Professional Information for IMATINIB ZYDUS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

IMATINIB 100 ZYDUS, 100 mg film-coated tablets

IMATINIB 400 ZYDUS, 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMATINIB 100 ZYDUS: Each film-coated tablet contains 100 mg imatinib (as mesilate).

IMATINIB 400 ZYDUS: Each film-coated tablet contains 400 mg imatinib (as mesilate).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

IMATINIB 100 ZYDUS: Light yellow to yellow coloured, round shaped film-coated tablets debossed with '1470' on one side and scored on other side. The tablets should be free from any physical defects.

IMATINIB 400 ZYDUS: Light yellow to yellow coloured, ovaloid shaped film coated tablets debossed with '1473' on one side and scored on other side. The tablets should be free from any physical defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMATINIB ZYDUS is indicated for:

- treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML) (for paediatric use, see section 4.2);
- 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 section 4.2);
- 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 and eosinophilia;
- treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement;
- treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST);
- adjuvant treatment of adult patients following resection of Kit-positive GIST;
- treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

The effectiveness of IMATINIB ZYDUS 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 (see section 5). Increased survival in controlled trials has been demonstrated only in newly diagnosed chronic phase CML.

4.2 Posology and method of administration

Therapy should be initiated by a medical practitioner experienced in the treatment of patients with

malignancies.

Posology

Dosage in CML

The recommended dosage of IMATINIB ZYDUS 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 to 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 reactions 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 cytogenic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenic 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 IMATINIB ZYDUS in children below 2 years of age.

Dosage in Ph+ ALL

The recommended dose of IMATINIB ZYDUS is 600 mg/day for patients with Ph+ ALL.

Dosage in MDS/MPD

The recommended dose of IMATINIB ZYDUS is 400 mg/day for patients with MDS/MPD.

Dosage in SM

For patients with SM associated with eosinophilia, a clonal haematological disease related to the fusion kinase FIP1L1-PDGFRα, 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 reactions if assessments demonstrate an insufficient response to therapy.

Dosage in HES/GEL

For HES/CEL patients with demonstrated FIP1L1-PDGFRα 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 reactions if assessments demonstrate an insufficient response to therapy.

Dosage in GIST

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

A dose increase from 400 mg to 600 mg or to 800 mg for patients may be considered in the absence of adverse reactions if assessments demonstrate an insufficient response to therapy. Treatment with IMATINIB ZYDUS in GIST patients should be continued until disease progression. The recommended dose of IMATINIB ZYDUS is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. In the adjuvant setting the optimal treatment duration with IMATINIB ZYDUS is not known.
Efficacy has been demonstrated for a mean duration of one year.

Dosage in DFSP

The recommended dose of IMATINIB ZYDUS 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 IMATINIB ZYDUS 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, IMATINIB ZYDUS should be withheld until bilirubin levels have returned to a < 1,5 x IULN and transaminase levels to < 2,5 x IULN.

Treatment with IMATINIB ZYDUS 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.

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

SM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1,0 x10^9/L and/or platelets< 50 x10^9/L	1. Stop IMATINIB ZYDUS until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with IMATINIB ZYDUS at previous dose (i.e. before severe adverse reaction).

Chronic phase CML, MDS/MPD, SM, HES/CEL and GIST (starting dose 400 mg).	ANC < 1,0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop IMATINIB ZYDUS until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with IMATINIB ZYDUS 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 IMATINIB ZYDUS at reduced dose of 300 mg.
Paediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1,0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop IMATINIB ZYDUS until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with IMATINIB ZYDUS 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 IMATINIB ZYDUS 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 x10^9/L and/or platelets < 10 x10^9/L	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of IMATINIB ZYDUS to 400 mg[b]. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg[d] 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop IMATINIB ZYDUS until ANC 1 x10^9/L and platelets ≥ 20 x10^9/L, then resume treatment at 300 mg[d].
DFSP	ANC < 1,0 x10^9/L	1. Stop IMATINIB

(starting dose 800 mg)	and/or platelets < 50 x10^9/L	ZYDUS until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L 2. Resume treatment with IMATINIB ZYDUS at 600 mg. 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 IMATINIB ZYDUS at reduced dose of 400 mg.
ANC = absolute neutrophil count [a] occurring after at least 1 month of treatment [b] 260 mg/m^2 in children [c] or 340 mg/m^2 in children [d] or 200 mg/m^2 in children		

Children

There is no experience with the use of IMATINIB ZYDUS in children with CML below 2 years of age. There is very limited experience with the use of IMATINIB ZYDUS in children below 3 years of age in other indications.

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 (see section 4.8 and section 5.2).

Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidney. Since the renal clearance of imatinib is negligible, a decrease in free medicine 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. The dose can be reduced if not tolerated, or increased for lack of efficacy (see section 4.4). There are insufficient data on patients with chronic renal failure or on dialysis to make a dose recommendation.

Elderly patients

No significant age-related pharmacokinetic differences have been observed in adult patients in clinical trials. No specific dose recommendation is necessary in the elderly.

Method of administration

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).

4.3 Contraindications

- hypersensitivity to imatinib or to any of the excipients listed in section 6.1;
- safety during pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

IMATINIB ZYDUS should be taken with food and a large glass of water to minimise the risk of gastrointestinal disturbances.

When IMATINIB ZYDUS is co-administered with other medicines, there is a potential for medicine interactions. Caution should be used when taking IMATINIB ZYDUS with protease inhibitors, azole antifungals, certain macrolides (see section 4.5), CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives (see section 4.5).

Concomitant use of IMATINIB ZYDUS and medicines 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 ZYDUS, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and IMATINIB ZYDUS should be avoided (see section 4.5).

Hypothyroidism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with IMATINIB ZYDUS (see section 4.5). Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.

Hepatotoxicity

Metabolism of IMATINIB ZYDUS 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 (see sections 4.2, 4.8 and 5.2). 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 ZYDUS is combined with chemotherapy regimens also known to

be associated with hepatic dysfunction (see section 4.5 and 4.8).

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 ZYDUS. Therefore, it is highly recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in older people and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.

Patients with cardiac disease

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

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

Gastrointestinal haemorrhage

In a study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoral haemorrhages were reported (see section 4.8). 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 (see section 4.8). When needed, discontinuation of IMATINIB ZYDUS 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 ZYDUS (see section 4.8).

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 ZYDUS.

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 ZYDUS should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

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 ZYDUS (see section 4.8). If laboratory or clinical findings associated with TMA occur in a patient receiving IMATINIB ZYDUS, 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 ZYDUS should not be resumed.

Laboratory tests

Complete blood counts must be performed regularly during therapy with IMATINIB ZYDUS. Treatment of CML patients with IMATINIB ZYDUS 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 ZYDUS may be interrupted or the dose may be reduced, as recommended in section

4.2.

Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving IMATINIB ZYDUS.

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 (see section 4.2 and 5.2).

Long-term treatment with IMATINIB ZYDUS 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.

Cerebrovascular events

Cerebrovascular adverse events identified as class related adverse events have occurred in patients treated with TKI (tyrosine kinase inhibitor) containing medicines. These class-related cerebrovascular adverse events, shared to a variable degree by all TKIs, are cerebrovascular accident (CA), transient ischaemic attack (TIA), ischaemic stroke (IS) and cerebral infarction (CI). These cerebrovascular events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

Advise to the healthcare professionals

The above-mentioned cerebrovascular adverse events may occur in patients on treatment with TKI-containing medicines with or without risk factors for these events and may occur at any time

during treatment with TKIs.

Patients on treatment with TKI-containing medicines should be carefully monitored, and relevant risk factors managed to reduce the risk of these class-related cerebrovascular adverse events. Treatment with TKI-containing medicines should be discontinued, and alternative treatment options be considered in patients who develop these class-related cerebrovascular adverse events.

Paediatric population

There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. In an observational study 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 ZYDUS treatment is recommended (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Active substances that may increase IMATINIB ZYDUS 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 ZYDUS concentrations. There was a significant increase in exposure to imatinib (the mean C_{max} and AUC of imatinib rose by 26 % and 40 %, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be taken when administering IMATINIB ZYDUS with inhibitors of the CYP3A4 family.

Active substances that may decrease IMATINIB ZYDUS 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 ZYDUS, 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, phenytoin, fosphenytoin, phenobarbital and primidone. The plasma AUC for imatinib decreased by 73 % compared to patients not on EIAEDs. In two published studies, concomitant administration of imatinib and a product ccontainng St John’s wort led to 30 – 32 % reduction in the AUC of imatinib. Concomitant use of rifampicin or other strong CYP3A4 inducers and IMATINIB ZYDUS should be avoided.

Active substances that may have their plasma concentration altered by IMATINIB ZYDUS

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 ZYDUS with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). IMATINIB ZYDUS may increase plasma concentration of other CYP3A4 metabolised medicines (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).

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

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 warfarin.

In vitro IMATINIB ZYDUS inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. IMATINIB ZYDUS 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 ZYDUS 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 ZYDUS inhibits paracetamol O-glucuronidation with Ki value of 58,5 µmol/L. This inhibition has not been observed *in vivo* after the administration of IMATINIB ZYDUS 400 mg and paracetamol 1000 mg. Higher doses of IMATINIB ZYDUS and paracetamol have not been studied.
Caution should therefore be exercised when using high doses of IMATINIB ZYDUS and paracetamol concomitantly.

In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be decreased when IMATINIB ZYDUS is co-administered (see section 4.4). 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 ZYDUS with chemotherapy (see section 5.1), but interactions between imatinib and chemotherapy regimens are not well characterised. IMATINIB ZYDUS 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 (see section 4.8). Therefore, the use of IMATINIB ZYDUS in combination requires special precaution.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are limited data on the use of IMATINIB ZYDUS in pregnant women. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken IMATINIB ZYDUS. Studies in animals have however shown reproductive toxicity (see section 5.3) and the potential risk for the foetus is unknown. IMATINIB ZYDUS should not be used during pregnancy unless clearly necessary (see section 4.3). If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Breastfeeding

There is limited information on IMATINIB ZYDUS distribution on human milk. Studies in two breastfeeding women revealed that both IMATINIB ZYDUS and its active metabolite can be distributed into human milk. Therefore, women taking IMATINIB ZYDUS should not breastfeed (see section 4.3).

Fertility

In non-clinical studies, the fertility of male and female rats was not affected (see section 5.3). Studies on patients receiving IMATINIB ZYDUS and its effect on fertility and gametogenesis have not been performed. Patients concerned about their fertility on IMATINIB ZYDUS treatment should consult with their doctor.

4.7 Effects 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 ZYDUS. Therefore, caution should be recommended when driving a car or operating machinery.

4.8 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 medicines.

In clinical trials in CML, medicine discontinuation for medicine-related adverse reactions 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 GIST the study medicine was discontinued for medicine-related adverse reactions in 4 % of patients.

The most commonly reported (≥ 10 %) medicine-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 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 by reducing the dose of IMATINIB ZYDUS.

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.

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 ZYDUS temporarily and with diuretics and other appropriate supportive care measures. However, 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.

Adverse reactions

Within each frequency grouping, undesirable effects are presented in order of frequency, the most frequent first.

Infections and infestations

Less frequent: herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1], sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis, fungal infection

Frequency unknwon: hepatitis B reactivation*

Neoplasms benign and malignant (including cysts and polyps)

Less frequent: tumour lysis syndrome

Frequency unknown: tumour haemorrhage/tumour necrosis*

Blood and the lymphatic system disorders

Frequent: neutropenia, thrombocytopenia, anaemia, pancytopenia, febrile neutropenia

Less frequent: thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy, haemolytic anaemia, thrombotic microangiopathy

Immune system disorders

Frequency unknown: anaphylactic shock*, angioedema

Metabolism and nutrition disorders

Frequent: anorexia

Less frequent: hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia,

hyperglycaemia, hyponatraemia, hyperkalaemia, hypomagnesaemia

Psychiatric disorders

Frequent: insomnia

Less frequent: depression, decreased libido, anxiety, confusional state

Nervous system disorders

Frequent: headache[2], dizziness, paraesthesia, taste disturbance, hypoaesthesia

Less frequent: migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral haemorrhage, increased intracranial pressure, convulsions, optic neuritis

Frequency unknown: cerebral oedema*

Eye disorders

Frequent: eyelid oedema, increased lacrimation, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision

Less frequent: eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema, cataract, glaucoma, papilloedema

Frequency unknown: vitreous haemorrhage*

Ear and labyrinth disorders

Less frequent: vertigo, tinnitus, hearing loss

Cardiac disorders

Less frequent: palpitations, tachycardia, cardiac failure, congestive[3], pulmonary oedema, dysrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina

pectoris, pericardial effusion

Frequency unknown: pericarditis*, cardiac tamponade*

Vascular disorders[4]

Frequent: flushing, haemorrhage

Less frequent: hypertension, haematoma, subdural haematoma, peripheral coldness, hypotension, Raynaud's phenomenon

Frequency unknown: thrombosis/embolism*

Respiratory, thoracic and mediastinal disorders

Frequent: dyspnoea, epistaxis, cough

Less frequent: pleural effusion[5], pharyngolaryngeal pain, pharyngitis, pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage

Frequency unknown: acute respiratory failure[11]*, interstitial lung disease*

Gastrointestinal disorders

Frequent: nausea, diarrhoea, vomiting, dyspepsia, abdominal pain[6], flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis

Less frequent: stomatitis, mouth ulceration, gastrointestinal haemorrhage[7], eructation, melaena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis, colitis, ileus, inflammatory bowel disease

Frequency unknown: Ileus/intestinal obstruction*, tumor haemorrhage/tumor necrosis, gastrointestinal perforation*, diverticulitis*, gastric antral vascular ectasia (GAVE)

Hepato-biliary disorders

Frequent: increased hepatic enzymes

Less frequent: hyperbilirubinaemia, hepatitis, jaundice, hepatic failure[8], hepatic necrosis

Skin and subcutaneous tissue disorders

Frequent: periorbital oedema, dermatitis/eczema/rash, pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction

Less frequent: pustular rash, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, exfoliative dermatitis, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions, acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, vesicular rash, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP)

Frequency unknown: palmoplantar erythrodysesthesia syndrome*, lichenoid keratosis*, lichen planus*, toxic epidermal necrolysis*, drug rash with eosinophilia and systemic symptoms (DRESS)*, pseudoporphyria*

Musculoskeletal and connective tissue disorders

Frequent: muscle spasm and cramps, musculoskeletal pain including myalgia[9], arthralgia, bone pain[10], joint swelling

Less frequent: joint and muscle stiffness, muscular weakness, arthritis, rhabdomyolysis/ myopathy

Frequency unknown: avascular necrosis/hip necrosis*, growth retardation in children*

Renal and urinary disorders

Less frequent: renal pain, haematuria, acute renal failure, increased urinary frequency

Frequency unknown: chronic renal failure

Reproductive system and breast disorders

Less frequent: gynaecomastia, erectile dysfunction, menorrhagia, irregular menstruation, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema, haemorrhagic corpus luteum/haemorrhagic ovarian cyst

General disorders and administration site conditions

Frequent: fluid retention and oedema, fatigue, weakness, pyrexia, anasarca, chills, rigors

Less frequent: chest pain, malaise

Investigations

Frequent: increased weight, decreased weight

Less frequent: increased blood creatinine, increased blood creatine phosphokinase, increased blood lactate dehydrogenase, increased blood alkaline phosphatase, increased blood amylase

*These types of reactions have been reported mainly from post-marketing experience. 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] 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] Reported more commonly in patients with GIST and in patients with transformed CML (CML-APand 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 109/L) and thrombocytopenias (platelet count < 50 x 109/l) being between 4 and 6 times higher in blast crisis and accelerated phase (59 – 64 % and 44 – 63 % for neutropenia and thrombocytopenia, respectively) as compared to newly diagnosed patients in chronic phase CML (16,7 % neutropenia and 8,9 % thrombocytopenia). In newly diagnosed chronic phase CML grade 4 neutropenia (ANC < 0,5 x 109/L) and thrombocytopenia (platelet count < 10 x 109/L) were observed in 3,6 % and < 1 % of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with IMATINIB

ZYDUS, but can in rare cases lead to permanent discontinuation of treatment.

In paediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

In the study in patients with unresectable and/or metastatic GIST, grade 3 and 4 anaemia was reported in 5,4 % and 0,7 % of patients, respectively, and may have been related to gastrointestinal or intra-tumoural bleeding in at least some of these patients. Grade 3 and 4 neutropenia was seen in 7,5 % and 2,7 % of patients, respectively, and grade 3 thrombocytopenia in 0,7 % of patients. No patient developed grade 4 thrombocytopenia. The decreases in white blood cell (WBC) and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.

Biochemistry

Severe elevation of transaminases (< 5 %) or bilirubin (< 1 %) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1 % of CML patients. In GIST patients, 6,8 % of grade 3 or 4 ALT (alanine aminotransferase) elevations and 4,8 % of grade 3 or 4 AST (aspartate aminotransferase) elevations were observed. Bilirubin elevation was below 3 %.

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

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 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of IMATINIB ZYDUS is important. It allows continued monitoring of the benefit/risk balance of IMATINIB ZYDUS. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Experience with doses greater than 800 mg is limited. Isolated cases of overdose have been reported. In the event of overdosage, the patient should be observed and appropriate supportive treatment given.

A patient with myeloid blast crisis inadvertently took imatinib 1200 mg for 6 days and experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin. Treatment was temporarily interrupted and there was complete reversal of all abnormalities within one week. Treatment was resumed at a dose of 400 mg without recurrence of problems.

Another patient developed severe muscle cramps after taking imatinib1600 mg daily for six days. Following interruption of treatment, complete resolution of muscle cramps occurred and treatment was subsequently resumed. Another patient who was prescribed 400 mg daily took imatinib 800 mg on day 1 and 1200 mg on day 2. Treatment was interrupted, no adverse events occurred and the patient resumed treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.34 Other

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 (DDR_1 and DDR_2), 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.

5.2 Pharmacokinetic properties

Absorption

Mean absolute bioavailability for imatinib is 98 %. The coefficient of variation for plasma imatinib AUG is in the range of 40 – 60 % 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 medicine 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

CYP3A4 is the major enzyme responsible for metabolism for imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism.

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.

Elimination

Elimination is predominantly in the faeces, mostly as metabolites.Based on the recovery of

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

Plasma pharmacokinetics

Following oral administration in healthy volunteers, the $t_{½}$ 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.

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.

Further population pharmacokinetic (PK) analysis in a phase III study in newly diagnosed CML patients showed that the effect of covariate and co-medication on both clearance and volume appears to be small and is not sufficiently pronounced to warrant dose adjustment.

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 medicine 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 medicine 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 (see sections 4.2 and 4.4).

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 (see sections 4.2, 4.4 and 4.8).

5.3. Preclinical safety data

No information of relevence available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal anhydrous silica

Crospovidone (E1201)

Magnesium stearate (E572)

Microcrystalline cellulose (E460)

Tablet coating:

Opadry yellow (containing hypromellose (E464), iron oxide yellow (E172), macrogol (E1521), talc (E553b) and titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

Protect from moisture.

6.5 Nature and contents of container

Clear PVC/ACLAR and aluminium blister strips in a carton containing 20, 30 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

IMATINIB 100 ZYDUS: 54/34/0877

IMATINIB 400 ZYDUS: 54/34/0878

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Will be allocated by SAHPRA upon registration.

10. DATE OF REVISION OF THE TEXT

Not applicable.