IMATINIB GP PHARM
IMATINIB 100 mg and 400 mg
Coated Tablets

GP Pharm

Argentine Industry — Sale under filed prescription

COMPOSITION:
Each **IMATINIB GP PHARM 100** tablet contains: Imatinib (equiv. to Imatinib mesylate 119.5 mg) 100 mg
Excipients: Mannitol CD, Crospovidone CL, Microcrystalline cellulose, Talc, Colloidal silicon dioxide, Magnesium stearate, LAY AL HL15457T, Iron oxide Yellow Iron.
Each **IMATINIB GP PHARM 400** tablet contains: Imatinib (equiv.to Imatinib mesylate 478 mg) 400 mg Mannitol CD, Crospovidone CL, Microcrystalline cellulose, Talc, Colloidal silicon dioxide, Magnesium stearate, LAY AL HL15457T, Iron oxide Yellow Iron.
ATC classification: L01XE01
THERAPEUTIC ACTION Antineoplastic, protein tyrosine kinase inhibitor.
INDICATIONS
Imatinib is indicated for the treatment of:
. Adult and pediatric patients with newly diagnosed Philadelphia chromosome positive (Ph +) chronic myeloid leukemia (CML) (bcr-abl) for whom bone marrow transplantation is not considered first-line treatment.
. Adult and pediatric patients with Ph + CML in chronic phase after failure of interferon-alpha treatment, or in accelerated phase or blast crisis.
. Adult and pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph + ALL), integrated with chemotherapy.
. Adult patients with refractory or relapsed Ph + ALL, as monotherapy.
. Adult patients with myelodysplastic / myeloproliferative syndromes (MDS / SMP) associated with rearrangement of the platelet-derived growth factor receptor (PDGFR) gene.
. Adult patients with aggressive systemic mastocytosis (MSA / ASM) without the D816V c-Kit mutation as determined with an FDA approval test or with unknown c-Kit mutational status.
. Adult patients with advanced hypereosinophilic syndrome (HES) and / or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement.
. Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and / or metastatic DFSP who are not of choice for surgery
. Adult patients with Kit (CD 117) positive unresectable and / or metastatic malignant gastrointestinal stromal tumors (GIST).
. Adult patients at significant risk of relapse after GIST Kit (CD117) positive resection, as adjunctive treatment. Patients who are at low or very low risk of relapse should not receive adjuvant treatment.
The effect of Imatinib on the outcome of bone marrow transplantation has not been determined.
In adult and pediatric patients, the effectiveness of Imatinib is based on overall hematologic and cytogenetic response rates and progression-free survival in CML, on hematologic and cytogenetic response rates in Ph + ALL, MDS / SMP, on rates of Hematologic response in HES / CEL and in objective response rates in adult patients with unresectable and / or metastatic DFSP. Experience with imatinib in patients with MDS / PMS associated with PDGFR gene rearrangement is very limited. Except for newly diagnosed CML in the chronic phase, there are no controlled trials demonstrating clinical benefit or increased survival for these diseases.
PHARMACOLOGICAL CHARACTERISTICS
Mechanism of action
Imatinib is a protein tyrosine kinase inhibitor molecule that strongly
Inhibits Bcr-Abl tyrosine kinase, as well as several receptor tyrosine kinases: Kit, the proto-encoded precursor cell factor (SCF) receptor. c-Kit oncogene, discoidin domain receptors (DDR1 and DDR2), colony stimulating factor receptor (CSF-1R), and platelet-derived growth factor α and β receptors (PDGFR-α and PDGFR-β). Imatinib can also inhibit cellular processes mediated by the activation of these receptor kinases.
In vivo, imatinib inhibits tumor growth of murine myeloid cells transfected with BCR-ABL, as well as BCR-ABL positive leukemia lines derived from patients with blast crisis CML.
Imatinib is also a receptor tyrosine kinase inhibitor for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF and SCF-mediated cellular events.
In vitro, imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation.
Pharmacodynamic properties
Imatinib is a protein tyrosine kinase inhibitor that potently inhibits Bcr-Abl tyrosine kinase in vitro, at the cellular level, and in vivo.
The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as new leukemic cells of the Philadelphia chromosome positive CML and in patients with acute lymphoblastic leukemia (ALL). In vivo the compound shows antitumor activity as a single agent in animal models using Bcr-Abl positive tumor cells.
Imatinib is also a receptor tyrosine kinase inhibitor for platelet-derived growth factor (PDGF), PDGFR, and inhibits cellular processes mediated by PDGF and FCT. Constitutive activation of the PDGF receptor or Abl protein tyrosine kinase has been implicated in the pathogenesis of SMD / SMP, SHE / LEC and DFSP as a consequence of fusion to different proteins or the constitutive production of PDGF. Imatinib inhibits the signaling and proliferation of cells generated by unregulated PDGFR activity and Abl kinase activity.
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Pharmacokinetic properties
Imatinib pharmacokinetics have been evaluated in a dosage range of 25 to 1,000 mg. Plasma pharmacokinetic profiles were analyzed on day 1 and on day 7 or day 28, when plasma concentrations had reached steady state.
Absorption and Distribution
Imatinib is well absorbed after oral administration with Cmax reached within 2-4 hours after dosing. The mean absolute bioavailability is 98%. The mean AUC of imatinib increases proportionally with increasing doses ranging from 25 mg to 1,000 mg. There are no significant changes in the pharmacokinetics of imatinib at repeat doses, and the accumulation is 1.5 to 2.5 times at steady state when imatinib is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in in vitro experiments is approximately 95%, mainly to albumin and α1-acid glycoprotein.
Biotransformation
The main circulating metabolite in humans is the N-demethylated derivative of piperazine, which shows a potency in vitro similar to that of the starting compound. The plasma AUC for the metabolite was only 16% of the AUC for imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the starting compound.
Imatinib together with its metabolite N-desmethyl reached approximately 5% of the circulating radioactivity (AUC (0-48h)). The remaining circulating radioactivity corresponded to a number of minor metabolites.
The in vitro results showed that CYP3A4 is the main human P450 enzyme that catalyzes the biotransformation of imatinib. Of a series of concomitant medications (acetaminophen, acyclovir, allopurinol, amphotericin, cytarabine, erythromycin, fluconazole, hydroxyne, norfloxacin, penicillin V) only erythromycin (IC50 50 µM) and fluconazole (IC50 118 µM) showed possible inhibition of imatinib metabolism with possible imatinib metabolism. clinical relevance.
In vitro, imatinib was shown to be a competitive inhibitor of marker substrates for CYP2C9, CYP2D6 and CYP3A4 / 5. Ki values in human liver microsomes were 27, 7.5 and 7.9 µmol / l, respectively. Peak plasma concentrations of imatinib in patients are 2–4 µmol / L, consequently, 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 did inhibit the metabolism of paclitaxel as a result of competitive inhibition of CYP2C8 (Ki = 34.7 µM). This Ki value is much higher than the expected plasma level of imatinib in patients, therefore an interaction is not expected in the co-administration of both 5-fluorouracil or paclitaxel and Imatinib.
Elimination
Imatinib elimination is predominantly in the faeces, mainly as metabolites. Based on recovery of compound (s) after an oral dose of 14C-labeled imatinib, approximately 81% of the dose was eliminated within 7 days, in faeces (68% of the dose) and urine (13% of the dose). dose). Unchanged Imatinib accounted for 25% of the dose (5% urine, 20% feces), the rest being metabolites.
After oral administration in healthy volunteers, the elimination half-lives of imatinib and its main active metabolite, the N-demethyl derivative (CGP74588), are approximately 18 and 40 hours, respectively.
Typically, the clearance of Imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L / hr, whereas for a 50-year-old patient weighing 100 kg, clearance increases to 14 L / hr. The 40% interpatient variability in clearance does not justify initial dose adjustment based on body weight and / or age, but indicates the need for close monitoring of treatment-related toxicity.
DOSAGE AND METHOD OF ADMINISTRATION
Treatment should be initiated by a physician experienced in treating patients with hematologic malignancies and malignant sarcomas, as appropriate.
The prescribed dose should be administered orally, during a meal and with a large glass of water. Doses of 400 or 600 mg should be administered once a day, while the daily dose of 800 mg should be administered in doses of 400 mg twice a day, in the morning and in the evening.
For patients who cannot swallow the coated tablets, you can dissolve them in a glass of water or apple juice. The number of tablets needed should be placed in an appropriate volume of drink (approximately 50 ml for a 100 mg tablet and 200 ml for a 400 mg tablet) and then mixed with a spoon.
The suspension should be administered immediately after complete disintegration of the tablet (s).
Dosage for CML in adult patients
The recommended dose of imatinib for adult patients with chronic phase CML is 400 mg / day. The chronic phase of CML is defined by the following criteria: blasts <15% in blood and bone marrow, basophils in peripheral blood <20%, platelets> 100 x 10^9 / L
The recommended dose of imatinib for adult patients in the accelerated phase is 600 mg / day. The accelerated phase is defined by the presence of any of the following parameters: blasts ≥ 15% but <30% in blood or bone marrow, blasts plus promyelocytes ≥ 30% in blood or bone marrow (provided blasts <30%) , basophils in peripheral blood ≥ 20%, platelets <100 x 10^9 / l not related to treatment.
The recommended dose of imatinib for adult patients in blast crisis is 600 mg / day. Blast crisis is defined as blasts ≥30% in blood or bone marrow, or extramedullary disease other than hepatosplenomegaly.
Dose increases from 400 mg to 600 mg or 800 mg in patients in the chronic phase of the disease, or from 600 mg to a maximum of 800 mg (administered in doses of 400 mg twice daily) in patients in the accelerated phase or blast crisis, can be considered in the absence of severe adverse reactions and severe neutropenia or thrombocytopenia not related to leukemia, under the following circumstances: disease progression (at any time); if a satisfactory haematological response is not achieved after at least 3 months of treatment; if a cytogenetic response is not achieved after 12 months of treatment, or loss of the hematological and / or cytogenetic response previously achieved. Due to the possibility of an increased incidence of adverse reactions at higher doses, patients should be closely monitored after dose escalation.
Dosage for CML in children
Dosage in children should be based on body surface area (mg / m^2). A dose of 340 mg / m^2 per day is recommended in children with CML in chronic phase and CML in advanced phases (not exceeding the total dose of 600 mg). The treatment can be administered once a day or, alternatively, the dose can be divided into two administrations - one in the morning and one in the evening. The dosage recommendation is currently based on a small number of pediatric patients. There is no experience in treating children under 1 year of age.
Dosage for Ph + ALL in adult patients
The recommended dose of Imatinib for adult patients with Ph + ALL is 600 mg / day. Hematologists with experience in the management of this disease must supervise treatment during all phases.
For adult patients with relapsed or refractory Ph + ALL, monotherapy with imatinib 600 mg / day is safe, effective, and can be administered until disease progression.
Dosage for Ph + ALL in children
The dose for children should be based on 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). Imatinib treatment can be given as a daily dose.
Dosage for SMD / SMP
The recommended dose of Imatinib for adult patients with MDS / PMS is 400 mg / day.
Adult patients with ASM
Determine the status of the D816V c-Kit mutation before initiating therapy. The recommended dose of Imatinib is 400 mg / day for adult ASM patients without the D816V c-Kit mutation. If the mutational status of c-Kit is not known or available, treatment with Imatinib 400 mg / day may be considered for patients with ASM who do not respond satisfactorily to other therapies. For patients with MAP associated with eosinophilia, a clonal hematologic disease related to the FIP1L1-PDGFRα fusion kinase, a starting dose of 100 mg / day is recommended. Increasing the dose from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if evaluations demonstrate insufficient response to treatment.
Dosage for SHE / LEC
The recommended dose of Imatinib is 400 mg / day for adult patients with HES / CEL.
For HES / CEL patients with proven FIP1L1-PDGFRα kinase fusion, a starting dose of 100 mg / day is recommended. Increasing the dose from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if evaluations demonstrate an insufficient response to treatment.
Dosage for DFSP
The recommended dose of Imatinib for adult patients with DFSP is 800 mg / day.
Dosage in GIST
The recommended dose of Imatinib is 400 mg / day for patients with inoperable and / or metastatic GIST. A dose increase of up to 800 mg daily (given as 400 mg twice daily), as clinically indicated, may be considered in patients showing clear signs or symptoms of disease progression at a lower dose and in the absence of serious adverse reactions.
The recommended dose of Imatinib is 400 mg / day for adjunctive treatment of adult patients after GIST resection. The optimal duration of treatment has not yet been established. The duration of treatment in the clinical trial supporting this indication was 36 months
Dose adjustment for adverse reactions
Non-haematological adverse reactions
If a severe non-haematological adverse reaction develops with the use of Imatinib, treatment will be discontinued until the reaction has resolved. Afterward, treatment can be resumed as appropriate depending on the initial severity of the reaction.
If there are increases in bilirubin> 3 times the upper limit of normal (ULN) or in liver transaminases> 5 times the ULN, Imatinib should be discontinued until bilirubin levels have returned to <1.5 times ULN and levels transaminases at <2.5 times the ULN. Imatinib treatment can then be continued at the reduced daily dose. In adults the dose should be reduced from 400 mg to 300 mg or from 600 mg to 400 mg, or from 800 mg to 600 mg, and in children from 340 to 260 mg / m^2 / day.
Hematologic adverse reactions
Dose reduction or treatment interruption is recommended if severe neutropenia and thrombocytopenia occur, as indicated in the table below.
Dose adjustment for neutropenia and thrombocytopenia:

ASM associated with eosinophilia (initial dose 100 mg)	ANC <1.0 x 10^9 / L and / or platelets <50 x 10^9 / L	1. Interrupt Imatinib until ANC ≥ 1.5 x 10^9 / L and platelets ≥ 75 x 10^9 / L. 2. Resume treatment with imatinib at the previous dose (before the adverse reaction).
HES / ECL (starting dose 100 mg)	ANC <1.0 x 10^9 / L and / or platelets <50 x 10^9 / L	1. Interrupt Imatinib until ANC ≥ 1.5 x 10^9 / L and platelets ≥ 75 x 10^9 / L. 2. Resume treatment with Imatinib at the previous dose (before the adverse reaction).
Chronic phase CML, SMD / SMP and GIST (starting dose 400 mg) HES / ECL (400 mg dose)	ANC <1.0 x 10^9 / L and / or platelets <50 x 10^9 / L	1. Interrupt Imatinib until ANC ≥ 1.5 x 10^9 / L and platelets ≥ 75 x 10^9 / L. 2. Resume treatment with Imatinib at the dose of 400 mg. 3. If ANC <1.0 x 10^9 / L and / or platelets <50 x 10^9 / L recurs, repeat step 1 and resume Imatinib at the reduced dose of 300 mg.
LMC accelerated phase and blast crisis and Ph + ALL (initial dose 600 mg)	ANC <0.5 x 10^9 / L and / or platelets <10 x 10^9 / L	1. Check if cytopenia is related to leukemia (bone marrow aspirate or biopsy). 2. If the cytopenia is not related to leukemia, reduce the dose of Imatinib to 400 mg. 3. If cytopenia persists for 2 weeks, reduce to 300 mg. 4. If cytopenia persists for 4 weeks and remains unrelated to leukemia, discontinue Imatinib until ANC ≥ 1 x 10^9 / L and platelets ≥ 20 x 10^9 / L, then resume treatment with 300 mg.
DFSP (at a dose of 800 mg) RAN <1.0 x 10^9 / L		1. Stop Imatinib until ANC ≥ 1.5 x 10^9 / L and platelets ≥ 75 x 10^9 / L. 2. Resume treatment with imatinib at 600 mg. 3. In case of recurrence of ANC <1.0 x 10^9 / L and / or platelets <50 x 10 9 / L, repeat step 1 and restart Imatinib with a reduced dose of 400mg / m^2.
Pediatric chronic phase CML (at doses of 340 mg / m^2)	ANC <1.0 x 10^9 / L and / or platelets <50 x 10^9 / L	1. Withdraw Imatinib until ANC ≥ 1.5 x 10^9 / L and platelets ≥ 75 x 10^9 / L. 2. Resume treatment with Imatinib at the previous dose (before the adverse reaction). 3. If ANC <1.0 x 10^9 / l and / or platelets <50 x 10^9 / L recurs, repeat step 1 and resume Imatinib at the reduced dose of 260 mg / m^2

ANC = Absolute Neutrophil Count.

Special populations
Hepatic impairment: Imatinib is primarily metabolized by the liver. Patients with mild, moderate or severe hepatic impairment should receive the recommended minimum dose of 400 mg daily. The dose can be reduced if it is not well tolerated.
CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.
WARNINGS AND PRECAUTIONS
When imatinib is administered with other medications there is a potential for drug interactions. Caution should be exercised when taking imatinib with protease inhibitors, azole antifungals, some macrolides, CYP3A4 substrates with a narrow therapeutic window (eg cyclosporine, pimocide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives.
Concomitant use of imatinib and medications that induce CYP3A4 (eg, dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, or Hypericum perforatum, (also known as St. John's wort) can significantly reduce exposure to Imatinib, potentially increasing the risk. treatment failure Therefore, the concomitant use of strong CYP3A4 inducers and imatinib should be avoided.
Hypothyroidism
During treatment with Imatinib, clinical cases of hypothyroidism have been reported in thyroidectomized patients receiving levothyroxine replacement therapy. In these patients, thyroid stimulating hormone levels (TSH levels) should be closely monitored.
Hepatotoxicity
Imatinib metabolism is primarily hepatic, and only 13% of excretion is through the kidneys. In patients with hepatic impairment (mild, moderate, or severe), peripheral blood counts and liver enzymes should be carefully monitored. It should be taken into account that GIST patients may present with liver metastases that can lead to liver failure.
Cases of liver damage, including liver failure and liver necrosis, have been observed with imatinib. When imatinib is combined with high-dose chemotherapy regimens, an increase in severe liver reactions has been observed. Liver function should be closely monitored when Imatinib is combined with chemotherapy regimens known to be also associated with liver disorders.
Fluid retention and edema
Cases of severe fluid retention (pleural effusion, edema, pulmonary edema, ascites, superficial edema) have been reported in approximately 2.5% of newly diagnosed CML patients treated with Imatinib, therefore weighing the patients is highly recommended. patients on a regular basis. Rapid and unexpected weight gain should be carefully considered, and if deemed necessary, supportive and therapeutic measures should be taken. In clinical trials, there was an increased incidence of these events in elderly patients and in those with a previous history of heart disease. Therefore, caution should be exercised in patients with cardiac dysfunction.
Patients with heart disease
Patients with heart disease, risk factors for heart failure, or a history of kidney failure should be carefully monitored, and any patient with signs and symptoms consistent with heart or kidney 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 degranulation of HES cells after initiation of imatinib treatment. The situation was reported to be reversible after administration of systemic corticosteroids, measures of circulatory support, and temporary withdrawal of Imatinib. Since cardiac adverse reactions have been reported infrequently with imatinib, the benefit / risk balance of Imatinib treatment in patients with HES / CEL should be carefully evaluated before initiating treatment.
Myelodysplastic / myeloproliferative syndromes with PDGFR gene rearrangement could be associated with eosinophilia. Therefore, evaluation by a cardiologist, echocardiography, and serum troponin determination should be considered in patients with HES / CEL, and in patients with MDS / PMS associated with eosinophilia, before Imatinib is administered. If any are not normal, at the beginning of treatment, follow-up by a cardiologist and prophylactic use of systemic corticosteroids (1-2 mg / kg) for 1 to 2 weeks concomitantly with Imatinib should be considered.
Gastrointestinal bleeding
In the study in patients with unresectable and / or metastatic GIST, both gastrointestinal and intra-tumor hemorrhages were reported. Based on the available data, no predisposing factors (eg tumor size, tumor location, coagulation disorders) have been identified that pose GIST patients at increased risk for any type of bleeding.
Since increased vascularity and the propensity for bleeding is part of the nature and clinical course of GIST, standardized practices and procedures for the control and management of bleeding should be applied in all patients.
In addition, cases of gastric antral vascular ectasia (EVAG), a rare cause of gastrointestinal bleeding, have been reported in post-marketing experience in patients with CML, ALL, and other diseases. If necessary, discontinuation of Imatinib may be considered.
Tumor lysis syndrome
Before initiating treatment with imatinib, correction of clinically significant dehydration and treatment of high uric acid levels are recommended, due to the possible appearance of tumor lysis syndrome (TLS).
Reactivation of the hepatitis B virus
Reactivations of hepatitis B have occurred in patients who are chronic carriers of this virus after patients have received BCR-ABL tyrosine kinase inhibitors. In some cases, acute liver failure or fulminant hepatitis occurred, leading to liver transplantation or fatal outcome.
Patients should be tested for HBV infection before starting treatment with Imatinib. Experts in liver disease and in the treatment of hepatitis B should be consulted before starting treatment in patients with a positive serology for hepatitis B (including patients with active disease) and patients who test positive for HBV infection during treatment. Carriers of HBV requiring treatment with imatinib should be closely monitored for signs and symptoms of active HBV infection throughout treatment and for several months after treatment ends.
Phototoxicity
Direct sun exposure should be avoided or minimized due to the risk of phototoxicity associated with imatinib

treatment. Patients should be instructed to take measures such as protective clothing and sunscreen with a high protection factor (SPF).

Lab tests

Complete blood counts should be taken regularly during treatment with imatinib. Imatinib treatment of patients with CML has been associated with neutropenia or thrombocytopenia. However, the presence of these cytopenias is probably related to the phase of the disease being treated, being more frequent in patients in accelerated phase of CML or blast crisis, compared to patients in chronic phase of CML. Imatinib treatment may be interrupted or the dose reduced. Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving imatinib. In patients with impaired renal function, plasma exposure to imatinib appears to be higher than in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (GAA), an imatinib-binding protein, in these patients. Patients with renal impairment should receive the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if it is not well tolerated. Long-term treatment with imatinib may be associated with a clinically significant decrease in renal function. Therefore, renal function should be assessed prior to initiation of imatinib treatment and closely monitored during treatment, paying particular attention to patients with risk factors for renal impairment. If renal impairment is observed, treatment and appropriate measures should be instituted in accordance with standard therapeutic guidelines.

Interaction with other medicinal products and other forms of interaction

Active substances that may increase plasma concentrations of imatinib:

Substances that inhibit the activity of cytochrome P450, CYP3A4 isoenzyme (eg, protease inhibitors such as indinavir, lopinavir / ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, some voriconazole, some voriconazole macrolides such as erythromycin, clarithromycin, and telithromycin) may reduce metabolism and increase imatinib concentrations. There was a significant increase in imatinib exposure (mean Cmax and AUC of imatinib increased 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 exercised when imatinib is administered with inhibitors of the CYP3A4 family.

Active substances that can reduce the plasma concentrations of imatinib:

Substances that are inducers of CYP3A4 activity (eg, dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, fosphenytoin, primidone, or Hypericum perforatum, also known as St. John's wort) can significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure. Pretreatment with multiple doses of rifampin, 600 mg followed by a single 400 mg dose of imatinib, represents a reduction in Cmax, and AUC (0-∞) of at least 54% and 74% of the respective values without rifampicin treatment. Similar results were observed in patients with malignant gliomas treated with imantinib while taking enzyme-inducing antiepileptic drugs such as carbamazepine, oxcarbazepine, and phenytoin. The plasma AUC of imatinib decreased by 73% compared to patients who were not being treated with enzyme-inducing antiepileptic drugs. Concomitant use of rifampin or another strong CYP3A4 inducer and imatinib should be avoided.

Active substances to which imatinib can alter their plasma concentration

Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2 and 3.5-fold, respectively, indicating that imatinib inhibits CYP3A4. Therefore, caution is advised when imatinib is administered with CYP3A4 substrates with a narrow therapeutic window (eg, cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, dihergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, and quinidine). Imatinib may increase the plasma concentration of other drugs metabolised by CYP3A4 (eg triazolo-benzodiazepines, dihydropyridine, calcium channel blockers, certain HMG-CoA reductase inhibitors, ie statins, etc.).

Patients requiring anticoagulants should receive standard or low molecular weight heparin instead of coumarin derivatives such as warfarin, due to the known increased risk of bleeding in combination with the use of imatinib (eg bleeding).

In vitro, imatinib inhibits the activity of the cytochrome P450, isoenzyme CYP2D6 at concentrations similar to those that affect CYP3A4 activity. Imatinib doses of 400 mg twice daily showed an inhibitory effect on the metabolism of metoprolol mediated by CYP2D6, with an increase in Cmax and AUC of metoprolol of approximately 23% (90% CI [1,16-1, 30]). Dose adjustments do not appear to be necessary when imatinib is co-administered with CYP2D6 substrates, however caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol, clinical supervision should be considered.

In vitro, imatinib inhibits the O-glucuronidation of paracetamol with a KI value of 58.5 micromoles / l. This inhibition has not been observed in vivo after the administration of imatinib and paracetamol 1000 mg. Higher doses of imatinib and paracetamol have not been studied.

Therefore, you should exercise caution when using high doses of imatinib and paracetamol concomitantly.

In thyroidectomized patients receiving levothyroxine treatment, plasma levothyroxine exposure may be decreased when imatinib is co-administered. Therefore, caution is advised. However, the mechanism of the observed interaction is currently unknown. There is clinical experience with the co-administration of imatinib with chemotherapy in patients with Ph + ALL, but the drug-drug interactions between imatinib and chemotherapy regimens are not well characterized. Imatinib adverse events, eg hepatotoxicity, myelosuppression or others, may be increased and it has been reported that concomitant use with L-asparaginase may be associated with increased hepatotoxicity. Therefore, the use of imatinib in combination requires special precaution.

Fertility, pregnancy and lactation

Women of childbearing age

Women of childbearing potential must be advised to use effective contraception during treatment.

Pregnancy

There are limited data on the use of imatinib in pregnant women. During the post-marketing phase, there have been reports of miscarriages and congenital abnormalities in women who have taken imatinib. However, studies in animals have shown reproductive toxicity and the risk to the fetus is unknown. Imatinib should not be used during pregnancy unless clearly necessary. If used during pregnancy, the patient must be informed of the potential risk to the fetus.

Lactation

There is limited information on the distribution of imatinib in human milk. Studies in two lactating women revealed that both imatinib and its active metabolite can be excreted in human milk. The milk-plasma ratio, studied in a single patient, has been established to be 0.5 for imatinib and 0.9 for the metabolite, suggesting a greater distribution of the metabolite in milk. Considering the combined concentration of imatinib and the metabolite and the maximum daily amount of milk intake by infants, the total exposure is expected to be low (~ 10% of a therapeutic dose). However, since the effects of low-dose exposure to imatinib by an infant are unknown, women taking imatinib should not breast-feed their infants.

Fertility

In preclinical studies the fertility of male and female rats was not affected. No studies have been performed in patients treated with imatinib and its effect on fertility and gametogenesis. Patients concerned about their fertility during treatment with imatinib should consult their doctor.

Effects on ability to drive and use machines

Patients should be warned that adverse reactions such as dizziness, blurred vision, or drowsiness may occur during imatinib treatment. Therefore, caution should be recommended when driving a car or operating machinery

ADVERSE REACTIONS

Patients in advanced stages of malignant processes may have multiple clinical symptoms that can make the attribution of causality of adverse reactions difficult, given the variety of symptoms related to the underlying disease, its progression and the joint administration of numerous drugs.

In clinical trials in CML, discontinuation of treatment due to drug-related adverse reactions was seen in 2.4% of newly diagnosed patients, 4% of patients in late chronic phase after treatment failure with interferon, 4% of patients in accelerated phase after failure of interferon treatment and 5% of patients in blast crisis after failure of interferon treatment. In GIST 4% of patients discontinued study medication due to adverse drug reactions.

Adverse reactions in all indications were similar with two exceptions. More myelosuppression was observed in patients with CML than with GIST, which is probably due to the underlying disease. In the study in patients with unresectable and / or metastatic GIST, 7 (5%) patients presented Common Toxicity Criteria (CTC) grade 3/4: gastrointestinal bleeding (3 patients), intra-tumor bleeding (3 patients) or both (1 patient). The location of the gastrointestinal tumor could have been the cause of the gastrointestinal bleeding. Gastrointestinal and tumor bleeds can be severe and sometimes fatal.

The most commonly reported treatment-related adverse reactions (≥ 10%) in both conditions were mild: nausea, vomiting, diarrhea, abdominal pain, fatigue, myalgia, muscle cramps, and rash. A common finding in all studies was superficial edema, being described mainly as periorbital or lower limb edema. However, these edema were rarely severe and could be treated with diuretics, other supportive measures, or by reducing the dose of imatinib. When imatinib was combined with high-dose chemotherapy in patients with Ph + ALL, transient liver toxicity in the form of elevated transaminases and hyperbilirubinemia was observed.

Taking into account the limited safety database, the adverse reactions reported so far in children are consistent with the known safety profile in adult patients with Ph + ALL. The database for children with Ph + ALL is very limited, although no new safety issues have been identified.

Various adverse reactions such as pleural effusion, ascites, pulmonary edema, and rapid weight gain with or without superficial edema can be jointly described as "fluid retention." These reactions can usually be treated by temporarily withdrawing imatinib treatment, and administering diuretics and other supportive therapeutic measures. However, some of these reactions can be serious or life-threatening. Several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure, and kidney failure. No special findings regarding safety were observed in pediatric clinical trials.

Adverse reactions are detailed below the reported adverse reactions, except isolated cases, by organs and systems 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). Adverse reactions are listed in decreasing order of frequency within each frequency range.

Summary of Adverse reactions

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
Not known: Hepatitis B virus reactivation *

Benign, malignant and unspecified neoplasms (including cysts and polyps)

Rare: Tumor lysis syndrome
Not known: Tumor hemorrhage / tumor necrosis *

Immune system disorders

Not known: Anaphylactic shock *

Blood and lymphatic system disorders

Very common: Neutropenia, thrombocytopenia, anemia
Common: Pancytopenia, febrile neutropenia
Uncommon:
Thrombocytopenia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
Rare: Hemolytic anemia

Metabolism and nutrition disorders

Common: Anorexia
Uncommon: Hypokalemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia
Rare: Hyperkalaemia, hypomagnesemia

Psychiatric disorders

Common: Insomnia
Uncommon: Depression, decreased libido, anxiety
Rare: Confusion

Nervous system disorders

Very common: Headache[2]
Frequent: Dizziness, paraesthesia, taste disturbances, hypoaesthesia
Uncommon: Migraine, drowsiness, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, brain hemorrhage
Rare: Increased intracranial pressure, seizures, optic neuritis
Not known: Cerebral edema *

Eye disorders

Frequent: Eyelid edema, increased lacrimation, conjunctival hemorrhage, conjunctivitis, dry eye, blurred vision
Uncommon: Eye irritation, eye pain, orbital edema, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema
Rare: Cataract, glaucoma, papilloedema
Not known: Vitreous hemorrhage*

Ear and labyrinth disorders

Uncommon: Vertigo, tinnitus, hearing loss

Cardiac disorders

Uncommon: Palpitations, tachycardia, congestive heart failure[3], pulmonary edema
Rare: Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Not known: Pericarditis*, cardiac tamponade*

Vascular disorders[4]

Frequent: Hypertension, bruising, subdural hematoma, peripheral cooling, hypotension, Raynaud's phenomenon
Not known: Thrombosis / embolism *

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea, epistaxis, cough
Uncommon: Pleural effusion[5], pharyngolaryngeal pain, pharyngitis
Rare: Pleural pain, pulmonary fibrosis, pulmonary hypertension, pulmonary hemorrhage
Not known frequency: Acute respiratory failure[11]*, interstitial lung disease *

Gastrointestinal disorders

Very common: Nausea, diarrhea, vomiting, dyspepsia, abdominal pain[6]
Frequent: Flatulence, bloating, gastroesophageal reflux, constipation, dry mouth, gastritis
Uncommon: Stomatitis, mouth ulceration, gastrointestinal bleeding,[7] belching, melena, esophagitis, ascites, gastric ulcer, hematemesis, cheilitis, dysphagia, pancreatitis
Rare: Colitis, ileus, inflammatory bowel disease
Not known frequency:
Iliac / intestinal obstruction*, gastrointestinal perforation*, diverticulitis*, gastric antral vascular ectasia (EVAG*

Hepatobiliary disorders

Common: Increased liver enzymes
Uncommon: Hyperbilirubinaemia, hepatitis, jaundice
Rare: Heart failure[8], liver necrosis

Skin and subcutaneous tissue disorders

Very common: Periorbital edema, dermatitis / eczema / rash
Frequent: Pruritus, facial edema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction
Uncommon: Pustular rash, contusion, increased sweating, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, hypopigmentation of the skin, exfoliative dermatitis, onychoclasis, folliculitis, petechiae, psoriasis, purpura, hyperpigmentation of the skin, bullous eruptions
Rare: Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discoloration, angioneurotic edema, vesicular rash, erythema multiforme, leukocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalized pustular rash (AGEP)
Not known frequency:
Palmoplantar erythrodysesthesia syndrome*, lichenoid keratosis *, lichen planus*, toxic epidermal necrolysis*, drug eruption with eosinophilia and systemic symptoms (DRESS)*

Musculoskeletal and connective tissue disorders

Very common: Muscle spasms and cramps, musculoskeletal pain including myalgia[9], arthralgia, bone pain[10]
Common: swelling of the joints
Uncommon: Stiffness of joints and muscles
Rare: Muscle weakness, arthritis, rhabdomyolysis / myopathy
Not known frequency: Avascular necrosis / hip necrosis *, growth retardation in children*

Renal and urinary disorders

Uncommon: Kidney pain, hematuria, acute renal failure, increased urinary frequency
Not known Chronic renal failure

Reproductive system and breast disorders

Uncommon: Gynecomastia, erectile dysfunction, menorrhagia, irregular menstruation, sexual dysfunction, nipple pain, breast enlargement, scrotal edema
Rare: Hemorrhagic corpus luteum / hemorrhagic ovarian cyst

General disorders and administration site conditions

Very common: fluid retention and edema, fatigue
Frequent: Weakness, pyrexia, anasarca, chills, stiffness
Uncommon: Chest pain, malaise

Complementary explorations

Very common: Weight gain
Common: Weight loss
Uncommon: Increased serum creatinine, increased serum creatine phosphokinase, increased serum lactate dehydrogenase, increased serum alkaline phosphatase
Rare: Increased serum amylase: These types of reactions have been reported primarily from post-marketing experience with Imatinib1. Pneumonia was reported more frequently in patients with transformed CML and in patients with GIST.

[2] Headache was the most frequent in patients with GIST.
[3] Based on the results per patient-year, cardiac disorders, including congestive heart failure, were observed more frequently in patients with transformed CML than in patients with chronic CML.
[4] Hot flashes were more frequent in patients with GIST and bleeding (hematoma, hemorrhage) were more frequent in patients with GIST and with transformed CML (CML-FA and CML-CB).
[5] Pleural effusion was reported more frequently in patients with GIST and in patients with transformed CML (CML-accelerated phase and CML-blast crisis) than in patients with chronic CML.
[6] Abdominal pain and gastrointestinal bleeding were seen more frequently in patients with GIST.
[7] Some fatal cases of liver failure and liver necrosis have been reported.
[8] Musculoskeletal pain during or after imatinib treatment, observed post marketing.
[9] Musculoskeletal pain and related events were observed more frequently in patients with CML than in patients with GIST.
[10] Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia, and other severe comorbidities.

Laboratory test abnormalities

Hematology

Cytopenias, particularly neutropenia and thrombocytopenia, have been observed in all studies in CML, suggesting a higher frequency at high doses ≥ 750 mg (phase I study). However, the presence of cytopenias was also clearly dependent on the stage of the disease, the frequency of neutropenias (ANC <1.0 x 10^9 / L) and thrombocytopenias (platelet count <50 x 10^9 / L) grade 3 or 4, being between 4 and 6 times higher in blast crisis and in accelerated phase (59–64% and 44–63% for neutropenia and thrombocytopenia, respectively) compared to patients with newly diagnosed chronic phase CML (16.7% neutropenia and 8.9% thrombocytopenia). 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 less than 1%, respectively, of newly diagnosed patients of CML in chronic phase. The median duration of neutropenic and thrombocytopenic episodes was typically 2 to 3 weeks and 3 to 4 weeks, respectively. These effects can usually be treated with dose reduction or discontinuation of imatinib treatment, but in rare cases can lead to definitive cessation of treatment. In pediatric CML patients, the most frequently observed toxicities were grade 3 or 4 cytopenias including neutropenia, thrombocytopenia, and anemia. These generally occur during the first months of treatment.

In a study in patients with unresectable and / or metastatic GIST, grade 3 and 4 anemias were reported in 5.4% and 0.7% of patients, respectively, which may be related to gastrointestinal or intratumoral bleeding at least in any of these cases. Grade 3 and 4 neutropenia was observed 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 decrease in leukocytes and neutrophil count occurred mainly during the first six weeks of treatment, with the values remaining relatively stable thereafter.

Biochemistry

A severe increase in transaminases (<5%) or bilirubin (<1%) was observed in patients with CML and was usually controlled with dose reduction or discontinuation (the median duration of these episodes was approximately one week) In less than 1% of patients with CML, treatment was permanently discontinued due to abnormal liver laboratory tests. In patients with GIST, a 6.8% increase in ALT (alanine aminotransferase) grade 3 or 4 and a 4.8% increase in AST (aspartate aminotransferase) grade 3 or 4 were observed. The increase in bilirubin was less than 3%.

There have been cases of cytolytic and cholestatic hepatitis and liver failure; in some of which the outcome was fatal, including a patient treated with high-dose acetaminophen.

Description of selected adverse reactions

Reactivation of hepatitis B

Hepatitis B reactivation has been reported in association with tyrosine kinase inhibitors

BCR-ABL. In some cases, acute liver failure or fulminant hepatitis has occurred, leading to liver transplantation or fatal outcome.

OVERDOSE

There is limited experience with doses above the recommended therapeutic doses. Isolated cases of overdose with imatinib have been reported spontaneously and in publications. In the event of an overdose, the patient should be under observation and appropriate symptomatic treatment should be administered. 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 (variable duration between 1 and 10 days): Nausea, vomiting, diarrhea, rash, erythema, edema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.

1800 to 3200 mg (up to 3200 mg daily for 6 days): Weakness, myalgia, increased creatine phosphokinase, increased bilirubin, gastrointestinal pain.

6400 mg (single dose): A case reported in the literature of a patient who developed 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.

A 3-year-old boy was exposed to a single 400 mg dose, experiencing vomiting, diarrhea, and anorexia, and another 3-year-old boy was exposed to a single 980 mg dose, experiencing a decrease in white blood cells and diarrhea. In the event of an overdose, the patient should be observed and receive appropriate supportive treatment.

In the event of an overdose, go to the nearest Hospital or contact the Poison Control Centers:

PRESENTATIONS

IMATINIB GP PHARM 100: Packs containing 10 and 180 coated tablets.
IMATINIB GP PHARM 400: Packages containing 10 and 30 coated tablets.
CONSERVATION: Keep in its original container at temperatures below 30°C and protected from humidity.

KEEP OUT OF THE REACH OF CHILDREN

"This medicine must be used exclusively under prescription and medical supervision and cannot be repeated without a new prescription."

M.S.A. by the H.M.S.D.N. Certificate N°56.375.

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