adult and pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy.
• Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
• Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
• Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with F1P1L1-PDGFRα rearrangement.
• Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
• Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
The effectiveness of Imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and ASM and on objective response rates in GIST and DFSP, and on recurrence-free survival in adjuvant GIST. The experience with Imatinib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited. Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival in diseases.

4.2 Posology and Method of Administration
Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies and malignant sarcomas, as appropriate.
The prescribed dose should be administered orally with a meal and a large glass of water to minimize the risk of gastrointestinal disturbances. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.
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).
Treatment should be continued as long as the patient continues to benefit.
Monitoring of response to Imatinib therapy in Ph+ CML patients should be performed routinely and when therapy is modified, to identify suboptimal response, loss of response to therapy, poor patient compliance, or possible drug-drug interaction. Results of monitoring should guide appropriate CML management.

General target population:
Dosage in CML
The recommended dosage of Imatinib is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis.
Dose increase from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg daily in 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 hematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved hematological and/or cytogenetic response.
Dosage in Ph+ ALL
The recommended dose of Imatinib is 600 mg/day for adult patients with Ph+ ALL.
Dosage in MDS/MPD
The recommended dose of Imatinib is 400 mg/day for adult patients with MDS/MPD.
Dosage in ASM
The recommended dose of Imatinib is 400 mg/day for adult patients with ASM without the D816V c-KIT mutation or mutational status unknown or not responding satisfactorily to other therapies.
For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFR-alpha, a starting dose of 100 mg/day is recommended. A 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.
Dosage in HES/CEL
The recommended dose of Imatinib is 400 mg/day for adult patients with HES/CEL.
For HES/CEL patients with demonstrated FIP1L1-PDGFR-alpha fusion kinase, a starting dose of 100 mg/day is recommended. A 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.
Dosage in GIST
The recommended dose of Imatinib is 400 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. A dose increase from 400 mg to 600 mg or 800 mg for patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.
The recommended dose of Imatinib is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. In clinical trials one year of Imatinib and three years of Imatinib were studied. In the patient population defined in a study, three years of Imatinib is recommended. The optimal treatment duration with Imatinib is not known.
Dosage in DFSP
The recommended dose of Imatinib is 800 mg/day for adult patients with DFSP.
Dose adjustments for adverse drug reactions
Non-hematological adverse drug reactions
If a severe non-hematological adverse drug reaction develops with Imatinib use, treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.
If elevations in bilirubin >3x institutional upper limit of normal (IULN) or in liver transaminases >5x IULN occur, Imatinib should be withheld until bilirubin levels have returned to a <1.5x IULN and transaminase levels to <2.5x IULN. Treatment with Imatinib may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg, or from 600 to 400 mg, or from 800 mg to 600 mg, and in pediatric patients from 340 to 260 mg/m^2/day.
Hematological adverse drug reactions
Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.
Table 1 Dose adjustments for neutropenia and thrombocytopenia

ASM associated with eosinophilia and HES/CEL with FIP1L1-PDGFR-alpha fusion kinase (starting dose 100 mg)	ANC < 1,0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Imatinib until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Imatinib at previous dose (i.e. before severe adverse drug reaction).
Chronic phase CML, MDS/MPD, ASM, HES/CEL and GIST (starting dose 400 mg)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Imatinib until ANC ≥ 1.5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Imatinib at previous dose (i.e. before severe adverse drug reaction). 3. In the event of recurrence of ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume Imatinib at reduced dose of 300 mg.
Pediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1,0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Imatinib until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Imatinib at previous dose (i.e. before severe adverse drug reaction) 3. In the event of recurrence of ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume Imatinib at reduced dose of 260 mg/m^2
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg[c])	[a]ANC < 0.5 x10^9/L and/or platelets < 10 x10^9/L	1. Check whether cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, reduce dose of Imatinib to 400 mg[c]. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg[d]. 4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop Imatinib until ANC > 1 x10^9/L and platelets > 20 x10^9/L, then resume treatment at 300 mg[d].
DFSP (starting dose 800 mg)	ANC < 1,0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop Imatinib until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with Imatinib at 600 mg 3. In the event of recurrence of ANC < 1,0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume Imatinib at reduced dose of 400 mg.

ANC = absolute neutrophil count
a occurring after at least 1 month of treatment
b or 260 mg/m^2 in pediatric patients
c or 340 mg/m^2 in pediatric patients
d or 200 mg/m^2 in pediatric patients

Special populations
Renal insufficiency
Imatinib and its metabolites are not significantly excreted via the kidney. Patients with renal dysfunction or on dialysis could be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy.
Hepatic impairment
Imatinib is mainly metabolized by the liver. Patients with mild, moderate or severe liver impairment should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated.
Pediatric patients (below 18 years)
There is no experience with the use of Imatinib in pediatric patients with CML below 2 years of age and with Ph+ALL below 1 year of age. There is very limited to no experience with the use of Imatinib in pediatric patients in other indications.
Dosing in pediatric patients should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with chronic phase and advanced phase CML and Ph+ALL (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose in CML and Ph+ALL. In CML, alternatively the daily dose may be split into two administrations – one in the morning and one in the evening.
Geriatric patients (65 years or above)
No significant age related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose recommendation is necessary in the elderly.

4.3 Contraindications
Use in patients with a hypersensitivity to the active substance or to any of the excipients is contraindicated.

4.4 Special Warnings and Precautions for Use
When Imatinib is co-administered with other medications, there is a potential for drug interactions. Caution should be used when taking Imatinib with rifampicin or other strong CYP3A4 inducers, ketoconazole or other strong CYP3A4 inhibitors, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide) or CYP2C9 substrates with a narrow therapeutic window (e.g. warfarin and other coumarin derivatives).
Hypothyroidism
Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with Imatinib. Thyroid-Stimulating Hormone levels should be closely monitored in such patients.
Hepatotoxicity
In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored.
When Imatinib is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been uncommon reports of acute liver failure. Monitoring of hepatic function is recommended in circumstances where Imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction.
Fluid retention
Occurrences of severe fluid retention (pleural effusion, edema, pulmonary edema, ascites, and superficial edema) have been reported in approximately 2,5% of newly diagnosed CML patients taking Imatinib. Therefore, it is recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In studies, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease.
Patients with cardiac disease or renal failure
Patients with cardiac disease, risk factors for cardiac failure 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.
In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of Imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Imatinib. Myelodysplastic (MDS)/myeloproliferative diseases (MPD) and systemic mastocytosis might 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 to 2 mg/kg) for one to two weeks concomitantly with Imatinib should be considered at the initiation of therapy.
Gastrointestinal hemorrhage
In studies, patients with unresectable or metastatic malignant GIST 211 patients (12,9%) reported Grade 3/4 hemorrhage at any site. In the study in patients with unresectable or metastatic malignant GIST, eight patients (5.4%) were reported to have had gastrointestinal (GI) hemorrhage and four patients (2,7%) were reported to have had hemorrhages at the site of tumor deposits. The tumor hemorrhages have been either intra-abdominal or intra-hepatic, depending on the anatomical location of tumor lesions. GI sites of tumor may have contributed to GI bleeding in this reported patient population. In addition, gastric antral vascular ectasia (GAVE), a rare cause of GI hemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases. Patients should therefore be monitored for gastrointestinal symptoms at the start of and during therapy with Imatinib. When needed, Imatinib discontinuation may be considered.
Tumor lysis syndrome
Cases of tumor lysis syndrome (TLS) have been reported in patients treated with Imatinib. Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Imatinib.
Hepatitis B reactivation
Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as Imatinib. Some cases involving drugs of the BCR-ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.
Patients should be tested for hepatitis B infection before initiating treatment with Imatinib. Patients currently on Imatinib should have baseline testing for hepatitis B infection in order to identify chronic carriers of the virus. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for hepatitis B infection during treatment. Carriers of hepatitis B virus who require treatment with imatinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.
Laboratory tests
Haematology
Complete blood counts must be performed regularly during therapy with Imatinib. Treatment of CML patients with Imatinib has been associated with neutropenia or thrombocytopenia, However, the occurrence of these cytopenias is dependent on the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with Imatinib may be interrupted or the dose be reduced.
Liver Function
Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving Imatinib. Non-hematological adverse drug reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with Imatinib.
Renal function
Imatinib and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect Imatinib kinetics. In patients with impaired renal function, Imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. There is no correlation between Imatinib exposure and the degree of renal impairment, as classified by the measurement of creatinine clearance (CrCL), between patients with mild (CrCL: 40 to 59 mL/min) and severe (CrCL: <20 mL/min) renal impairment. However, the starting dose of Imatinib can be reduced if not tolerated.
Long-term treatment with Imatinib may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of Imatinib therapy and closely monitored during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction. If renal dysfunction is observed, appropriate management and treatment should be initiated in accordance with standard treatment guidelines.
Pediatric patients (below 18 years)
There have been case reports of growth retardation occurring in children and pre-adolescents receiving Imatinib. The long-term effects of prolonged treatment with Imatinib on growth in pediatric patients are unknown. Therefore, close monitoring of growth in children under Imatinib treatment is recommended.
Driving and using machines
Reports of motor vehicle accidents have been received in patients receiving Imatinib. While most of these reports are not suspected to be caused by Imatinib, patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with Imatinib. Therefore, caution should be recommended when driving a car or operating machinery.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Observed interactions resulting in a concomitant use not recommended
Drugs that may decrease Imatinib plasma concentrations
Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imatinib. Pretreatment with multiple doses of rifampicin, 600 mg daily for 8 days, followed by a single 400 mg dose of Imatinib, increased Imatinib oral-dose clearance by 3,8 fold, which represents mean decreases C_{max}, $AUC_{0-\infty}$ and AUC_{0-24} by 54%, 68% and 74%, of the respective values without rifampicin treatment. Similar results were observed in patients with malignant gliomas treated with Imatinib while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. In published studies, concomitant administration of Imatinib and a product containing St. John's wort led to a 30 to 32% reduction in the AUC of Imatinib. In patients where rifampicin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.
Other interactions that may affect exposure to Imatinib or other drugs
Drugs that may increase imatinib plasma concentrations
Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) could decrease metabolism and increase Imatinib concentrations. There was a significant increase in exposure to Imatinib (the mean C_{max} and AUC of Imatinib rose by 26% and 40%, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be taken when administering Imatinib with inhibitors of the CYP3A4 family.
Drugs that may have their plasma concentration altered by Imatinib
Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2 and 3.5 fold, respectively, indicating an inhibition of the CYP3A4 by Imatinib. Therefore, caution is recommended when administering Imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide). Imatinib may increase plasma concentration of other CYP3A4 metabolized drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).
Imatinib also inhibits CYP2C9 and CYP2C19 activity in vitro. PT prolongation was observed following co-administration with warfarin. When giving coumarins, short-term PT monitoring is therefore necessary at the start and end of Imatinib therapy and when altering the dosage. Alternatively, the use of low-molecular weight heparin should be considered.
In vitro, Imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23%. Co-administration of Imatinib with CYP2D6 substrates, such as metoprolol, does not seem to be a risk factor for drug-drug interactions and dose adjustment may not be necessary.
In vitro, Imatinib inhibits the acetaminophen O-glucuronidate pathway (Ki 58.5 microM).
Co-administration of Imatinib (400 mg/day for eight days) with acetaminophen/paracetamol (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of acetaminophen/paracetamol.
Imatinib pharmacokinetics was not altered in the presence of single-dose acetaminophen/ paracetamol.
There is no PK or safety data on the concomitant use of Imatinib at doses >400 mg/day or the chronic use of concomitant acetaminophen/paracetamol and Imatinib.

4.6 Fertility, pregnancy and lactation
Pregnancy
Risk summary
Imatinib can cause fetal harm when administered to a pregnant woman based on findings from animal reproduction studies. There are no clinical trials on the use of Imatinib in pregnant women. There have been postmarketing reports of spontaneous abortions and infant congenital anomalies from women who have taken Imatinib. Reproductive studies in rats have demonstrated that imatinib mesylate induced teratogenicity (increased incidence of congenital abnormalities) following prenatal exposure to imatinib mesylate at doses equal to the highest recommended human dose of 800 mg/day based on body surface area. Imatinib should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus.
Lactation
Risk summary
Both Imatinib and its active metabolite can be transferred into human milk. The effects of low-dose exposure of the infant to imatinib are unknown, because of the potential for serious adverse drug reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least 15 days after stopping treatment with Imatinib.
Fertility
Females
Females of reproductive potential should be advised to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Imatinib during treatment and for at least 15 days after stopping treatment with Imatinib.
Infertility
Human studies on male patients receiving Imatinib and its effect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on Imatinib treatment should consult with their physician. 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 male rats. In pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by Imatinib.

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

4.8 Undesirable Effects
Summary of the safety profile
The overall safety profile of Imatinib in human clinical use has been well-characterized through more than 12 years of Imatinib experience. During clinical development, the majority of patients experienced adverse events at some point in time. The most frequently reported ADRs were neutropenia, thrombocytopenia, anaemia, headache, dyspepsia, oedema, weight increased, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhoea, rash, fatigue, and abdominal pain. Events were of mild to moderate grade, and only 2 to 5% of patients permanently discontinued therapy due to drug-related events.
The safety profile of Imatinib in adult and paediatric patients with Ph+ Leukaemias is similar.
The differences in the safety profile between Ph+ leukaemias and solid tumours are a higher incidence and severity of myelosuppression in Ph+ leukaemias, and GI and intra-tumoural haemorrhages in GIST patients and are probably due to disease-related factors. Myelosuppression, GI adverse events, oedema, and rashes are common between these two patient populations. Other GI conditions, such as gastrointestinal obstruction, perforation and ulceration, appear to be more indication-specific. Other prominent adverse events that have been observed after exposure to Imatinib, and which may be causally related, include hepatotoxicity, acute renal failure, hypophosphataemia, severe respiratory adverse reactions, and tumour lysis syndrome and growth retardation in children.
Depending on severity of events, dose adjustment may be required. In very few cases will the medication have to be discontinued based on ADRs.
Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions (Table 2 and Table 3) are listed by MedDRA system organ class.
Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common; common; uncommon; rare; very rare. Adverse reactions and their frequencies reported in Table 2 are based on the registration studies for CML and GIST.

Table 2 Adverse drug reactions in clinical studies for CML and GIST

Infections and infestations	
Uncommon:	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia1, sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis
Rare:	Fungal infection
Blood and lymphatic system disorders	
Very common:	Neutropenia, thrombocytopenia, anaemia
Common:	Pancytopenia, febrile neutropenia
Uncommon:	Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
Rare:	Haemolytic anaemia
Metabolism and nutrition disorders	
Common:	Anorexia
Uncommon:	Hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia
Rare:	Hyperkalaemia, hypomagnesaemia

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Psychiatric disorders	
Common:	Insomnia
Uncommon:	Depression, libido decreased, anxiety
Rare:	Confusional state
Nervous system disorders	
Very common:	Headache[2]
Common:	Dizziness, paraesthesia, taste disturbance, hypoaesthesia
Uncommon:	Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral haemorrhage
Rare:	Increased intracranial pressure, convulsions, optic neuritis
Eye disorders	
Common:	Eyelid oedema, lacrimation increased, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision
Uncommon:	Eye irritation, eye pain, orbital oedema, , scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema
Rare:	Cataract, glaucoma, papilloedema
Ear and labyrinth disorders	
Uncommon:	Vertigo, tinnitus, hearing loss
Cardiac disorders	
Uncommon:	Palpitations, tachycardia, cardiac failure, congestive[3], pulmonary oedema
Rare:	Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Vascular disorders[4]	
Common:	Flushing, haemorrhage
Uncommon:	Hypertension, haematoma, subdural haematoma, peripheral coldness, hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, epistaxis, cough
Uncommon:	Pleural effusion[5], pharyngolaryngeal pain, pharyngitis
Rare:	Pleuritis, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage
Gastrointestinal disorders	
Very common:	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain[6]
Common:	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis
Uncommon:	Stomatitis, mouth ulceration, gastrointestinal haemorrhage[7], eructation, melena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis
Rare:	Colitis, ileus, inflammatory bowel disease
Hepatobiliary disorders	
Common:	Increased hepatic enzymes
Uncommon:	Hyperbilirubinaemia, hepatitis, jaundice
Rare:	Hepatic failure[9], hepatic necrosis[9]
Skin and subcutaneous tissue disorders	
Very common:	Periorbital edema, dermatitis/eczema/rash
Common:	Pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction
Uncommon:	Rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hyperchidrosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions
Rare:	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	
Very common:	Muscle spasm and cramps, Musculoskeletal pain including myalgia, arthralgia, bone pain[8]
Common:	Joint swelling
Uncommon:	Joint and muscle stiffness
Rare:	Muscular weakness, arthritis
Renal and urinary disorders	
Uncommon:	Renal pain, haematuria, renal failure acute, urinary frequency increased
Reproductive system and breast disorders	
Uncommon:	Gynaecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema
General disorders and administration site conditions	
Very common:	Fluid retention and oedema, fatigue
Common:	Weakness, pyrexia, anasarca, chills, rigors
Uncommon:	Chest pain, malaise
Investigations	
Very common:	Weight increased
Common:	Weight decreased
Uncommon:	Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased
Rare:	Blood amylase increased

1 Pneumonia was reported most commonly in patients with transformed CML and in patients with GIST.
2 Headache was the most common in GIST patients.
3 On a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML.
4 Flushing was most common in GIST patients and bleeding (hematoma, hemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC).
5 Pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML.
6/7 Abdominal pain and gastrointestinal hemorrhage were most commonly observed in GIST patients.
8 Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.
9 Some fatal cases of hepatic failure and of hepatic necrosis have been reported.
The following types of ADRs have been reported from post-marketing experience and from additional clinical studies with Imatinib. They include spontaneous case reports as well as serious ADRs from smaller or ongoing clinical studies and the expanded access programs. Because these ADRs are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Imatinib exposure.

Table 3 Adverse drug reactions from post-marketing reports

Investigations	
Not known:	Not known: Hepatitis B reactivation
Nervous system disorders	
Uncommon:	Cerebral oedema
Eye disorders	
Rare:	Vitreous haemorrhage
Cardiac disorders	
Rare:	Pericarditis, cardiac tamponade
Vascular disorders	
Uncommon:	Thrombosis/embolism
Very rare:	Anaphylactic shock
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Acute respiratory failure[1], interstitial lung disease
Gastrointestinal disorders	
Uncommon:	Ileus/intestinal obstruction, tumour haemorrhage/tumour necrosis, gastrointestinal perforation[2]
Rare:	Diverticulitis, gastric antral vascular ectasia (GAVE)
Skin and subcutaneous tissue disorders	
Uncommon:	Palmar-plantar erythrodysaesthesia syndrome
Rare:	Lichenoid keratosis, lichen planus, pemphigus
Very rare:	Toxic epidermal necrolysis
Not known:	Drug rash with eosinophilia and systemic symptoms (DRESS), pseudoporphyria
Musculoskeletal and connective tissue disorders	
Very common:	Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain, spinal pain)
Uncommon:	Osteonecrosis
Rare:	Rhabdomyolysis/myopathy
Not known:	Growth retardation in children
Reproductive disorders	
Very rare:	Haemorrhagic corpus luteum / haemorrhagic ovarian cyst
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Rare:	Tumour lysis syndrome

1 Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions
2 Some fatal cases of gastrointestinal perforation have been reported

Description of selected adverse drug reactions
Myelosuppression
Myelosuppression is very common in cancer patients treated with Imatinib. Myelosuppression, thrombocytopenia, neutropenia and anaemia were the most frequently reported Grade 3 and 4 laboratory abnormalities. Overall, myelosuppression experienced with Imatinib in CML patients was generally reversible and in most patients did not result in dose interruption or dose reduction. Few patients required drug discontinuation. Other events of pancytopenia, lymphopenia and bone marrow depression have also been reported.
Haematologic depression appeared greatest at the highest doses and also appeared to be dependent on the stage of CML disease, with Grade 3 or 4 neutropenia and thrombocytopenia between 4 and 6 times higher in blast and accelerated phase as compared to newly diagnosed patients in CP CML. These events can usually be managed with either a dose reduction or interruption, but they rarely require discontinuation of treatment with Imatinib. The incidence of hematologic toxicities is less in patients with solid tumours (i.e. GIST) than in patients with Ph+ leukaemias, with Grade 3/4 neutropenia and thrombocytopenia occurring approximately 10% and 1%, respectively.
Haemorrhage
CNS and GI haemorrhages are not uncommon in CML patients with compromised marrow function at baseline. Haemorrhages are well-recognized part of the disease complications in an acutely ill population of leukaemic patients, and may result from thrombocytopenia, or less commonly, platelet dysfunction. However, not all patients experiencing CNS and GI haemorrhages during therapy with Imatinib are thrombocytopenic.
The most common manifestation of clinically significant bleeding was GI haemorrhage, which occurred most commonly in advanced CML patients and in metastatic GIST patients, where bleeding might occur as part of the underlying disease due to tumour bleeding from tumour haemorrhage/tumour necrosis. In first line CML and in adjuvant GIST setting, the observed frequencies of GI haemorrhage were generally the lowest. Gastric antral vascular ectasia (GAVE) is also rarely reported with Imatinib use in the post-marketing setting.
Oedema and Fluid Retention
Oedema is a common toxicity of Imatinib appearing in greater than 50% of all patients across all indications. Oedema is dose-related and there appears to be a correlation with its occurrence and plasma levels. The most common manifestation is periorbital oedema and somewhat less common is lower extremity oedema. Specific therapy is not usually required. Other fluid retention events occur much less commonly, but due to the location of the anatomic site may be potentially serious. The most frequent fluid retention event was pleural effusion, most commonly observed in advanced CML and metastatic GIST patients. The frequency of cardiac failure was generally low in patients with oedema and fluid retention. It was higher in advanced CML than in other groups. This could be explained by the worse medical condition of advanced CML patients. The same trend was observed for renal failure in patients with oedema and fluid retention.
In a study, the frequency of events suggesting congestive heart failure was 1.5% on Imatinib vs. 1.1% on IFN-alpha in patients with newly-diagnosed CML. The frequency was appreciably higher in patients with transformed CML (accelerated phase or blast crisis), higher age, or with a baseline haemoglobin of less than 8 g/dL. Congestive Heart Failure (CHF) and left ventricular dysfunction have since been continuously monitored in the PSUR. Across all indications a higher frequency of CHF events observed in patients with CML than in patients with GIST might indicate differences of some of these disease-related risk factors. In addition, a published special safety analysis of cardiac events within the EORTC study of 942 patients with unresectable or metastatic GIST concluded that Imatinib does not induce left ventricular failure in GIST patients where the observed rate was approximately 0.2% while it can be up to 2% in a population with pre-existing cardiac disease.
Skin Rashes and Severe Cutaneous Adverse Reactions
A generalized erythematous, maculopapular, pruritic skin rash has been reported that can fade despite continued therapy. Some patients may have pruritus without accompanying rash, and sometimes there is an exfoliative component. Re-exposure in some patients has resulted in reappearance of rash, but not in all patients. These eruptions generally respond to antihistamines and topical steroids. Occasionally, systemic steroids are required.
Skin rashes have been observed in up to one third of patients treated with imatinib across all indications. These are frequently pruritic and most commonly appear as erythematous, maculopapular or exfoliative lesions on the forearm, the trunk or the face or generalized with systemic expression. Skin biopsies have revealed a toxic drug reaction with a mixed cellular infiltrate. Although most rashes are mild and self-limiting more severe rare cases such as Stevens-Johnson toxic epidermal necrolysis, Erythema multiforme or DRESS may require interruption or discontinuation of treatment. Not surprisingly skin reactions were seen at a higher rate than placebo in the adjuvant GIST trial.
Hepatotoxicity
Hepatotoxicity, occasionally severe, may occur, and has been observed preclinically and clinically. LFT abnormalities usually consisted of mild elevations in transaminases, although a minority of patients had elevated levels of bilirubin. Onset is generally within the first two months of therapy, but has occurred as late as 6 to 12 months after commencing therapy. The levels generally normalize after withholding therapy for 1 to 4 weeks.
Hypophosphataemia
Low serum phosphate and hypophosphataemia (up to Grade 3 or 4) has been observed relatively commonly across all indications, however the origin and the clinical significance of this finding have not been established. Imatinib has been shown to inhibit the differentiation of human monocytes into osteoclasts. The decrease was accompanied by a decrease in the resorptive capacity of these cells. A dose-dependent decrease of RANK-L was observed in osteoclasts in the presence of Imatinib. Sustained inhibition of osteoclastic activity may lead to counter regulatory response resulting in increased levels of PTH. The clinical relevance of the preclinical findings is yet unclear and an association with skeletal AEs such as bone fractures has not been demonstrated.
In the clinical development program serum phosphate was not routinely measured in all studies. Although it was initially hypothesized that hypophosphataemia might be dose-dependent, 24 month interpretable results from the Phase III TOPS study designed to investigate dose dependency of safety endpoints in patients with newly diagnosed CML, have shown that Grade 3 or 4 decreased serum phosphate or serum calcium has been experienced by 19.1% vs.15.5% and 5.1% vs. 0.9% of patients receiving 400 mg and 800 mg, respectively.
Gastrointestinal Obstruction, Perforation or Ulceration
GI ulceration, which may represent in extreme cases local irritation by Imatinib, has been observed in a small proportion of patients across all indications. Tumour haemorrhage/tumour necrosis, obstruction and GI perforation seem to be disease-related and have occurred exclusively or more frequently amongst GIST patients. In the case of metastatic GIST, tumor necrosis may occur in the context of tumor response, rarely leading to perforation. GI obstruction/ileus occurred most commonly in the GIST population where it may be caused by tumor obstruction from metastatic GIST and in the adjuvant setting by adhesions from previous GI surgery.
Tumour lysis syndrome
A causal relationship between tumour lysis syndrome and Imatinib treatment is deemed possible, although some cases were confounded by concomitant medications and other independent risks.
Growth retardation in pediatric patients
Imatinib appears to affect the stature of children, especially children who are pre-pubertal. A causal relationship between growth retardation in pediatric patients and Imatinib treatment could not be ruled out although for some cases of growth retardation in CML there was limited information.
Severe respiratory adverse drug reaction
Severe respiratory events, sometimes fatal, have been observed with Imatinib treatment, including acute respiratory failure, pulmonary hypertension, interstitial lung disease and pulmonary fibrosis. Pre-existing cardiac or pulmonary conditions that may be associated with severe respiratory events have been reported in many of these cases.
Laboratory test abnormalities
Haematology
CML-associated cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses ≥750 mg (phase I study). However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients. The frequency of Grade 3 or 4 neutropenias (ANC <1.0x10^9/L) and thrombocytopenias (platelet count <50x10^9/L) being between 4 and 6 times higher in blast crisis and accelerated phase (59 to 64% and 44 to 63% for neutropenia and thrombocytopenia, respectively) as compared to newly diagnosed patients in chronic phase CML (16,7% neutropenia and 8,9% thrombocytopenia). In newly diagnosed chronic phase CML Grade 4 neutropenia (ANC <0,5x10^9/L) and thrombocytopenia (platelet count <10x10^9/L) were observed in 3,6% and <1 % of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a dose reduction or an interruption of treatment with Imatinib, but can in rare cases lead to permanent discontinuation of treatment. In pediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.
In patients with unresectable or metastatic malignant GIST, Grade 3 and 4 anaemias were reported in 5.4% and 0.7% of patients, respectively, and may have been related to gastrointestinal or intra-tumoural bleeding in at least some of these patients. Grade 3 and 4 neutropenia were seen in 7.5% and 2.7% of patients, respectively, and Grade 3 thrombocytopenia in 0.7% of patients. No patient developed Grade 4 thrombocytopenia. The decreases in WBC and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.
Biochemistry
Severe elevation of transaminases (<5%) or bilirubin (<1%) has been seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week) of Imatinib. Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of CML patients. In GIST patients, 6.8% of Grade 3 or 4 SGPT (serum glutamic pyruvic transferase) elevations and 4.8% of Grade 3 or 4 SGOT (serum glutamic oxaloacetic transferase) elevations were observed. Bilirubin elevation was below 3%.
There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of which outcome was fatal.

4.9 Overdose
Experience with higher than therapeutic doses is limited. Isolated cases of Imatinib overdosage have been reported spontaneously and in the literature. Generally the reported outcome in these cases was improvement or recovery. In the event of overdosage the patient should be observed and appropriate symptomatic treatment should be given.
Events that have been reported at different dose ranges are as follows:
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, increased transaminases.
8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.
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 dose experienced decreased white blood cell count and diarrhea.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties
Mechanism of action (MOA)
Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the BCR-ABL tyrosine kinase (TK), as well as several receptor TKs: KIT, the receptor for stem cell factor (SCF) coded for by the KIT proto-oncogene, the discoidin domain receptors (DDR1) and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.
Pharmacodynamics (PD)
Imatinib is a protein-tyrosine kinase inhibitor, which potently inhibits the breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase at the in vitro, cellular, in vivo levels. The compound selectively inhibits proliferation and induces apoptosis in BCR-ABL positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukemia (ALL) patients. In colony transformation assays using ex vivo peripheral blood and bone marrow samples, Imatinib shows selective inhibition of BCR-ABL positive colonies from CML patients.
In vivo the compound shows anti-tumor activity as a single agent in animal models using BCR-ABL positive tumor cells.
Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), KIT, and inhibits PDGF- and SCF-mediated cellular events. In vitro, Imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumour (GIST) cells, which express an activating KIT mutation. Constitutive activation of the PDGFR or the ABL protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of MDS/MPD, HES/CEL and DFSP. In addition, constitutive activation of KIT or the PDGFR has been implicated in the pathogenesis of ASM. Imatinib inhibits signaling and proliferation of cells driven by dysregulated PDGFR, KIT and ABL kinase activity.

5.2 Pharmacokinetic Properties
The pharmacokinetics of Imatinib have been evaluated over a dosage range of 25 to 1,000 mg. Plasma pharmacokinetic profiles were analyzed on day 1 and on either day 7 or day 28, by which time plasma concentrations had reached steady state.
Absorption
Mean absolute bioavailability for the capsule formulation imatinib is 98%. The coefficient of variation for plasma imatinib AUC is in the range of 40% to 60% after an oral dose. When given with a high fat meal, the rate of absorption of Imatinib was minimally reduced (11% decrease in C_{max} and prolongation of t_{max} by 1,5 h), with a small reduction in AUC (7,4%) compared to fasting conditions.
Distribution
At clinically relevant concentrations of Imatinib, binding to plasma proteins was approximately 95% on the basis of in vitro experiments, mostly to albumin and alpha-acid-glycoprotein, with little binding to lipoprotein.
Biotransformation/metabolism
The main circulating metabolite in humans is the N-demethylated piperazine derivative (CGP71588), which shows similar in vitro potency as the parent compound. The plasma AUC for this metabolite was found to be only 16% of the AUC for Imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the parent compound.
Elimination
Based on the recovery of compound(s) after an oral ^{14}C-labelled 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.
The mean apparent elimination half-life estimated from the single dose PK study was 13.5 hours. The half-life of all ^{14}C-labelled components in plasma was from 41-72 hours.
Plasma pharmacokinetics
Following oral administration in healthy volunteers, the $t_{1/2}$ was approximately 18 h, suggesting that once-daily dosing is appropriate. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25 to 1,000 mg Imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1,5 to 2,5 fold at steady state when dosed once daily.
Special populations
Based on population pharmacokinetic analysis, there was a small effect of age on the volume of distribution (12% increase in patients >65 years old). This change is not thought to be clinically significant. The effect of body weight on the clearance of Imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8.5 L/h, while for a patient weighing 100 kg the clearance will rise to 11,8 L/h. These changes are not considered sufficient to warrant dose adjustment based on kg bodyweight. There is no effect of gender on the kinetics of Imatinib.
Further population PK analysis in the study in newly diagnosed CML patients showed that the effect of covariates and co-medications on both clearance and volume of distribution appears to be small and is not sufficiently pronounced to warrant dose adjustment.
Pediatric patients (below 18 years)
As in adult patients, Imatinib was rapidly absorbed after oral administration in pediatric patients in studies. Dosing in children at 260 and 340 mg/m^2 achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients. The comparison of $AUC_{0\text{-}24h}$ on Day 8 and Day 1 at 340 mg/m^2 dose level revealed a 1.7 fold drug accumulation after repeated once daily dosing.
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.
Organ function impairment
Imatinib and its metabolites are not excreted via the kidney to a significant extent. Patients with mild and moderate impairment of renal function appear to have a higher plasma exposure than patients with normal renal function. The increase is approximately 1.5 to 2 fold, corresponding to a 1.5 fold elevation of plasma AGP, to which Imatinib binds strongly. The free drug clearance of Imatinib is probably similar between patients with renal impairment and those with normal renal function, since renal excretion represents only a minor elimination pathway for Imatinib.
Although the results of pharmacokinetic analysis showed that there is considerable inter-subject variation, the mean exposure to Imatinib did not increase in patients with varying degrees of liver dysfunction as compared to patients with normal liver function.
PACK SIZES:-
6x10's (60 Tablets)
(Alu-Alu blisters having 10 Tablets in each and packed in unit carton with leaflet).
STORAGE CONDITIONS:-
Do not Store above 30C, Protect from Sunlight & Moisture.
DOSAGE AND INSTRUCTION:-
As Directed by physician.
Keep out of reach of children.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
ہدایات: دوا کو ۳۰ ڈگری سینٹی گریڈ درجہ حرارت سے زیادہ پر نہ رکھیں
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

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