accord

PRESCRIBING INFORMATION
(For the Use of a Registered Medical Practitioner or a Hospital or Laboratory only)

IMNIB 400
Imatinib Mesylate Tablets 400 mg

PRODUCT NAME
IMNIB 400 mg

STRENGTH OF ACTIVE SUBSTANCE
Each film coated tablet contains:
Imatinib Mesylate 478 mg equivalent to Imatinib 400 mg

DESCRIPTION
Brownish orange, oval shaped, biconvex, film-coated tablets, debossed with "IM" and "T2"on either side of breakline on one side and plain on the other side.

PHARMACODYNAMICS/PHARMACOKINETICS

Pharmacodynamic Properties:
Mechanism of action
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 c-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.
Pharmacodynamic effects
Imatinib is a protein-tyrosine kinase inhibitor which potently inhibits the Bcr-Abl tyrosine kinase at the *in vitro*, cellular and *in vivo* levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukaemia (ALL) patients.
In vivo the compound shows anti-tumour activity as a single agent in animal models using Bcr-Abl positive tumour cells.
Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), PDGF-R, and inhibits PDGF-mediated cellular events. Constitutive activation of the PDGF receptor 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. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR and Abl kinase activity.
Clinical studies in CML
The effectiveness of Imatinib is based on overall haematological and cytogenetic response rates and progression-free survival. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.
A large, international, open-label, non-controlled phase II study was conducted in patients with Philadelphia chromosome positive (Ph+) CML in the blast crisis phase of the disease. In addition, children have been treated in two phase I studies (in patients with CML or Ph+ acute leukaemia) and one phase II study.
In all clinical studies 38–40% of patients were > 60 years of age and 10–12% of patients were >70 years of age.
Myeloid blast crisis:260 patients with myeloid blast crisis were enrolled. 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 protocol was subsequently amended to allow higher dosing and the remaining 223 patients were started at 600 mg.
The primary efficacy variable was the rate of haematological response, reported as either complete haematological response, no evidence of leukaemia, or return to chronic phase CML using the same criteria as for the study in accelerated phase. In this study, 31% of patients achieved a haematological response (36% in previously untreated patients and 22% in previously treated patients). The rate of response was also higher in the patients treated at 600 mg (33%) as compared to the patients treated at 400 mg (16%, p=0.0220). The current estimate of the median survival of the previously untreated and treated patients was 7.7 and 4.7 months, respectively.
***Lymphoid blast crisis*: a** limited number of patients were enrolled in phase I studies (n=10). The rate of haematological response was 70% with duration of 2–3 months.

Table 1: Response in adult CML studies

	Study0102 38-month data Myeloid blast crisis (n=260)
	% of patients (CI_{95}%)
Haematological response[1] Complete haematological response (CHR) No evidence of leukaemia (NEL) Return to chronic phase (RTC)	31% (25.2–36.8) 8% 5% 18%
Majorcytogenetic response[2] Complete (Confirmed[3]) [95%CI] Partial	15% (11.2–20.4) 7% (2%)[0.6–4.4] 8%

1. Haematological response criteria (all response to be confirmed after ≥4 weeks):
CHR: 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, platelets ≥ 20 x 10^9/l.
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.
BM – bone marrow, PB- peripheral blood
2. Cytogenetic response criteria:
A major response combines both complete and partial response; complete (0% Ph+metaphases), partial (1-35%)
3. Complete Cytogenetic response confirmed by a second marrow cytogenetic evaluation performed at least one month after the initial bone marrow study.
Paediatric patients: A total of 26 paediatric patients of age < 18 years with either chronic phase CML (n=11) or CML in blast crisis or Ph+ acute leukaemias (n=15) were enrolled in a dose-escalation phase I trial. This was a population of heavily pretreated patients, as 46% had received prior BMT and 73% a prior multi-agent chemotherapy. Patients were treated at doses of Imatinib of 260 mg/m^2/day (n=5), 340 mg/m^2/day (n=9), 440 mg/m^2/day (n=7) and 570 mg/m^2/day (n=5). Out of 9 patients with chronic phase CML and cytogenetic data available, 4 (44%) and 3 (33%) achieved a complete and partial cytogenetic response, respectively, for a rate of MCyR of 77%.
A total of 51 paediatric patients with newly diagnosed and untreated CML in chronic phase have been enrolled in an open-label, multicentre, single-arm phase II trial. Patients were treated with Imatinib 340 mg/m^2/day, with no interruptions in the absence of dose limiting toxicity. Imatinib treatment induces a rapid response in newly diagnosed paediatric CML patients with a CHR of 78% after 8 weeks of therapy. The high rate of CHR is accompanied by the development of a complete cytogenetic response (CCyR) of 65% which is comparable to the results observed in adults. Additionally, partial cytogenetic response (PCyR) was observed in 16% for a MCyR of 81%. 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 5.6 months.
The European Medicines Agency has waived the obligation to submit the results of studies with Imatinib in all subsets of the paediatric population in Philadelphia chromosome (bcr-abl translocation)-positive chronic myeloid leukaemia.
Clinical studies in Ph+ ALL
Newly diagnosed Ph+ ALL: In a controlled study (ADE10) of Imatinib versus chemotherapy induction in 55newly diagnosed patients aged 55years and over, Imatinib used as single agent induced a significantly higher rate of complete haematological response than chemotherapy (96.3% vs. 50%; p=0.0001). When salvage therapy with Imatinib was administered in patients who did not respond or who responded poorly to chemotherapy, it resulted in 9patients (81.8%) out of 11 achieving a complete haematological response. This clinical effect was associated with a higher reduction in bcr-abl transcripts in the Imatinib-treated patients than in the chemotherapy arm after 2weeks of therapy (p=0.02). All patients received Imatinib and consolidation chemotherapy (see Table 2) after induction and the levels of bcr-abl transcripts were identical in the two arms at 8weeks. As expected on the basis of the study design, no difference was observed in remission duration, disease-free survival or overall survival, although patients with complete molecular response and remaining in minimal residual disease had a better outcome in terms of both remission duration (p=0.01) and disease-free survival (p=0.02). The results observed in a population of 211 newly diagnosed Ph+ ALL patients in four uncontrolled clinical studies (AAU02, ADE04, AJP01 and AUS01) are consistent with the results described above.
Imatinib in combination with chemotherapy induction (see Table 2) resulted in a complete haematological response rate of 93% (147 out of 158 evaluable patients) and in a major cytogenetic response rate of 90% (19 out of 21 evaluable patients). The complete molecular response rate was 48% (49 out of 102 evaluable patients). Disease-free survival (DFS) and overall survival (OS) constantly exceeded 1 year and were superior to historical control (DFS p<0.001; OS p<0.0001) in two studies (AJP01 and AUS01).

Table 2: Chemotherapy regimen used in combination with Imatinib

Study ADE10	
Prephase	DEX 10 mg/m^2 oral, days 1-5; CP 200 mg/ m^2i.v., days 3, 4, 5; MTX 12 mg intrathecal, day 1
Remission induction	DEX 10 mg/ m^2 oral, days 6-7, 13-16; VCR 1 mg i.v., days 7, 14; IDA 8 mg/ m^2i.v. (0.5 h), days 7, 8, 14, 15; CP 500 mg/ m^2i.v.(1 h) day 1; Ara-C 60 mg/ m^2i.v., days 22-25, 29-32
Consolidation therapyI, III, V	MTX 500 mg/ m^2i.v. (24 h), days 1, 15; 6-MP 25 mg/ m^2 oral, days 1-20
Consolidation therapy II, IV	Ara-C 75 mg/ m^2i.v. (1 h), days 1-5; VM26 60 mg/ m^2i.v. (1 h), days 1-5
Study AAU02	
Induction therapy (*de novo* Ph+ ALL)	Daunorubicin 30 mg/ m^2 i.v., days 1-3, 15-16; VCR 2 mg total dose i.v., days 1, 8, 15, 22; CP 750 mg/m^2i.v., days 1, 8; prednisone 60 mg/m^2 oral, days 1-7, 15-21; IDA 9 mg/m^2 oral, days 1-28; MTX 15 mg intrathecal, days 1, 8, 15, 22; Ara-C 40 mg intrathecal, days 1, 8, 15, 22; methylprednisolone 40 mg intrathecal, days 1, 8, 15, 22
Consolidation (*de novo* Ph+ ALL)	Ara-C 1,000 mg/m^2/12h i.v.(3h), days1-4; mitoxantrone 10mg/m^2i.v. days3-5; MTX 15 mg intrathecal, day1; methylprednisolone 40 mg intrathecal, day1
Study ADE04	
Prephase	DEX 10 mg/ m^2 oral, days 1-5; CP 200 mg/ m^2i.v., days 3-5; MTX 15mg intrathecal, day 1
Induction therapy I	DEX 10 mg/ m^2 oral, days 1-5; VCR 2 mg i.v., days 6, 13, 20; daunorubicin 45 mg/ m^2i.v., days 6-7, 13-14
Induction therapy II	CP 1 g/ m^2i.v. (1 h), days 26, 46; Ara-C 75 mg/m^2i.v. (1 h), days 28-31, 35-38, 42-45; 6-MP 60 mg/ m^2 oral, days 26-46
Consolidation therapy	DEX 10 mg/ m^2oral, days 1-5; vindesine 3 mg/ m^2i.v., day 1; MTX 1.5 g/ m^2i.v. (24 h), day 1; etoposide 250 mg/ m^2 i.v. (1 h) days 4-5; Ara-C 2x 2 g/ m^2i.v. (3 h, q 12 h), day 5
Study AJP01	
Induction therapy	CP 1.2 g/ m^2i.v. (3 h), day 1; daunorubicin 60 mg/ m^2i.v. (1 h), days 1-3; vincristine 1.3 mg/ m^2i.v., days 1, 8, 15, 21; prednisolone 60 mg/ m^2/day oral
Consolidation therapy	Alternating chemotherapy course: high dose chemotherapy with MTX 1 g/ m^2i.v. (24 h), day 1, and Ara-C 2 g/ m^2i.v. (q 12 h), days 2-3, for 4 cycles
Maintenance	VCR 1.3 g/ m^2i.v., day 1; prednisolone 60 mg/m^2 oral, days 1-5
Study AUS01	
Induction-consolidation therapy	Hyper-CVAD regimen: CP 300 mg/ m^2i.v. (3 h, q 12 h), days 1-3; vincristine 2 mg i.v., days 4, 11; doxorubicine 50 mg/ m^2i.v. (24 h), day 4; DEX 40 mg/day on days 1-4 and 11-14, alternated with MTX 1 g/ m^2i.v. (24 h), day 1, Ara-C 1 g/ m^2 i.v. (2 h, q 12 h), days 2-3 (total of 8 courses)
Maintenance	VCR 2 mg i.v. monthly for 13 months; prednisolone 200 mg oral, 5 days per month for 13 months
All treatment regimens include administration of steroids for CNS prophylaxis.	
Ara-C: cytosine arabinoside; CP: cyclophosphamide; DEX: dexamethasone; MTX: methotrexate; 6- MP: 6-mercaptopurine VM26: Teniposide; VCR: vincristine; IDA: idarubicine; i.v.: intravenous	

Relapsed/refractory Ph+ ALL:
WhenImatinib was used as single agent in patients with relapsed/refractory Ph+ ALL, it resulted, in the 53 out of 411 patients evaluable for response, in a haematological response rate of 30% (9% complete) and a major cytogenetic response rate of 23%. (Of note, out of the 411 patients, 353 were treated in an expanded access program without primary response data collected.) The median time to progression in the overall population of 411 patients with relapsed/refractory Ph+ ALL ranged from 2.6 to 3.1 months, and median overall survival in the 401 evaluable patients ranged from 4.9 to 9 months. The data was similar when re-analysed to include only those patients age 55 or older.
Clinical studies in MDS/MPD
Experience with Imatinib in this indication is very limited and is based on haematological and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit or increased survival. One open label, multicentre, phase II clinical trial (study B2225) was conducted testing Imatinib 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 who were treated with Imatinib 400 mg daily. Three patients presented a complete haematological response (CHR) and one patient experienced a partial haematological response (PHR). At the time of the original analysis, three of the four patients with detected PDGFR gene rearrangements developed haematological response (2 CHR and 1 PHR). The age of these patients ranged from 20 to 72 years. In addition a further 24 patients with MDS/MPD were reported in 13 publications. 21 patients were treated with Imatinib 400 mg daily, while the other 3 patients received lower doses. In eleven patients PDGFR gene rearrangements were detected, 9 of them achieved a CHR and 1 PHR. The age of these patients ranged from 2 to 79 years. In a recent publication updated information from 6 of these 11 patients revealed that all these patients remained in cytogenetic remission (range 32-38 months). The same publication reported long term follow-up data from 12 MDS/MPD patients with PDGFR gene rearrangements (5 patients from study B2225). These patients received Imatinib for a median of 47 months (range 24 days – 60 months). In 6 of these patients follow-up now exceeds 4 years. Eleven patients achieved rapid CHR; ten had complete resolution of cytogenetic abnormalities and a decrease or disappearance of fusion transcripts as measured by RT-PCR. Haematological and cytogenetic responses have been sustained for a median of 49 months (range 19-60) and 47 months (range 16-59), respectively. The overall survival is 65 months since diagnosis (range 25-234). Imatinib administration to patients without the genetic translocation generally results in no improvement.
There are no controlled trials in paediatric patients with MDS/MPD. Five (5) patients with MDS/MPD associated with PDGFR gene re-arrangements were reported in 4 publications. The age of these patients ranged from 3 months to 4 years and Imatinib was given at dose 50 mg daily or doses ranging from 92.5 to 340 mg/m^2 daily. All patients achieved complete haematological response, cytogenetic response and/or clinical response.
Clinical studies in HES/CEL
One open-label, multicentre, phase II clinical trial (study B2225) was conducted testing Imatinib in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. In this study, 14 patients with HES/CEL were treated with 100 mg to 1,000 mg of Imatinib daily. A further 162 patients with HES/CEL, reported in 35 published case reports and case series received Imatinib at doses from 75 mg to 800 mg daily. Cytogenetic abnormalities were evaluated in 117 of the total population of 176 patients. In 61 of these 117 patients FIP1L1-PDGFRα fusion kinase was identified. An additional four HES patients were found to be FIP1L1-PDGFRα-positive in other 3 published reports. All 65 FIP1L1-PDGFRα fusion kinase positive patients achieved a CHR sustained for months (range from 1+ to 44+ months censored at the time of the reporting). As reported in a recent publication 21 of these 65 patients also achieved complete molecular remission with a median follow-up of 28 months (range 13-67 months). The age of these patients ranged from 25 to 72 years. Additionally, improvements in symptomatology and other organ dysfunction abnormalities were reported by the investigators in the case reports. Improvements were reported in cardiac, nervous, skin/subcutaneous tissue, respiratory/thoracic/mediastinal, musculoskeletal/connective tissue/vascular, and gastrointestinal organ systems.
There are no controlled trials in paediatric patients with HES/CEL. Three (3) patients with HES and CEL associated with PDGFR gene re-arrangements were reported in 3 publications. The age of these patients ranged from 2 to 16 years and Imatinib was given at dose 300mg/m^2 daily or doses ranging from 200 to 400mg daily. All patients achieved complete haematological response, complete cytogenetic response and/or complete molecular response.
Clinical studies in DFSP
One phase II, open label, multicentre clinical trial (study B2225) was conducted including 12 patients with DFSP treated with Imatinib 800 mg daily. The age of the DFSP patients ranged from 23 to 75 years; DFSP was metastatic, locally recurrent following initial resective surgery and not considered amenable to further resective surgery at the time of study entry. The primary evidence of efficacy was based on objective response rates. Out of the 12 patients enrolled, 9 responded, one completely and 8 partially. Three of the partial responders were subsequently rendered disease free by surgery. The median duration of therapy in study B2225 was 6.2 months, with a maximum duration of 24.3 months. A further 6DFSP patients treated with Imatinib were reported in 5 published case reports, their ages ranging from 18months to 49 years. The adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) Imatinib daily. The median duration of therapy in the published literature ranged between 4 weeks and more than 20 months. The translocation t(17:22)[(q22:q13)], or its gene product, was present in nearly all responders to Imatinib treatment.
There are no controlled trials in paediatric patients with DFSP. Five (5) patients with DFSP and PDGFR gene re-arrangements were reported in 3 publications. The age of these patients ranged from newborn to 14 years and Imatinib was given at dose 50mg daily or doses ranging from 400 to 520mg/m^2 daily. All patients achieved partial and/or complete response.
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 Imatinib is 98%. There was high between-patient variability in plasma Imatinib AUC levels 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. The effect of prior gastrointestinal surgery on drug absorption has not been investigated.
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
The main circulating metabolite in humans is the N-demethylatedpiperazine derivative, which shows similar *in vitro* potency to the parent. 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.
Imatinib and the N-demethyl metabolite together accounted for about 65% of the circulating radioactivity (AUC(0-48h)). The remaining circulating radioactivity consisted of a number of minor metabolites.
The *in vitro* results showed that CYP3A4 was the major human P450 enzyme catalysing the biotransformation of Imatinib. Of a panel of potential comedications (acetaminophen, aciclovir, allopurinol, amphotericin, cytarabine, erythromycin, fluconazole, hydroxyurea, norfloxacin, penicillin V) only erythromycin (IC_{50} 50 µM) and fluconazole (IC_{50} 118 µM) showed inhibition of Imatinib metabolism which could have clinical relevance.
Imatinib was shown *in vitro* to be a competitive inhibitor of marker substrates for CYP2C9, CYP2D6 and CYP3A4/5. K_i values in human liver microsomes were 27, 7.5 and 7.9 µmol/l, respectively. Maximal plasma concentrations of Imatinib in patients are 2–4 µmol/l, consequently an inhibition of CYP2D6 and/or CYP3A4/5-mediated metabolism of co-administered drugs is possible. Imatinib did not interfere with the biotransformation of 5-fluorouracil, but it inhibited paclitaxel metabolism as a result of competitive inhibition of CYP2C8 (K_i = 34.7 µM). This K_i value is far higher than the expected plasma levels of Imatinib in patients; consequently no interaction is expected upon co-administration of either 5-fluorouracil or paclitaxel and Imatinib.
Elimination
Based on the recovery of compound(s) after an oral ^{14}C-labelled dose of Imatinib, approximately 81% of the dose was recovered within 7 days in faeces (68% of dose) and urine (13% of dose). Unchanged Imatinib accounted for 25% of the dose (5% urine, 20% faeces), the remainder being metabolites.
Plasma pharmacokinetics
Following oral administration in healthy volunteers, the t½ 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 25–1,000 mg Imatinib after oral administration. There was no change in the kinetics of Imatinib on repeated dosing, and accumulation was 1.5–2.5-fold at steady state when dosed once daily.
Pharmacokinetics in GIST patients
In patients with GIST steady-state exposure was 1.5-fold higher than that observed for CML patients for the same dosage (400 mg daily). Based on preliminary population pharmacokinetic analysis in GIST patients, there were three variables (albumin, WBC and bilirubin) found to have a statistically significant relationship with Imatinib pharmacokinetics. Decreased values of albumin caused a reduced clearance (CL/f); and higher levels of WBC led to a reduction of CL/f. However, these associations are not sufficiently pronounced to warrant dose adjustment. In this patient population, the presence of hepatic metastases could potentially lead to hepatic insufficiency and reduced metabolism.
Population pharmacokinetics
Based on population pharmacokinetic analysis in CML patients, there was a small effect of age on the volume of distribution (12% increases in patients > 65 years old). This change is not thought to be clinically significant. The effect of bodyweight 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.
Pharmacokinetics in paediatric population
As in adult patients, Imatinib was rapidly absorbed after oral administration in paediatric patients in both phase I and phase II studies. Dosing in children at 260 and 340 mg/m^2/day achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients. The comparison of $AUC_{(0-24)}$ on day 8 and day 1 at the 340 mg/m^2/day dose level revealed a 1.7-fold drug accumulation after repeated once-daily dosing.
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.

INDICATION
Imatinib is indicated for the treatment of
- Paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- Paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- Adult patients with Ph+ CML in blast crisis.
- Adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (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 advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.
- Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

The effect of Imatinib on the outcome of bone marrow transplantation has not been determined.
In adult and paediatric patients, 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 on objective response rates in adult patients with unresectable and/or metastatic DFSP. The experience with Imatinib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited. There are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

RECOMMENDED DOSAGE
Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.
Posology for CML in adult patients
The recommended dosage of Imatinib is 400 mg/day for adult patients in chronic phase CML. Chronic phase CML is defined when all of the following criteria are met: blasts < 15% in blood and bone marrow, peripheral blood basophils < 20%, platelets > 100 x 10^9/l.
The recommended dosage of Imatinib is 600 mg/day for adult patients in accelerated phase. Accelerated phase is defined by the presence of any of the following: blasts ≥ 15% but < 30% in blood or bone marrow, blasts plus promyelocytes ≥ 30% in blood or bone marrow (providing < 30% blasts), peripheral blood basophils ≥ 20%, platelets < 100 x 10^9/l unrelated to therapy.
The recommended dose of Imatinib is 600 mg/day for adult patients in blast crisis. Blast crisis is defined as blasts ≥ 30% in blood or bone marrow or extramedullary disease other than hepatosplenomegaly.
Treatment duration: In clinical trials, treatment with Imatinib was continued until disease progression. The effect of stopping treatment after the achievement of a complete cytogenetic response has not been investigated.
Dose increases 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 (given as 400 mg twice daily) in patients with accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory haematological 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 haematological and/or cytogenetic response. Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.
Posology for CML in children
Dosing for children 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 CML and advanced phase CML (not to exceed the total dose of 800 mg). Treatment can be given as a once daily dose or alternatively the daily dose may be split into two administrations – one in the morning and one in the evening. The dose recommendation is currently based on a small number of paediatric patients. There is no experience with the treatment of children below 2 years of age.
Dose increases from 340 mg/m^2 daily to 570 mg/m^2 daily (not to exceed the total dose of 800 mg) may be considered in children in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory haematological 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 haematological and/or cytogenetic response. Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.
Posology for Ph+ ALL in adult patients
The recommended dose of Imatinib is 600 mg/day for adult patients with Ph+ ALL. Haematological experts in the management of this disease should supervise the therapy throughout all phases of care.
Treatment schedule: On the basis of the existing data, Imatinib has been shown to be effective and safe when administered at 600 mg/day in combination with chemotherapy in the induction phase, the consolidation and maintenance phases of chemotherapy for adult patients with newly diagnosed Ph+ ALL. The duration of Imatinib therapy can vary with the treatment programme selected, but generally longer exposures to Imatinib have yielded better results.
For adult patients with relapsed or refractory Ph+ALL Imatinib monotherapy at 600 mg/day is safe, effective and can be given until disease progression occurs.
Posology for Ph+ ALL in children
Dosing for children 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 Ph+ ALL (not to exceed the total dose of 600 mg).
Posology for MDS/MPD
The recommended dose of Imatinib is 400 mg/day for adult patients with MDS/MPD.
Treatment duration: In the only clinical trial performed up to now, treatment with Imatinib was continued until disease progression. At the time of analysis, the treatment duration

was a median of 47 months (24 days - 60 months).

Posology for HES/CEL

The recommended dose of Imatinib is 100 mg/day for adult patients with HES/CEL.
Dose increase from 100 mg to 400 mg may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.
Treatment should be continued as long as the patient continues to benefit.

Posology for DFSP

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

ROUTE OF ADMINISTRATION

Oral

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

When Imatinib is co-administered with other medicinal products, there is a potential for drug interactions. Caution should be used when taking Imatinib with protease inhibitors, azole antifungals, certain macrolides, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives.
Concomitant use of Imatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imatinib, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and Imatinib should be avoided.

Hypothyroidism

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

Hepatotoxicity

Metabolism of Imatinib is mainly hepatic, and only 13% of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored. It should be noted that GIST patients may have hepatic metastases which could lead to hepatic impairment.
Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with Imatinib. When Imatinib is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions has been detected. Hepatic function should be carefully monitored 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, oedema, pulmonary oedema, ascites, superficial edema) have been reported in approximately 2.5% of newly diagnosed CML patients taking Imatinib. Therefore, it is highly 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 clinical trials, there was an increased incidence of these events in older people and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.

Patients with cardiac disease

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. As cardiac adverse events have been reported uncommonly with Imatinib, a careful assessment of the benefit/risk of Imatinib therapy should be considered in the HES/CEL population before treatment initiation. Myelodysplastic/myeloproliferative diseases with PDGFR gene re-arrangements could be associated with high eosinophil levels. Evaluation by a cardiology specialist, performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD associated with high eosinophil levels before Imatinib is administered. If either is abnormal, follow-up with a cardiology specialist and the prophylactic use of systemic steroids (1–2 mg/kg) for one to two weeks concomitantly with Imatinib should be considered at the initiation of therapy.

Gastrointestinal haemorrhage

In the study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoural haemorrhages were reported. Based on the available data, no predisposing factors (e.g. tumour size, tumour location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of haemorrhage. Since increased vascularity and propensity for bleeding is a part of the nature and clinical course of GIST, standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied.

Tumor lysis syndrome

Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Imatinib.

Laboratory tests

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 likely to be related to 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 may be reduced.
Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving Imatinib.
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. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated.

Paediatric population

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 children are unknown. Therefore, close monitoring of growth in children under Imatinib treatment is recommended.

Interaction with other medicaments

Active substances that may increase Imatinib plasma concentrations:
Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. protease inhibitors such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin) 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.
Active substances that may decrease Imatinib plasma concentrations:
Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or *Hypericum perforatum*, also known as St. John's Wort) may significantly reduce exposure to Imatinib, potentially increasing the risk of therapeutic failure. Pretreatment with multiple doses of rifampicin 600 mg followed by a single 400 mg dose of Imatinib resulted in decrease in C_{max} and $AUC_{(0-\infty)}$ by at least 54% 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 and phenytoin. The plasma AUC for Imatinib decreased by 73% compared to patients not on EIAEDs. Concomitant use of rifampicin or other strong CYP3A4 inducers and Imatinib should be avoided.
Active substances that may have their plasma concentration altered by Imatinib
Imatinib increases the mean C_{max} 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. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine).
Imatinib may increase plasma concentration of other CYP3A4 metabolised drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).
Because of known increased risks of bleeding in conjunction with the use of Imatinib (e.g. haemorrhage), patients who require anticoagulation should receive low-molecular-weight or standard heparin, instead of coumarin derivatives such as warfarin.
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 an inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23% (90%CI [1.16-1.30]). Dose adjustments do not seem to be necessary when Imatinib is co-administrated with CYP2D6 substrates, however caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol clinical monitoring should be considered.
In vitro, Imatinib inhibits paracetamol O-glucuronidation with Ki value of 58.5 micromol/l. This inhibition has not been observed *in vivo* after the administration of Imatinib 400 mg and paracetamol 1000 mg. Higher doses of Imatinib and paracetamol have not been studied.
Caution should therefore be exercised when using high doses of Imatinib and paracetamol concomitantly.
In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be decreased when Imatinib is co-administered. Caution is therefore recommended. However, the mechanism of the observed interaction is presently unknown.
In Ph+ ALL patients, there is clinical experience of co-administering Imatinib with chemotherapy, but drug-drug interactions between Imatinib and chemotherapy regimens are not well characterised. Imatinib adverse events, i.e. hepatotoxicity, myelosuppression or others, may increase and it has been reported that concomitant use with L-asparaginase could be associated with increased hepatotoxicity. Therefore, the use of Imatinib in combination requires special precaution.

Pregnancy and Lactation

Use in pregnancy:
There are limited data on the use of Imatinib in pregnant women. Studies in animals have however shown reproductive toxicity and the potential risk for the foetus is unknown. Imatinib should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.
Use in breast-feeding:
There is limited information on Imatinib distribution on human milk. Studies in two breast-feeding women revealed that both Imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio studied in a single patient was determined to be 0.5 for Imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of Imatinib and the metabolite and the maximum daily milk intake by infants, the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to Imatinib are unknown, women taking Imatinib should not breast-feed.

UNDESIRABLE EFFECTS

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequency categories are defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of frequency, the most frequent first.
Adverse reactions and their frequencies reported in Table 3 are based on the main registration studies.

Table 3: Adverse reaction in clinical studies

Infections and Infestations	
Uncommon:	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1], sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis
Rare:	Fungal infection
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Rare:	Tumour lysis syndrome
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
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:	Pleuritic pain, 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, melaena, 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[8], hepatic necrosis
Skin and subcutaneous tissue disorders	
Very common:	Periorbital oedema, 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, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions
Rare:	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angio neurotic 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[9]
Common:	Joint swelling
Uncommon:	Joint and muscle stiffness
Rare:	Muscular weakness, arthritis, rhabdomyolysis/myopathy
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
Rare:	Haemorrhagic corpus luteum/haemorrhagic ovarian cyst
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 (haematoma, haemorrhage) 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 haemorrhage were most commonly observed in GIST patients.
8 Some fatal cases of hepatic failure and of hepatic necrosis have been reported.
9 Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.
The following types of reactions have been reported mainly from post-marketing experience with Imatinib. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory studies in unapproved indications. Because these reactions 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 4: Adverse reactions from post-marketing reports

Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Not known:	Tumour haemorrhage/tumour necrosis
Immune system disorders	
Not known:	Anaphylactic shock
Nervous system disorders	
Not known:	Cerebral oedema
Eye disorders	
Not known:	Vitreous haemorrhage
Cardiac disorders	
Not known:	Pericarditis, cardiac tamponade
Vascular disorders	
Not known:	Thrombosis/embolism
Respiratory, thoracic and mediastinal disorders	
Not known:	Acute respiratory failure[1], interstitial lung disease
Gastrointestinal disorders	
Not known:	Ileus/intestinal obstruction, gastrointestinal perforation, diverticulitis
Skin and subcutaneous tissue disorders	
Not known:	Palmoplantar erythrodysesthesia syndrome
Not known:	Lichenoid keratosis, lichen planus
Not known:	Toxic epidermal necrolysis
Not known:	Drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	
Not known:	Avascular necrosis/hip necrosis
Not known:	Growth retardation in children

1 Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions.

Laboratory test abnormalities

Haematology
In CML, 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, the frequency of grade 3 or 4 neutropenias (ANC < 1.0 x 10^9/l) and thrombocytopenias (platelet count < 50 x 10^9/l) being between 4 and 6 times higher in blast crisis and accelerated phase (59–64% and 44–63% 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 < 0.5 x 10^9/l) and thrombocytopenia (platelet count < 10 x 10^9/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 reduction of the dose or an interruption of treatment with Imatinib, but can in rare cases lead to permanent discontinuation of treatment. In paediatric 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 the study in patients with unresectable and/or metastatic GIST, grade 3 and 4 anaemia was 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 was 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 white blood cell (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%) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of CML patients. In GIST patients (study B2222), 6.8% of grade 3 or 4 ALT (alanine aminotransferase) elevations and 4.8% of grade 3 or 4 AST (aspartate aminotransferase) elevations were observed. Bilirubin elevation was below 3%.
There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of them outcome was fatal, including one patient on high dose paracetamol.

OVERDOSE AND TREATMENT

Experience with doses higher than the recommended therapeutic dose is limited. Isolated cases of Imatinib overdose have been reported spontaneously and in the literature. In the event of overdose the patient should be observed and appropriate symptomatic treatment given. Generally the reported outcome in these cases was "improved" or "recovered".
Events that have been reported at different dose ranges are as follows:
Adult population
1200 to 1600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.
1800 to 3200 mg (as high as 3200 mg daily for 6 days): Weakness, myalgia, increased creatine phosphokinase, increased bilirubin, gastrointestinal pain.
6400 mg (single dose): One case reported in the literature of one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, decreased neutrophil count, increased transaminases.
8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.
Paediatric population
One 3-year-old male exposed to a single dose of 400 mg experienced vomiting, diarrhoea and anorexia and another 3-year-old male exposed to a single dose of 980 mg experienced decreased white blood cell count and diarrhoea.
In the event of overdose, the patient should be observed and appropriate supportive treatment given.

INGREDIENTS

Active Ingredients:
Imatinib Mesylate

Inactive Ingredients:
Hypromellose 6 cps
Microcrystalline Cellulose PH 102
Crospovidone
Colloidal Anhydrous Silica
Magnesium Stearate

Tablet coat:
HPMC 2910 / Hypromellose 6 cp
Talc
Macrogol / PEG 8000
Iron oxide yellow (E172)
Iron oxide red (E172)

STORAGE CONDITION

Do not store above 25°C.

DOSAGE FORMS OR PRESENTATION

IMNIB 400 is available in PVC/PVDC –Alu Blister pack of 10 tablets, each carton contains 3 Blisters.

NAME AND ADDRESS OF MANUFACTURER

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