Package Insert

1. Name of the product

Imarem 100 mg film-coated tablets
Imarem 400 mg film-coated tablets

2. Name and Strength of Active Ingredient

Imarem 100mg contains 100 mg imatinib (as mesilate).
Imarem 400mg contains 400 mg imatinib (as mesilate).

3. Dosage form

Film-coated tablet.

Imarem, 100mg: Dark yellow to brownish-orange, round shaped, film-coated tablets with a breakline on one side and '100' on the other side.
Imarem, 400mg: Dark yellow to brownish-orange, ovaloid shaped, film-coated tablets with a breakline on one side and '400' on the other side.

4. Pharmacological Properties

Pharmacodynamics
Pharmacotherapeutic group: protein-tyrosine kinase inhibitor, ATC code: L01XE01

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 patients 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 stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumour (GIST) cells, which express an activating kit mutation. Constitutive activation of the 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.

Pharmacokinetics

Pharmacokinetics of imatinib

The pharmacokinetics of imatinib have been evaluated over a dosage range of 25 to 1,000 mg.

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.

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, the $t_{½}$ 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.

Population pharmacokinetics

There is no effect of gender on the kinetics of imatinib.

Pharmacokinetics in children

As in adult patients, imatinib is rapidly absorbed after oral administration in paediatric patients.

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 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.

5. Clinical Particulars

Indications
Imarem is indicated for the treatment of

- adult and pediatric patients with newly diagnosed chronic myeloid leukemia (CML) as well as for the treatment of adult and pediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- adjuvant treatment of adult patients following resection of GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- adult and pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic 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 hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα re-arrangement.
- adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
- adult patients with aggressive systemic mastocytosis (ASM) without the D816V cKit mutation or with c-Kit mutational status unknown.

The effectiveness of Imarem is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and ASM and on objective response rates in GIST and DFSP, and on recurrence-free survival in adjuvant GIST (see section Pharmacodynamics). The experience with imatinib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited. Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

Posology and method of 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 to minimise the risk of gastrointestinal irritations. 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 mineral water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 ml for a 100 mg tablet, and 200 ml for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

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

Monitoring of response to imatinib therapy in Ph+ CML patients should be performed routinely and when therapy is modified, to identify suboptimal response, loss of response to therapy, poor patient compliance, or possible drug-drug interaction. Results of monitoring should guide appropriate CML management.

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

Dose increases from 400 mg to 600 mg to a maximum of 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: 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.

Posology for Ph+ ALL
The recommended dose for Imarem is 600 mg/day for adult patients with Ph+ ALL. See section on special populations for children.

Posology for MDS/MPD
The recommended dose of Imarem is 400 mg/day for adult patients with MDS/MPD.

Posology in ASM
The recommended dose of Imarem is 400 mg/day for adult patients with ASM without the D816V c-KIT mutation or mutational status unknown or not responding satisfactorily to other therapies.

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

Posology for HES/CEL

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

Posology for GIST

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

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

The recommended dose of Imarem is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST.

Posology for DFSP

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

Dose adjustment for adverse reactions

Non-haematological adverse reactions

If a severe non-haematological adverse reaction develops with Imarem 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, Imarem should be withheld until bilirubin levels have returned to < 1.5 x IULN and transaminase levels to < 2.5 x IULN. Treatment with Imarem may then be continued at a reduced daily dose. In adults the dose should be reduced from 600 to 400 mg, or from 800 mg to 600 mg, and in children from 340 to 260 mg/m^2/day.

Haematological adverse reactions

Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.

Dose adjustments for neutropenia and thrombocytopenia:

ASM associated with eosinophilia and HES/CEL with FIP1L1-PDGFR-alpha fusion kinase (starting dose 100 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Imarem until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with Imarem at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, MDS/MPD, ASM, HES/CEL and GIST (starting dose 400 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Imarem until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with Imarem at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume Imarem at reduced dose of 300 mg.
Paediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Imarem until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with Imarem at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x10^9/l and/or platelets < 50 x10^9/l, repeat step 1 and resume Imarem at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg[c])	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of Imarem to 400 mg[b]. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg/m^2. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop Imarem until ANC ≥1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 300 mg[d].
DFSP (starting dose 800 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop Imarem until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with Imarem at 600 mg. 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume Imarem at reduced dose of 400 mg.
ANC = absolute neutrophil count		
[a] occurring after at least 1 month of treatment [b] or 260 mg/m^2 in children [c] or 340 mg/m^2 in children [d] or 200 mg/m^2 in children		

Special populations

Paediatric use: There is no experience in children with CML below 2 years of age and with Ph+ALL below 1 year of age. There is very limited experience in children with MDS/MPD, DFSP and HES/CEL.

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 and Ph+ALL (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose in CML and Ph+ALL. In CML, alternatively the daily dose may be split into two administrations – one in the morning and one in the evening.

Hepatic insufficiency: 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.

Renal insufficiency: Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy.

Older people: Imatinib pharmacokinetics have not been specifically studied in older people. 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 older people.

Contraindications
Hypersensitivity to the active substance or to any other ingredients of the product.

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, bortezomid, 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
Thyroid-stimulating hormone (TSH) levels should be closely monitored in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib.

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.

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 oedema) 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., Increased incidence of these events was observed in elderly patients 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
Gastric antral vascular ectasia (GAVE), a rare cause of gastrointestinal haemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases. When needed, discontinuation of Imarem treatment should be considered.

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.

Hepatitis B reactivation
Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in

acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with Imarem. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with Imarem should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Thrombotic microangiopathy

BCR-ABL tyrosine kinase inhibitors (TKls) have been associated with thrombotic microangiopathy (TMA), including individual case reports for imatinib. If laboratory or clinical findings associated with TMA occur in a patient receiving imatinib, treatment should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with imatinib should not be resumed.

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.

Long-term treatment with imatinib may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of imatinib therapy and closely monitored during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction. If renal dysfunction is observed, appropriate management and treatment should be prescribed in accordance with standard treatment guidelines.

Paediatric population

Growth retardation might occur 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 Imarem 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 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. Pre-treatment 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
Pregnancy
There are limited data on the use of imatinib in pregnant women. 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.

Breast-feeding
There is limited information on imatinib distribution on human milk. Since the effects of low-dose exposure of the infant to imatinib are unknown, women taking imatinib should not breast-feed.

Fertility
Patients concerned about their fertility on imatinib treatment should consult with their physician.

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

Side effects

Patients with advanced stages of malignancies may have numerous confounding medical conditions that make causality of adverse reactions difficult to assess due to the variety of symptoms related to the underlying disease, its progression, and the co-administration of numerous medicinal products.
Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as "fluid retention". These reactions can usually be managed by withholding imatinib temporarily and with diuretics and other appropriate supportive care measures. However, some of these reactions 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.

Adverse reactions
Adverse reactions reported as more than an isolated case are listed below by frequency.

Very Common: Neutropenia, thrombocytopenia, anemia, headache, nausea, diarrhea, vomiting, abdominal pain, rash, muscle cramps, fatigue, increase in weight.

Common: Pancytopenia, anorexia, insomnia, dizziness, dry eye, blurred vision, oedema on eyelid, hemorrhage, cough, flatulence, constipation, dry mouth, heartburn, dry skin, joint swelling, chills, decreased weight.

Uncommon: Shingles, cold, sinusitis, dermatological infection, upper respiratory tract infection, influenza, urinary tract infection, herpes simplex, pneumonia, increased appetite, hypokalemia, dehydration, gout, diabetes, depression, anxiety, migraine, eye pain, eye irritation, vertigo, hearing loss, palpitations, tachycardia, congestive cardiac failure, hypertension, dyspnea, psoriasis, increased sweating, renal pain, acute renal failure, increased urine frequency, erectile dysfunction, irregular menstruation.

Rare: Fungal infection, hyperkalemia, cataract, glaucoma, angina pectoris, thrombotic microangiopathy.

Symptoms and Treatment of Overdose
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 dose experienced decreased white blood cell count and diarrhoea.

In the event of overdose, the patient should be observed and appropriate supportive treatment given.

6. Pharmaceutical Particulars

Storage conditions
Do not store above 30 °C.
Protect from moisture.
Store in the original package.

Shelf-life
3 years

Pack-size available
Imarem 100 mg film-coated tablets: Packs containing 30 and 60 film-coated tablets.
Imarem 400 mg film-coated tablets: Packs containing 30 film-coated tablets.

Not all pack sizes may be marketed.

Instructions for use and handling
No special requirements.
Note: Imatinib should be kept out of the sight and reach of children.

7. Manufacturer

Remedica Ltd.
Aharnon Street, Limassol Industrial Estate,
3056 Limassol, Cyprus

8. Product registration holder

Eucogen Sdn. Bhd.,
No. 6A, Jalan Sungai Burung U 32/U, Bukit Rimau Seksyen 32, 40460 Shah Alam Selangor, Malaysia.

9. Date of revision of the text

01/2024

For internal use only: my-pi-imarem-fc-tabs-a6