For the use of an oncologist or a hospital or a laboratory only

# PRESCRIBING INFORMATION

# REDISTRA (IMATINIB TABLETS 100MG)

# REDISTRA (IMATINIB TABLETS 400MG)

## COMPOSITION

*REDISTRA (Imatinib Tablets 100 mg)*

Each film coated tablet contains:

Imatinib Mesylate Ph.Eur. equivalent to Imatinib 100 mg

Colours: Titanium Dioxide, Iron Oxide Yellow, Iron Oxide Red

*REDISTRA (Imatinib Tablets 400 mg)*

Each film coated tablet contains:

Imatinib Mesylate Ph.Eur. equivalent to Imatinib 400 mg

Colours: Titanium Dioxide, Iron Oxide Yellow, Iron Oxide Red

## PRODUCT DESCRIPTION:

*REDISTRA (Imatinib Tablets 100 mg)*

Yellow to brownish orange, round film coated tablets debossed with "1" on one side and score line on the other side.

*REDISTRA (Imatinib Tablets 400 mg)*

Yellow to brownish orange, ovaloid film coated tablets debossed with "4" on one side and score line on the other side.

## CLINICAL INFORMATION

**Therapeutic Indications:**

• Redistra is indicated for the treatment of adult and pediatric patients with newly diagnosed chronic myeloid leukemia (CML) as well as for the treatment of adult and pediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

• adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
• adjuvant treatment of adult patients following resection of GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
• adult and pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy.
• adult patients with relapsed or refractory Ph+ ALL as monotherapy.
• adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
• adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with F1P1L1-PDGFRÎ± rearrangement.
• adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).
• adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.
The effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and ASM and on objective response rates in GIST and DFSP, and on recurrence-free survival in adjuvant GIST (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 in diseases.

**Dosage and method of administration**

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies and malignant sarcomas, as appropriate.
The prescribed dose should be administered orally with a meal and a large glass of water to minimize the risk of gastrointestinal disturbances. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.
For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg tablet, and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).
Treatment should be continued as long as the patient continues to benefit.
Monitoring of response to Redistra therapy in Ph+ CML patients should be performed routinely and when therapy is modified, to identify suboptimal response, loss of response to therapy, poor patient compliance, or possible drug-drug interaction. Results of monitoring should guide appropriate CML management.

**General target population:**

*Dosage in CML*

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

Dose increase from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg daily in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia- related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved hematological and/or cytogenetic response.

See section on special populations for pediatric patients.

*Dosage in Ph+ ALL*

The recommended dose of Redistra is 600 mg/day for adult patients with Ph+ ALL. See section on special populations for pediatric patients.

*Dosage in MDS/MPD*

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

*Dosage in ASM*

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

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

*Dosage in HES/CEL*

The recommended dose of Redistra is 400 mg/day for adult patients with HES/CEL.

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

*Dosage in GIST*

The recommended dose of Redistra 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 Redistra is 400 mg/day for the adjuvant treatment of adult patients following complete gross resection of GIST. The optimal treatment duration with Redistra is not known.

*Dosage in DFSP*

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

**Dose adjustments for adverse drug reactions**

*Non-hematological adverse drug reactions*

If a severe non-hematological adverse drug reaction develops with Redistra 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, Redistra should be withheld until bilirubin levels have returned to a < 1.5 x IULN and transaminase levels to < 2.5 x IULN. Treatment with Redistra may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg, or from 600 to 400 mg, or from 800 mg to 600 mg, and in pediatric patients from 340 to 260 mg/$m^2$/day.

*Hematological adverse drug reactions*

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

**Table 1 Dose adjustments for neutropenia and thrombocytopenia**

| | | |
|---|---|---|
| ASM associated with eosinophilia and HES/CEL with FIP1L1- PDGFR-alpha fusion kinase (starting dose 100 mg) | ANC < 1.0 $x10^9$/L and/or platelets < 50 $x10^9$/L | 1. Stop Redistra until ANC ≥ 1.5 $x10^9$/L and platelets ≥ 75 $x10^9$/L.<br>2. Resume treatment with Redistra at previous dose (i.e. before severe adverse drug reaction). |
| Chronic phase CML, MDS/MPD, ASM, HES/CEL and GIST (starting dose 400 mg) | ANC < 1.0 $x10^9$/L and/or platelets < 50 $x10^9$/L | 1. Stop Redistra until ANC ≥ 1.5 $x10^9$/L and platelets ≥ 75 $x10^9$/L.<br>2. Resume treatment with Redistra at previous dose (i.e. before severe adverse drug reaction).<br>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 Redistra at reduced dose of 300 mg. |
| Pediatric chronic phase CML (at dose 340 mg/$m^2$) | ANC < 1.0 $x10^9$/L and/or platelets < 50 $x10^9$/L | 1. Stop Redistra until ANC ≥ 1.5 $x10^9$/L and platelets ≥ 75 $x10^9$/L.<br>2. Resume treatment with Redistra at previous dose (i.e. before severe adverse drug reaction)<br>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 Redistra at reduced dose of 260 mg/$m^2$. |

| | | |
|---|---|---|
| Accelerated phase CML and blast crisis and Ph+ ALL<br>(starting dose 600 mg[c]) | [a]ANC < 0.5 x$10^9$/L<br>and/or<br>platelets < 10 x$10^9$/L | 1. Check whether cytopenia is related to leukemia (marrow aspirate or biopsy).<br>2. If cytopenia is unrelated to leukemia, reduce dose of Redistra to 400 mg[b].<br>3. If cytopenia persists for 2 weeks, reduce further to 300 mg[d].<br>4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop Redistra until ANC ≥ 1 x$10^9$/L and platelets ≥ 20 x$10^9$/L, then resume treatment at 300 mg[d]. |
| DFSP<br>(starting dose 800 mg) | ANC < 1.0 x$10^9$/L<br>and/or<br>platelets < 50 x$10^9$/L | 1. Stop Redistra until ANC ≥ 1.5 x$10^9$/L and platelets ≥ 75 x$10^9$/L.<br>2. Resume treatment with Redistra at 600 mg<br>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 Redistra at reduced dose of 400 mg. |

ANC = absolute neutrophil count

[a] occurring after at least 1 month of treatment

[b] or 260 mg/$m^2$ in pediatric patients

[c] or 340 mg/$m^2$ in pediatric patients

[d] or 200 mg/$m^2$ in pediatric patients

**Special populations**

*Renal insufficiency*

Imatinib and its metabolites are not significantly excreted via the kidney. Patients with renal dysfunction or on dialysis could be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy (see section WARNINGS AND PRECAUTIONS).

*Hepatic impairment*

Imatinib is mainly metabolized by the liver. Patients with mild, moderate or severe liver impairment should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated (see sections WARNINGS AND PRECAUTIONS, ADVERSE DRUG REACTIONS AND CLINICAL PHARMACOLOGY).

*Pediatric patients (below 18 years)*

There is no experience with the use of Redistra in pediatric patients with CML below 2 years of age and with Ph+ALL below 1 year of age. There is very limited to no experience with the use of Redistra in pediatric patients in other indications.

Dosing in pediatric patients should be on the basis of body surface area (mg/m2). The dose of 340 mg/m2 daily is recommended for children with chronic phase and advanced phase CML and Ph+ALL (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose in CML and Ph+ALL. In CML, alternatively the daily dose may be split into two administrations – one in the morning and one in the evening.

*Geriatric patients (65 years or above)*

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

**CONTRAINDICATION**

Hypersensitivity to the active substance or to any of the excipients

**WARNINGS AND PRECAUTIONS**

When Imatinib is co-administered with other medicinal products, there is a potential for drug interactions. Caution should be used when taking Imatinib with protease inhibitors, azole antifungals, certain macrolides, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives.

Concomitant use of imatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imatinib, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and imatinib should be avoided.

*Hypothyroidism*

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

*Hepatotoxicity*

Metabolism of Imatinib is mainly hepatic, and only 13% of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored. It should be noted that GIST patients may have hepatic metastases which could lead to hepatic impairment.

Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When imatinib is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions has been detected. Hepatic function should be carefully monitored in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction

*Fluid retention*

Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial 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. There was an increased incidence of these events in older people and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.

*Patients with cardiac disease*

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

In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. As cardiac adverse events have been reported uncommonly with imatinib, a careful assessment of the benefit/risk of imatinib therapy should be considered in the HES/CEL population before treatment initiation.

Myelodysplastic/myeloproliferative diseases with PDGFR gene re-arrangements could be associated with high eosinophil levels. Evaluation by a cardiology specialist, performance of an echocardiogram and determination

of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD associated with high eosinophil levels before imatinib is administered. If either is abnormal, follow-up with a cardiology specialist and the prophylactic use of systemic steroids (1–2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

*Gastrointestinal haemorrhage*

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

In addition, 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 Imatinib treatment may be considered.

*Tumour 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 Imatinib. 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 Imatinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy

*Phototoxicity*

Exposure to direct sunlight should be avoided or minimised due to the risk of phototoxicity associated with imatinib treatment. Patients should be instructed to use measures such as protective clothing and sunscreen with

high sun protection factor (SPF).

*Thrombotic microangiopathy*

BCR-ABL tyrosine kinase inhibitors (TKIs) 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 dosemay be reduced, as recommended in dosage and recommendation. 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 inrenal 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*

There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. In the CML paediatric population, a statistically significant decrease (but of uncertain clinical relevance) in median height standard deviation scores after 12 and 24 months of treatment was reported in two small subsets irrespective of pubertal status or gender. Close monitoring of growth in children under imatinib treatment is recommended.

**INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS**

*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 Cmax and AUC of imatinib rose by 26% and 40%, respectively) in healthy subjects when it was co- administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be taken when administering Imatinib with inhibitors of the CYP3A4 family.

*Active substances that may decrease imatinib plasma concentrations:*

Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imatinib, potentially increasing the risk of therapeutic failure. Pretreatment with multiple doses of rifampicin 600 mg followed by a single 400 mg dose of Imatinib resulted in decrease in Cmax and AUC(0-∞) 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 Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, indicating an inhibition of the CYP3A4 by imatinib. Therefore, caution is recommended when administering Imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. 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 Cmax 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.

**FERTILITY, PREGNANCY AND LACTATION**

Pregnancy

*Women of childbearing potential*

Women of childbearing potential must be advised to use effective contraception during treatment and for at least 15 days after stopping treatment with Redistra

*Pregnancy*

There are limited data on the use of imatinib in pregnant women. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken Imatinib. It is however shown reproductive toxicity and the potential risk for the foetus is unknown in animals. 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. It is shown that both imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio single patient was determined to be 0.5 for imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of imatinib and the metabolite and the maximum daily milk intake by

infants, the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, women should not breast-feed during treatment and for at least 15 days after stopping treatment with Redistra

Fertility

The fertility of male and female rats was not affected, although effects on reproductive parameters were observed. There are no data on patients receiving Imatinib and its effect on fertility and gametogenesis have not been performed. Patients concerned about their fertility on Redistra treatment should consult with their physician.

**EFFECT ON ABILITY TO DRIVE AND USE MACHINES**

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.

**UNDESIRABLE 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.

The adverse reactions were similar in all indications, with two exceptions. There was more myelosuppression seen in CML patients than in GIST, which is probably due to the underlying disease. The most commonly reported drug-related adverse reactions in both settings were mild nausea, vomiting, diarrhoea, abdominal pain, fatigue, myalgia, muscle cramps and rash. Superficial oedemas were a common finding in all 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 by reducing the dose of Imatinib.

When imatinib was combined with high dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia were observed. Considering the limited safety database, the adverse events thus far reported in children are consistent with the known safety profile in adult patients with Ph+ ALL. The safety database for children with Ph+ALL is very limited though no new safety concerns have been identified.

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. There

were no special safety findings in paediatric patients.

**ADVERSE REACTIONS**

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequency categories are defined using the following convention: very common, common, uncommon, rare, very rare, not known. Within each frequency grouping, undesirable effects are presented in order of frequency, the most frequent first.

Adverse reactions and their frequencies are reported in Table 2.

**Table 2 Tabulated summary of adverse reactions**

| | |
|---|---|
| **Infections and infestations** | |
| Uncommon: | Herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1], sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis |
| Rare: | Fungal infection |
| Not known: | Hepatitis B reactivation* |
| **Neoplasm benign, malignant and unspecified (including cysts and polyps)** | |
| Rare: | Tumour lysis syndrome |
| Not known: | Tumour haemorrhage/tumour necrosis* |
| **Immune system disorders** | |
| Not known: | Anaphylactic shock* |
| **Blood and lymphatic system disorders** | |
| Very common: | Neutropenia, thrombocytopenia, anaemia |
| Common: | Pancytopenia, febrile neutropenia |
| Uncommon: | Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy |
| Rare: | Haemolytic anaemia, thrombotic microangiopathy |
| **Metabolism and nutrition disorders** | |
| Common: | Anorexia |
| Uncommon: | Hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia |
| Rare: | Hyperkalaemia, hypomagnesaemia |
| **Psychiatric disorders** | |
| Common: | Insomnia |
| Uncommon: | Depression, libido decreased, anxiety |
| Rare: | Confusional state |
| **Nervous system disorders** | |
| Very common: | Headache[2] |
| Common: | Dizziness, paraesthesia, taste disturbance, hypoaesthesia |

| | |
|---|---|
| Uncommon: | Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral haemorrhage |
| Rare: | Increased intracranial pressure, convulsions, optic neuritis |
| Not known: | Cerebral oedema* |
| **Eye disorders** | |
| Common: | Eyelid oedema, lacrimation increased, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision |
| Uncommon: | Eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema |
| Rare: | Cataract, glaucoma, papilloedema |
| Not known: | Vitreous haemorrhage* |
| **Ear and labyrinth disorders** | |
| Uncommon: | Vertigo, tinnitus, hearing loss |
| **Cardiac disorders** | |
| Uncommon: | Palpitations, tachycardia, cardiac failure congestive[3], pulmonary oedema |
| Rare: | Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion |
| Not known: | Pericarditis*, cardiac tamponade* |
| **Vascular disorders**[4] | |
| Common: | Flushing, haemorrhage |
| Uncommon: | Hypertension, haematoma, subdural haematoma, peripheral coldness, 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: | Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage |
| Not known: | Acute respiratory failure[11]*, interstitial lung disease* |
| **Gastrointestinal disorders** | |
| Very common: | Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain[6] |
| Common: | Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis |
| Uncommon: | Stomatitis, mouth ulceration, gastrointestinal haemorrhage[7], eructation, melaena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis |

| | |
|---|---|
| Rare: | Colitis, ileus, inflammatory bowel disease |
| Not known: | Ileus/intestinal obstruction*, gastrointestinal perforation*, diverticulitis*, gastric antral vascular ectasia (GAVE)* |
| **Hepatobiliary disorders** | |
| Common: | Increased hepatic enzymes |
| Uncommon: | Hyperbilirubinaemia, hepatitis, jaundice |
| Rare: | Hepatic failure[8], hepatic necrosis |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Periorbital oedema, dermatitis/eczema/rash |
| Common: | Pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction |
| Uncommon: | Rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions |
| Rare: | Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP) |
| Not known: | Palmoplantar erythrodysesthesia syndrome*, lichenoid keratosis*, lichen planus*, toxic epidermal necrolysis*, drug rash with eosinophilia and systemic symptoms (DRESS)*, pseudoporphyria* |
| **Musculoskeletal and** | |
| Very common: | Muscle spasm and cramps, musculoskeletal pain including myalgia[9], arthralgia, bone pain[10] |
| Common: | Joint swelling |
| Uncommon: | Joint and muscle stiffness |
| Rare: | Muscular weakness, arthritis, rhabdomyolysis/myopathy |
| Not known: | Avascular necrosis/hip necrosis*, growth retardation in children* |
| **Renal and urinary disorders** | |
| Uncommon: | Renal pain, haematuria, renal failure acute, urinary frequency increased |
| Not known: | Renal failure chronic |
| **Reproductive system and breast disorders** | |
| Uncommon: | Gynaecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema |
| Rare: | Haemorrhagic corpus luteum/haemorrhagic ovarian cyst |
| **General disorders and administration site conditions** | |

| | |
|---|---|
| Very common: | Fluid retention and oedema, fatigue |
| Common: | Weakness, pyrexia, anasarca, chills, rigors |
| Uncommon: | Chest pain, malaise |
| **Investigations** | |
| Very common: | Weight increased |
| Common: | Weight decreased |
| Uncommon: | Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased |
| Rare: | Blood amylase increased |

* These types of reactions have been reported mainly from post-marketing experience with Imatinib. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programmes, clinical pharmacology studies and exploratory studies in unapproved indications. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to imatinib exposure.

[1] Pneumonia was reported most commonly in patients with transformed CML and in patients with GIST.

[2] Headache was the most common in GIST patients.

[3] On a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML.

[4] Flushing was most common in GIST patients and bleeding (haematoma, haemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC).

[5] Pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML- AP and CML-BC) than in patients with chronic CML.

[6+7] Abdominal pain and gastrointestinal haemorrhage were most commonly observed in GIST patients.

[8] Some fatal cases of hepatic failure and of hepatic necrosis have been reported.

[9] Musculoskeletal pain during treatment with imatinib or after discontinuation has been observed in post-marketing.

[10] Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.

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

Laboratory test abnormalities

*Haematology*

In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses ≥ 750 mg. However, the occurrence of cytopenias was also clearly dependent on the stage of the disease, the frequency of grade 3 or 4 neutropenias (ANC < 1.0 x $10^9$/l) and thrombocytopenias (platelet count < 50 x $10^9$/l) being between 4 and 6 times higher in blast crisis and accelerated phase as compared to newly diagnosed patients in chronic phase CML. In newly

diagnosed chronic phase CML grade 4 neutropenia (ANC < 0.5 x $10^9$/l) and thrombocytopenia (platelet count < 10 x $10^9$/l) were observed. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with Imatinib, but can in rare cases lead to permanent discontinuation of treatment. In paediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

In patients with unresectable and/or metastatic GIST, grade 3 and 4 anaemia was reported and may have been related to gastrointestinal or intra-tumoural bleeding in at least some of these patients. Grade 3 and 4 neutropenia was seen and grade 3 thrombocytopenia in patients. No patient developed grade 4 thrombocytopenia. The decreases in white blood cell (WBC) and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.

*Biochemistry*

Severe elevation of transaminases (<5%) or bilirubin (<1%) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of CML patients. In GIST patients, grade 3 or 4 ALT (alanine aminotransferase) elevations and grade 3 or 4 AST (aspartate aminotransferase) elevations were observed. Bilirubin elevation was below 3%.

There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of them outcome was fatal, including one patient on high dose paracetamol.

Description of selected adverse reactions Hepatitis B reactivation

Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

**OVERDOSE AND TREATMENT**

Experience with doses higher than the recommended therapeutic dose is limited. Isolated cases of Imatinib overdose have been reported spontaneously and in the literature. In the event of overdose the patient should be observed and appropriate symptomatic treatment given. Generally the reported outcome in these cases was "improved" or "recovered". Events that have been reported at different dose ranges are as follows:

Adult population

*1200 to 1600 mg* (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.

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

*6400 mg (single dose):* 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

*Single dose of 400 mg*: vomiting, diarrhoea and anorexia

*Single dose of 980 mg*: decreased white blood cell count and diarrhoea.

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

**PHARMACOLOGICAL PROPERTIES**

Pharmacodynamic properties

*Mechanism of action*

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1 and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.

*Pharmacodynamic effects*

Imatinib is a protein-tyrosine kinase inhibitor which potently inhibits the Bcr-Abl tyrosine kinase at the in vitro, cellular and in vivo levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukaemia (ALL) patients.

In vivo the compound shows anti-tumour activity as a single agent in animal models using Bcr- Abl positive tumour cells.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), PDGF-R, and 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.

Pharmacokinetic properties

The pharmacokinetics of Imatinib have been evaluated over a dosage range of 25 to 1,000 mg. Plasma pharmacokinetic profiles were analysed on day 1 and on either day 7 or day 28, by which time plasma concentrations had reached steady state.

*Absorption*

Mean absolute bioavailability for imatinib is 98%. There was high between-patient variability in plasma imatinib AUC levels after an oral dose. When given with a high-fat meal, the rate of absorption of imatinib was minimally reduced (11% decrease in $C_{max}$ and prolongation of $t_{max}$ by 1.5 h), with a small reduction in AUC (7.4%) compared to fasting conditions. The effect of prior gastrointestinal surgery on drug absorption has not been investigated.

*Distribution*

At clinically relevant concentrations of imatinib, binding to plasma proteins was approximately 95% on the basis of in vitro experiments, mostly to albumin and alpha-acid-glycoprotein, with little binding to lipoprotein.

*Biotransformation*

The main circulating metabolite in humans is the N-demethylated piperazine derivative, which shows similar in vitro potency to the parent. The plasma AUC for this metabolite was found to be only 16% of the AUC for imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the parent compound.

Imatinib and the N-demethyl metabolite together accounted for about 65% of the circulating radioactivity ($AUC_{(0-48h)}$). The remaining circulating radioactivity consisted of a number of minor metabolites.

It is shown that CYP3A4 was the major human P450 enzyme catalysing the biotransformation of imatinib. Of a panel of potential comedications (acetaminophen, aciclovir, allopurinol, amphotericin, cytarabine, erythromycin, fluconazole, hydroxyurea, norfloxacin, penicillin V) only erythromycin ($IC_{50}$ 50 µM) and fluconazole ($IC_{50}$ 118 µM) showed inhibition of imatinib metabolism which could have clinical relevance. Imatinib was shown 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. Maximal plasma concentrations

of imatinib in patients are 2–4 μmol/l, consequently an inhibition of CYP2D6 and/or CYP3A4/5-mediated metabolism of co-administered drugs is possible. Imatinib did not interfere with the biotransformation of 5-fluorouracil, but it inhibited paclitaxel metabolism as a result of competitive inhibition of CYP2C8 (Ki = 34.7 μM). This Ki value is far higher than the expected plasma levels of imatinib in patients, consequently no interaction is expected upon co-administration of either 5-fluorouracil or paclitaxel and imatinib.

*Elimination*

Based on the recovery of compound(s) after an oral $^{14}$C-labelled dose of imatinib, approximately 81% of the dose was recovered within 7 days in faeces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% faeces), the remainder being metabolites.

*Plasma pharmacokinetics*

Following oral administration, the t½ was approximately 18 h, suggesting that once-daily dosing is appropriate. The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25–1,000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1.5–2.5-fold at steady state when dosed once daily.

*Pharmacokinetics in GIST patients*

In patients with GIST steady-state exposure was 1.5-fold higher than that observed for CML patients for the same dosage (400 mg daily). Based on preliminary population pharmacokinetic analysis in GIST patients, there were three variables (albumin, WBC and bilirubin) found to have a statistically significant relationship with imatinib pharmacokinetics. Decreased values of albumin caused a reduced clearance (CL/f); and higher levels of WBC led to a reduction of CL/f. However, these associations are not sufficiently pronounced to warrant dose adjustment. In this patient population, the presence of hepatic metastases could potentially lead to hepatic insufficiency and reduced metabolism.

*Population pharmacokinetics*

Based on population pharmacokinetic analysis in CML patients, there was a small effect of age on the volume of distribution (12% increase in patients > 65 years old). This change is not thought to be clinically significant. The effect of bodyweight on the clearance of imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8.5 l/h, while for a patient weighing 100 kg the clearance will rise to 11.8 l/h. These changes are not considered sufficient to warrant dose adjustment based on kg bodyweight. There is no effect of gender on the kinetics of imatinib.

*Pharmacokinetics in children*

As in adult patients, imatinib was rapidly absorbed after oral administration in paediatric patients in both phase I and phase II studies. Dosing in children at 260 and 340 mg/m$^2$/day achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients. The comparison of $AUC_{(0-24)}$ on day 8 and day 1 at the 340 mg/m$^2$/day dose level revealed a 1.7-fold drug accumulation after repeated once-daily dosing.
Based on pooled population pharmacokinetic analysis in paediatric patients with haematological disorders (CML, Ph+ALL, or other haematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in paediatric patients receiving 260 mg/m$^2$ once daily (not exceeding 400 mg once daily) or 340 mg/m$^2$ once daily (not exceeding 600 mg once daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once daily.

*Organ function impairment*
Imatinib and its metabolites are not excreted via the kidney to a significant extent. Patients with mild and moderate impairment of renal function appear to have a higher plasma exposure than patients with normal renal function. The increase is approximately 1.5- to 2-fold, corresponding to a 1.5-fold elevation of plasma AGP, to which imatinib binds strongly. The free drug clearance of imatinib is probably similar between patients with renal impairment and those with normal renal function, since renal excretion represents only a minor elimination pathway for imatinib.
Although the results of pharmacokinetic analysis showed that there is considerable inter-subject variation, the mean exposure to imatinib did not increase in patients with varying degrees of liver dysfunction as compared to patients with normal liver function.

**PHARMACEUTICAL INFORMATION**

Shelf Life

24 months

Storage conditions

Store below 30°C

Precautions for Storage

Keep out of reach of children.

Nature and contents of container

Dosage form: Film coated Tablets

Packaging

Alu-PVC/Aclar Blister Pack

REDISTRA (Imatinib Tablets 100 mg): Pack containing 15’s (1x15’s) and 60’s tablets (4x15’s blister).

REDISTRA (Imatinib Tablets 400 mg): Pack containing 10’s (1x10’s) and 30’s tablets (3x10’s blister).

**MANUFACTURED BY**

Dr. Reddy's Laboratories Ltd.,

Formulation Unit -VII,

Plot Nos, P1 to P9, Phase III, VSEZ, Duvvada, Visakhapatanam District -530046, Andhra Pradesh, India.

**PRODUCT REGISTRATION HOLDER**

Dr. Reddy's Laboratories Malaysia Sdn. Bhd. (1238154-X),

Unit 10-06, Menara MBMR,

No. 1, Jalan Syed Putra, 58000 Kuala Lumpur, Malaysia

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