Imanix

Imatinib

COMPOSITION

Imanix Tablet: Each film coated tablet contains Imatinib Mesilate BP equivalent to Imatinib 100 mg.
Imanix 400 Tablet: Each film coated tablet contains Imatinib Mesilate BP equivalent to Imatinib 400 mg.

CLINICAL PHARMACOLOGY

INDICATIONS

Imanix (Imatinib) is indicated for the

- treatment of adult and paediatric patients with newly diagnosed chronic myeloid leukaemia (CML) for paediatric use.
- treatment of adult and paediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy (for paediatric use see Dosage and method of administration).
- treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- treatment of adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- treatment of adult patients with systemic mastocytosis (SM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
- treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL).
- treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- adjuvant treatment of adult patients following resection of GIST.
- treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

The effectiveness of Imanix (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 SM, HES/CEL, on objective response rates and progression-free survival in unresectable and/or metastatic GIST, on recurrence free survival in adjuvant GIST, and on objective response rates in DFSP. Increased survival in controlled trials has been demonstrated only in newly diagnosed chronic phase CML and GIST.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.

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

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg tablet, and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Dosage in CML

The recommended dosage of Imanix (Imatinib) is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis.

Treatment should be continued as long as the patient continues to benefit.

Dose increase from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg daily in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-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.

Dosing in 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 and advanced phase CML (not to exceed the total dose of 600 mg daily). 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 use of Imanix (Imatinib) in children below 2 years of age.

Dosage in Ph+ ALL

The recommended dose of Imanix (Imatinib) is 600 mg/day for patients with Ph+ ALL.

Dosage in MDS/MPD

The recommended dose of Imanix (Imatinib) is 400 mg/day for patients with MDS/MPD.

Dosage in SM

The recommended dose of Imanix (Imatinib) is 400 mg/day for patients with SM without the D816V c-Kit mutation. If c-Kit mutational status is not known or unavailable, treatment with Imanix (Imatinib) at dose of 400 mg/day may be considered for patients with SM not responding satisfactorily to other therapies.

For patients with SM associated with eosinophilia, a clonal haematological disease related to the fusion kinase FIP1L1-PDGFR-alpha, a starting dose of 100 mg/day is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Dosage in HES/CEL

The recommended dose of Imanix (Imatinib) is 400 mg/day for patients with HES/CEL.

For HES/CEL patients with demonstrated FIP1L1-PDGFR-alpha fusion kinase, a starting dose of 100 mg/day is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Treatment should be continued as long as the patient continues to benefit.

Dosage in GIST

The recommended dose of Imanix (Imatinib) is 400 mg/day for patients with unresectable and/or metastatic, malignant GIST.

A dose increase from 400 mg to 600 mg or 800 mg for patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Treatment with Imanix (Imatinib) in GIST patients should be continued until disease progression.

The recommended dose of Imanix (Imatinib) is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. In the adjuvant setting the optimal treatment duration with Imanix (Imatinib) is not known.

Dosage in DFSP

The recommended dose of Imanix (Imatinib) is 800 mg/day for patients with DFSP.

Dose adjustments for adverse reactions

Non-haematological adverse reactions

If a severe non-haematological adverse reaction develops with Imanix (Imatinib) use, treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, Imanix (Imatinib) should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. Treatment with Imanix (Imatinib) may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg, or from 600 to 400 mg, or from 800 mg to 600 mg, and in children from 340 to 260 mg/m^2/day.

Hepatic insufficiency

Imanix (Imatinib) is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated (see Special warnings and precautions for use, Adverse effects, Pharmacodynamic properties and Pharmacokinetic properties).

Renal insufficiency

Imanix (Imatinib) and its metabolites are not significantly excreted via the kidney. Since the renal clearance of Imanix (Imatinib) is negligible, a decrease in free drug clearance is not expected in patients with renal insufficiency. Patients with mild or moderate renal dysfunction should be given the minimum recommended dose of 400 mg daily as starting dose. Although very limited information is available (see Pharmacodynamic properties and Pharmacokinetic properties), patients with severe renal dysfunction or on dialysis could also start at the same dose of 400 mg. However, in these patients caution is recommended. The dose can be reduced if not tolerated, or increased for lack of efficacy.

Elderly patients

No significant age related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose recommendation is necessary in the elderly.

CONTRAINDICATIONS

Imanix (Imatinib) is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

WARNING AND PRECAUTIONS

Imanix (Imatinib) should be taken with food and a large glass of water to minimise the risk of gastrointestinal disturbances.

When Imanix (Imatinib) is co-administered with other medications, there is a potential for drug interactions.

One patient, who was taking paracetamol/acetaminophen regularly for fever, died of acute liver failure. Although the aetiology is currently unknown, special caution should be exercised when using paracetamol/acetaminophen.

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

In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored.

When Imanix (Imatinib) is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia has been observed. Additionally, there have been uncommon reports of acute liver failure. Monitoring of hepatic function is recommended in circumstances where Imanix (Imatinib) is combined with chemotherapy regimens also known to be associated with hepatic dysfunction.

Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial oedema) have been reported in approximately 2.5% of newly diagnosed CML patients taking Imanix (Imatinib). Therefore, it is recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease.

Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

In patients with hypereosinophilic syndrome (HES) and cardiac involvement, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of Imanix (Imatinib) therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Imanix (Imatinib). Myelodysplastic/myeloproliferative diseases and systemic mastocytosis might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or SM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1 to 2 mg/kg) for one to two weeks concomitantly with Imanix (Imatinib) should be considered at the initiation of therapy.

In the Phase III GIST studies in patients with unresectable or metastatic malignant GIST 211 patients (12.9%) reported Grade 3/4 haemorrhage at any site. In the Phase II GIST study in patients with unresectable or metastatic malignant GIST (study B2222), eight patients (5.4%) were reported to have had gastrointestinal (GI) haemorrhage and four patients (2.7%) were reported to have had haemorrhages at the site of tumour deposits. The tumour haemorrhages have been either intra-abdominal or intra-hepatic, depending on the anatomical location of tumour lesions. GI sites of tumour may have contributed to reports of GI bleeding in this patient population.

ADVERSE EFFECTS

Patients with advanced stages of malignancies may have numerous confounding medical conditions that make causality of adverse events difficult to assess due to the variety of symptoms related to the underlying disease, its progression, and the co-administration of numerous medications.

Imanix (Imatinib) was generally well tolerated with chronic oral daily dosing in patients with CML including paediatric patients. The majority of adult patients experienced adverse events at some point in time, but most were of mild to moderate grade, and in clinical trials drug discontinuation for drug-related adverse events was observed in 2.4% of newly diagnosed patients, 4% of patients in late chronic phase after failure of interferon therapy, 4% of patients in accelerated phase after failure of interferon therapy and 5% of blast crisis patients after failure of interferon therapy. In the GIST study (B2222), Imanix (Imatinib) was discontinued for drug-related adverse events in 4% of patients.

The adverse reactions were similar in all indications, with two exceptions. There was less myelosuppression in GIST and intra-tumoral haemorrhage was only seen in the GIST population (see Special warnings and precautions for use). The most frequently reported drug-related adverse events were mild nausea, vomiting, diarrhoea, myalgia, muscle cramps and rash, which were easily manageable. Superficial oedemas were a common finding in all studies and were described primarily as periorbital or lower limb oedemas. However, these oedemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Imanix (Imatinib).

Overall the incidence of all grades of adverse reactions and the incidence of severe adverse reactions were similar between the 400 mg and 800 mg treatment groups except for oedema, which was reported more frequently in the 800 mg group in the phase III studies in patients with unresectable or metastatic malignant GIST (SWOG, EORTC studies).

When Imanix (Imatinib) was combined with high dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia were observed.

Miscellaneous adverse events such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as "fluid retention". These events can usually be managed by withholding Imanix (Imatinib) temporarily and/or with diuretics and/or other appropriate supportive care measures. However, a few of these events may be serious or life threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure.

Laboratory tests

Complete blood counts must be performed regularly during therapy with Imanix (Imatinib). Treatment of CML patients with Imanix (Imatinib) has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is dependent on the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with Imanix (Imatinib) may be interrupted or the dose be reduced, as recommended in Dosage and method of administration.

Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored regularly in patients receiving Imanix (Imatinib). As recommended in section Dosage and method of administration, non-haematological adverse reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with Imanix (Imatinib).

Imanix (Imatinib) and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect Imanix (Imatinib) kinetics. In patients with impaired renal function, Imanix (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 Imanix (Imatinib)-binding protein, in these patients. There is no correlation between Imanix (Imatinib) exposure and the degree of renal impairment, as classified by the measurement of creatinine clearance (CrCL), between patients with mild (CrCL: 40 to 59 mL/min) and severe (CrCL: <20 mL/min) renal impairment. However, as recommended in Dosage and method of administration, the starting dose of Imanix (Imatinib) can be reduced if not tolerated.

PREGNANCY & LACTATION

Imatinib can cause fetal harm when administered to a pregnant woman based on human and animal data. There are no clinical studies regarding use of Imatinib in pregnant women.

Imatinib and its active metabolite are excreted into human milk. Because of the potential for serious adverse reactions in breastfed infants from Imatinib, advise a lactating woman not to breastfeed during treatment and for 1 month after the last dose.

USE IN CHILDREN AND ADOLESCENTS

There is no experience with the use of Imanix (Imatinib) in children with CML below 2 years of age. There is very limited experience with the use of Imanix (Imatinib) in children below 3 years of age in other indications.

DRUG INTERACTIONS

Drugs that may alter Imanix (Imatinib) plasma concentrations

Drugs that may increase Imanix (Imatinib) plasma concentrations

Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) could decrease metabolism and increase Imanix (Imatinib) concentrations. There was a significant increase in exposure to Imanix (Imatinib) (the mean Cmax and AUC of Imanix (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 Imanix (Imatinib) with inhibitors of the CYP3A4 family.

Drugs that may decrease Imanix (Imatinib) plasma concentrations

Substances that are inducers of CYP3A4 activity could increase metabolism and decrease Imanix (Imatinib) plasma concentrations. Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imanix (Imatinib). Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 8 days, followed by a single 400 mg dose of Imanix (Imatinib), increased Imanix (Imatinib) oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents mean decreases Cmax, AUC(0-24) and AUC(0-?) by 54%, 68% and 74%, of the respective values without rifampin treatment. Similar results were observed in patients with malignant gliomas treated with Imanix (Imatinib) while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone. The plasma AUC for Imanix (Imatinib) decreased by 73% compared to patients not on EIAEDs. In two published studies, concomitant administration of Imanix (Imatinib) and a product containing St. John's wort led to a 30 to 32% reduction in the AUC of Imanix (Imatinib). In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Drugs that may have their plasma concentration altered by Imanix (Imatinib)

Imanix (Imatinib) increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, indicating an inhibition of the CYP3A4 by Imanix (Imatinib). Therefore, caution is recommended when administering Imanix (Imatinib) with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide). Imanix (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.).

Imanix (Imatinib) also inhibits CYP2C9 and CYP2C19 activity in vitro. PT prolongation was observed following co-administration with warfarin. When giving coumarins, short-term PT monitoring is therefore necessary at the start and end of Imanix (Imatinib) therapy and when altering the dosage. Alternatively, the use of low-molecular weight heparin should be considered.

In vitro, Imanix (Imatinib) inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imanix (Imatinib) at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol Cmax and AUC being increased by approximately 23%. Co-administration of Imanix (Imatinib) with CYP2D6 substrates, such as metoprolol, does not seem to be a risk factor for drug-drug interactions and dose adjustment may not be necessary.

In vitro, Imanix (Imatinib) inhibits paracetamol/acetaminophen O-glucuronidation.

OVERDOSAGE

Adult Overdose

1,200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash erythema, edema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.

Pediatric Overdose

One 3-year-old male exposed to a single dose of 400 mg experienced vomiting, diarrhea and anorexia and another 3-yearold male exposed to a single dose of 980 mg experienced decreased white blood cell count and diarrhea.

PHARMACEUTICAL INFORMATION

Storage Condition

Store below 30°C, dry place and away from light. Keep out of the reach of children.

Presentation & Packaging

Imanix Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.
Imanix 400 Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

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