PROFESSIONAL INFORMATION FOR

IMAVEC/IMAVEC 400 (capsules)

SCHEDULING STATUS:

S4

1. NAME OF MEDICINE

IMAVEC (100 mg, capsules)

IMAVEC 400 (400 mg, capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMAVEC: Each capsule contains imatinib mesylate equivalent to imatinib 100 mg.

IMAVEC 400: Each capsule contains imatinib mesylate equivalent to imatinib 400 mg.

Contains sugar (159, 64 mg lactose per capsule).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

IMAVEC: Pale yellow powder filled in hard gelatin capsule of size “1” with mud brown coloured cap and mud brown coloured body, printed with ITB.

IMAVEC 400: Light yellow granules filled in size 00EL hard gelatin capsules with brown cap and brown body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMAVEC is indicated for:

- The treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML).
- The treatment of adult and paediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
- The treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- The treatment of adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- The treatment of adult patients with myelodysplastic/ myeloproliferative diseases (MDS/ MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements.
- The treatment of adult patients with systemic mastocytosis (SM) without the D816V c-Kit mutation and eosinophilia.
- The treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.
- The treatment of adult patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- The adjuvant treatment of adult patients following resection of Kit-positive GIST.
- The treatment of adult patients with unresectable, recurrent and/ or metastatic dermatofibrosarcoma protuberans (DFSP).

The effectiveness of IMAVEC 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 free survival in unresectable and/or metastatic GIST, on recurrence free survival in

adjuvant GIST, and on objective response rates in DFSP. Increased survival in controlled trials has been demonstrated only in newly diagnosed chronic phase CML.

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 in adults:

The recommended dosage is 400 mg per day for patients in chronic phase CML and 600 mg per 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 drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances:

- Disease progression (at any time);
- Failure to achieve a satisfactory haematological response after at least 3 months of treatment;
- Failure to achieve a cytogenic response after 12 months of treatment; or
- Loss of a previously achieved haematological and/or cytogenic response. (ZA innovator PI pg4 L6)

Dosage in CML in Children

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 IMAVEC in children below 2 years of age.

Dosage in Ph+ ALL:

The recommended dose of IMAVEC is 600 mg per day for patients with Ph+ ALL.

Dosage in MDS/MPD:

The recommended dose of IMAVEC is 400 mg per day for patients with MDS/MPD.

Dosage in SM:

The recommended dose of IMAVEC is 400 mg per day for adult patients with SM without the D816V KIT mutation or mutational status unknown or not responding satisfactorily to other therapies.

For patients with SM associated with eosinophilia, a clonal haematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg per 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 / CEL:

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

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 medicine reactions if assessments demonstrate an insufficient response to therapy.

***Dosage in GIST**:*

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

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

Treatment with IMAVEC in GIST patients should be continued until disease progression.

The recommended dose of IMAVEC is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. The recommended minimum treatment duration is 36 months.

In the adjuvant setting the optimal treatment duration with IMAVEC is not known.

Efficacy has been demonstrated for a mean duration of one year.

Dosage in DFSP:

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

Treatment with IMAVEC may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 mg to 300 mg or from 600 mg to 400 mg, or from 800 mg to 600 mg and in children from 340 to 260 mg/m^2/day.

Haematological adverse 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

SM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1,0 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop IMAVEC until ANC ≥ 1,5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with IMAVEC 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 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop IMAVEC until ANC ≥ 1,5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with IMAVEC at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1,0 x 10^9/L and/or platelets < 50 x 10^9/L, repeat step 1 and resume IMAVEC 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 IMAVEC until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with IMAVEC 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 IMAVEC at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg[c])	[a]ANC < 0,5 x 10^9/L and/or platelets < 10 x 10^9/L	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of IMAVEC 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 IMAVEC until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L, then resume treatment at 300 mg[d].
DFSP (starting dose 800 mg)	ANC < 1,0 x 10^9/L and/or	1. Stop IMAVEC until ANC ≥ 1,5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with IMAVEC at

	platelets < 50 x 10^9/L	600 mg. 3. In the event of recurrence of ANC < 1,0 x 10^9/L and/or platelets < 50 x 10^9/L, repeat step 1 and resume IMAVEC 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 in children 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 IMAVEC in children below 3 years of age in other indications.

Dosing in children should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with chronic phase and advanced phase CML and Ph+ ALL (not to exceed the total dose of 600 mg daily). Treatment can be given as a once daily dose in CML and Ph+ ALL. In CML, alternatively the daily dose may be split into two administrations – one in the morning and one in the evening (see **section 5**).

Hepatic insufficiency

Since Imatinib is mainly metabolised through the liver, exposure to IMAVEC is expected to increase if liver function is impaired and IMAVEC should be used with caution in patients with hepatic impairment.

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. Cases of hepatic failure including fatal outcome have occurred in patients treated with imatinib (see **section 4.4, 4.8 and section 5.2**).

Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidneys. Since the renal clearance of imatinib is negligible, a decrease in free medicine clearance is not expected in patients with renal insufficiency.

Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated the dose may be increased for lack of efficacy (see **section 4.4 and 5.2**). 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,-which included over 20 % of patients age 65 and older.

No specific dose adjustment is necessary in the elderly.

Method of administration

There is a potential risk of reproductive toxicity for pregnant woman when handling the opening of IMAVEC capsules.

For doses other than 400 mg (see dosage recommendation below) 100 mg capsules are available.

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

For patients unable to swallow the capsules, their content may be dispersed in a glass of either still water or apple juice. The suspension should be administered immediately after its preparation.

4.3 Contraindications

- hypersensitivity to imatinib or to any of the excipients of IMAVEC listed in **section 6.1**.
- Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use

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

Co-administration of IMAVEC with other medicines may potentially cause medicine interactions. Caution should be used when taking IMAVEC with protease inhibitors, azole antifungals, certain macrolides (see **section 4.5**), other CYP3A4 substrates with a narrow therapeutic window (such as 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 IMAVEC 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 IMAVEC, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and IMAVEC should be avoided (see **section 4.5**).

Hypothyroidism:

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with IMAVEC. TSH levels should be closely monitored in such patients (see **section 4.5**).

Hepatotoxicity

Metabolism of IMAVEC 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 IMAVEC is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions have been detected in the form of transaminase elevation and hyperbilirubinaemia. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended in circumstances where IMAVEC 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 IMAVEC. Therefore, it is recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease.

Therefore, caution should be exercised in patients with cardiac dysfunction.

Patients with Cardiac disease or renal failure~~:~~

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

In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/ left ventricular dysfunction with HES cells 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. A careful assessment of the benefit/risk of IMAVEC therapy should be considered in the HES/CEL population before treatment initiation, as cardiac adverse reactions have been reported uncommonly with imatinib.

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 IMAVEC 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 IMAVEC should be considered at the initiation of therapy.

Gastrointestinal haemorrhage:

In a study in patients with unresectable or metastatic malignant GIST, patients reported both gastrointestinal and intra- tumoural haemorrhages (see section 4.8). In the Phase III GIST studies

in patients with unresectable or metastatic malignant GIST, 211 patients (12,9 %) reported Grade 3/4 haemorrhage at any site. In the Phase II GIST study in patients with unresectable or metastatic malignant GIST, eight patients (5,4 %) were reported to have had gastrointestinal (GI) haemorrhage and four patients (2,7 %) were reported to have had haemorrhages at the site of tumour deposits. The tumour haemorrhages have been either intra-abdominal or intrahepatic, depending on the anatomical location of tumour lesions. GI sites of tumour may have contributed to reports of GI bleeding in this patient population (see **section 4.8**).

In addition, gastric antral vascular ectasia (GAVE), a rare cause of GI haemorrhage, has been reported in post-marketing experience in patients with CML, ALL and other diseases. Patients should therefore be monitored for gastrointestinal symptoms at the start of and during imatinib therapy. When needed, imatinib discontinuation may be considered (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 imatanib treatment may be considered.

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

Tumour lysis syndrome (TLS):

Cases of Tumour Lysis Syndrome (TLS) have been reported in patients treated with IMAVEC. Due to the possibility of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of IMAVEC (see **section 4.8**).

Hepatitis B reactivation

Patients should be tested for hepatitis B infection before initiating treatment with IMAVEC.

Reactivation of hepatitis B which may progress to acute hepatic failure, fulminant hepatitis leading to liver transplantation or a fatal outcome has been reported in patients who are chronic carriers of this virus after treatment with BCR-ABL tyrosine kinase inhibition (TKI) such as in IMAVEC. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see **section 4.8**). HBV reactivation may occur at any time during treatment with IMAVEC. An increase in viral load or positive serology occurred upon HBV reactivation.

Patients currently on IMAVEC should be tested for HBV infection before initiating treatment with IMAVEC in order to identify chronic carriers of the virus. 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 diseases) and for those patients who test positive for HBV infections during treatment.

Carriers of HBV who require treatment with IMAVEC should be counselled and closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see **section 4.8**). When IMAVEC is co-administered with other medicines, there is a potential for interactions (see **section 4.5**). Caution should be used when taking imatinib with rifampicin or other strong CYP3A4 inducers, ketoconazole, or other strong CYP3A4 inhibitors, CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin or pimozide) or CYP2C9 substrates with a narrow therapeutic window (e.g. warfarin).

One patient, who was taking paracetamol regularly for fever, died of acute liver failure. Although the aetiology is currently unknown, special caution should be exercised when using paracetamol (see **section 4.5**).

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

Laboratory tests~~:~~

Complete blood counts must be performed regularly during therapy with IMAVEC. Treatment of CML patients with IMAVEC has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is dependent on the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with IMAVEC may be interrupted or the dose be reduced, in **section 4.2**.

Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored regularly in patients receiving IMAVEC (see **section 4.2**). As recommended in section 4.2, non-haematological adverse reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with IMAVEC.

IMAVEC and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect imatinib kinetics (see **section 5**). 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. There is no correlation between imatinib exposure and the degree of renal impairment, as classified by the measurement of creatinine clearance (CrCL), between patients with mild (CrCL: 40 to 59 mL/min) and severe (CrCL: < 20 mL/min) renal impairment. However, as recommended in **section 4.2**, the starting dose of imatinib can be reduced if not tolerated. 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 IMAVEC 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

Class related cerebrovascular adverse events have occurred in patients treated with TKI (tyrosine kinase inhibitor) containing medicines (e.g. cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction). 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 TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

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

Paediatric population

There have been reports of growth retardation occurring in children and pre-adolescents receiving IMAVEC. 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. Similar results have been observed in an observational study in the ALL paediatric population. Therefore, close monitoring of growth in children under IMAVEC treatment is recommended (see **section 4.8**).

Lactose monohydrate

IMAVEC 400 contains lactose.

Patients with the rare hereditary problems of galactose intolerance, galactosaemia, total lactase deficiency or glucose-galactose malabsorption or fructose intolerance should not take GRANICIP, which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Active substances *that may increase* IMAVEC *plasma concentrations*

Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. protease inhibitors such as indinavir, lopinavir/ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin) could reduce metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib (the mean C_{max} and AUC of imatinib rose by 26 % and 40 %, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Co-administration of imatinib with a single dose of ketoconazole (a CYP3A4 inhibitor) in healthy subjects significantly increased exposure to imatinib (mean C_{max} and AUC 26 % and 40 %, respectively). Caution is therefore required when IMAVEC is administered with inhibitors of the CYP3A4 family.

Active substances that may decrease IMAVEC plasma concentrations:

Substances that are inducers of CYP3A4 activity could increase metabolism and significantly decrease IMAVEC plasma concentrations, potentially increasing the risk of therapeutic failure. Co-medications which induce CYP3A4 [e.g.dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbitone, fosphenytoin, primidone or *Hypericum perforatum* (also known as St. John's Wort)] may significantly reduce exposure to IMAVEC.

Pre-treatment with multiple doses of rifampicin, 600 mg daily for 8 days, followed by a single 400 mg dose of imatinib,–resulted in increased imatinib oral-dose clearance by 3, 8-fold (90 % confidence interval = 3, 5 to 4, 3-fold), which represents mean decrease in C_{max}, AUC $_{(0\text{-}24)}$ and AUC($_{0}$-$_{\infty}$) by 54 %, 68% 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 medicines (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, phenobarbitone, 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 containing *Hypericum perforatum* (St. John's Wort) led to a 30 – 32 % reduction in the AUC of imatinib. In patients where rifampicin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered. Concomitant use of rifampicin or other strong CYP3A4 inducers and imatinib should be avoided.

Medicines that may have their plasma concentration altered by IMAVEC:

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 IMAVEC with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin or pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). IMAVEC may increase plasma concentrations of other CYP3A4 metabolised medicines (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.

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

Due to the 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, IMAVEC inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. IMAVEC at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23 % (90%CI [1,16-1,30]). Co-administration of imatinib with CYP2D6 substrates, such as metoprolol, does not seem to be a risk factor for medicine interactions and dose adjustment of IMAVEC may not be necessary.
Caution is however advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol clinical monitoring should be considered.

In vitro, IMAVEC inhibits paracetamol O-glucuronidation (Ki value of 58,5 µmol/L at therapeutic levels). This inhibition has not been observed *in vivo* after the administration of imatinib 400 mg and paracetamol 1000 mg. Higher doses of IMAVEC and paracetamol have not been studied. Patients should be warned to avoid or restrict the concomitant use of high doses over-the-counter and prescription medicines containing paracetamol and imatinib. Co-administration of IMAVEC (400 mg/day for eight days) with paracetamol (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of paracetamol. IMAVEC pharmacokinetics was not altered in the presence of single-dose paracetamol. There is no PK or safety data on the concomitant use of imatinib at doses > 400 mg/day or the chronic use of concomitant paracetamol and IMAVEC.

In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be decreased when IMAVEC 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 IMAVEC with chemotherapy (see **section 5.1**), but interactions between imatinib and chemotherapy regimens are not well characterised. IMAVEC 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 IMAVEC 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 and for at least 15 days after stopping treatment with IMAVEC.

Pregnancy

There are limited data on the use of IMAVEC in pregnant women. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken IMAVEC. Studies in animals have however shown reproductive toxicity (see **section 5.3**) and the potential risk for the foetus is unknown. Reproductive studies in rats have demonstrated that imatinib mesylate induced teratogenicity (increased incidence of congenital abnormalities) following prenatal exposure to imatinib mesylate at doses equal to the highest recommended human dose of 800 mg/day based on body surface area. IMAVEC 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 IMAVEC distribution on human milk. Studies in two breastfeeding women revealed that both IMAVEC and its active metabolite can be distributed into human milk. The milk plasma ratio studied in a 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 taking IMAVEC should not breastfeed during treatment and for at least 15 days after stopping treatment with IMAVEC (see **section 4.3**).

Fertility

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

Women of child-bearing potential must be advised to use highly effective contraception (methods that result in less than 1 % pregnancy rates) such as use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) during treatment with IMAVEC and for at least 15 days after stopping treatment with IMAVEC.

Human studies on male patients receiving IMAVEC and its effect on male fertility and spermatogenesis have not been performed.

Males using IMAVEC should use barrier contraceptives (condoms) for at least 15 days after stopping treatment with IMAVEC. Fertility was not affected in the preclinical fertility and early

embryonic development study although lower testes and epididymal weights as well as a reduced number of motile sperms were observed in the high dose males rats. In pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by IMAVEC.

4.7 Effects on ability to drive and use machines

Patients should be advised that they may experience undesirable effects such as dizziness, syncope, blurred vision, somnolence or other eye disorders during treatment with IMAVEC (see **section 4.8**). 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 medicine.

In clinical trials in CML, medicine discontinuation for treatment-related adverse events was observed in 2,4 % of newly diagnosed patients, 4 % of patients in late chronic phase after failure of interferon therapy, 4 % of patients in accelerated phase after failure of interferon therapy and 5 % of blast crisis patients after failure of interferon therapy. In a clinical trial involving patients with GIST, imatinib was discontinued for medicine-related adverse events in 4 % of patients.

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. In the study in patients with unresectable and/or metastatic GIST, 7 (5%) patients experienced CTC grade 3/4 GI bleeds (3 patients), intra-tumoural bleeds (3 patients) or both (1

patient). GI tumour sites may have been the source of the GI bleeds (see **section 4.4**). GI and tumoural bleeding may be serious and sometimes fatal.

Summary of the safety profile

During clinical development, the majority of patients experienced adverse events at some point in time. The most commonly reported (≥ 10 %) medicine-related adverse reactions in both settings were neutropenia, thrombocytopenia, anaemia, headache, dyspepsia, oedema, weight increased, musculoskeletal pain, mild nausea, vomiting, diarrhoea, abdominal pain, fatigue, myalgia, muscle cramps and rash. Events were of mild to moderate grade; 2 % to 5 % of patients permanently discontinued therapy due to medicine-related events. The safety profile of imatinib in adult and paediatric patients with Ph+ leukaemia is similar.

The differences in the safety profile between Ph+ leukaemia and solid tumours are a higher incidence and severity of myelosuppression in Ph+ leukaemia, and GI and intra-tumoural haemorrhages in GIST patients and are probably due to disease-related factors.

Myelosuppression, GI adverse events, oedema, and rashes are common in these two patient populations. Other GI conditions, such as gastrointestinal obstruction, perforation and ulceration, appear to be more indication-specific.

Other prominent adverse events that have been observed after exposure to GLEEVEC, and which may be causally related, include hepatotoxicity, acute renal failure, hypophosphataemia, severe respiratory adverse reactions, and tumour lysis syndrome and growth retardation in children.

Depending on severity of events, dose adjustment may be required.

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 IMAVEC.

When imatinib, as in IMAVEC, 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 events such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as "fluid retention". These events can usually be managed by interrupting IMAVEC therapy temporarily and/ or with diuretics and/ or other appropriate supportive care measures. However, some of these events may be serious or life-threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure. There were no special safety findings in paediatric clinical trials.

Adverse reactions and their frequencies are reported in Table 2.

Table 2: Tabulated summary of adverse reactions

The following adverse reactions have been classified according to the following categories, frequent, less frequent and frequency unknown.

MedDRA system organ class	**Frequency**	**Side effects**
Infection and infestations	Less frequent	• herpes simplex, herpes zoster, nasopharyngitis, pneumonia[1], gastroenteritis, sinusitis, cellulitis, influenza, urinary tract infection, fungal infection upper respiratory tract infection, sepsis

MedDRA system organ class	Frequency	Side effects
	Frequency unknown	• 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 febrile neutropenia, pancytopenia.
	Less Frequent	• Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy, haemolytic anaemia, thrombotic microangiopathy
Immune system disorders	Less frequent	• anaphylactic shock*, angioedema
	Frequent	• anorexia

MedDRA system organ class	Frequency	Side effects
Metabolism and nutrition disorders:	Less frequent	• dehydration, hyperuricaemia, hypokalaemia, increased appetite, decreased appetite, gout, hypophosphataemia, 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	• cerebral haemorrhage, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, sciatica, restless leg syndrome, tremor increased intracranial pressure, convulsions, cerebral oedema, optic neuritis.
	Frequency unknown	• cerebral oedema*
Eye disorders	Frequent	• eyelid oedema, conjunctivitis, increased lacrimation, blurred vision, conjunctival haemorrhage, dry eye
	Less frequent	• eye irritation, eye pain, optic neuritis, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema cataract, papilloedema, glaucoma.

MedDRA system organ class	Frequency	Side effects
	Frequency unknown	• vitreous haemorrhage*
Ear and labyrinth disorders	Less frequent	• Vertigo, tinnitus, hearing loss
Cardiac disorders	Less frequent	• Cardiac failure congestive,[3] pulmonary oedema, palpitations, tachycardia pericardial effusion, arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris.
	Frequency unknown	• pericarditis*, cardiac tamponade*
Vascular disorders[4]	Frequent	• Flushing, haemorrhage
	Less frequent	• hypertension, haematoma, subdural haematoma, peripheral coldness Raynaud's phenomenon, hypotension,
	Frequency unknown	• thrombosis/embolism*
Respiratory, thoracic and mediastinal disorders	Frequent	• epistaxis, dyspnoea, cough
	Less frequent	• Pleural effusion[5], pharyngolaryngeal pain, pharyngitis pulmonary fibrosis, pleuritic pain, pulmonary hypertension, pulmonary haemorrhage
	Frequency unknown	• acute respiratory failure[11]*, interstitial lung disease

MedDRA system organ class	Frequency	Side effects
Gastrointestinal disorders	Frequent	• Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain[6], abdominal distension, flatulence, constipation, gastro-oesophageal reflux, dry mouth, gastritis.
	Less frequent	• Gastrointestinal haemorrhage[7], melaena, oesophagitis, ascites, gastric ulcer, eructions, mouth ulceration, stomatitis, 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

MedDRA system organ class	Frequency	Side effects
	Less frequent	• Pustular rash, petechiae, contusion, increased sweating, urticaria, ecchymosis, increased tendency to bruise, onychoclasis, folliculitis, purpura, hypotrichosis, skin hyperpigmentation, skin hypopigmentation, psoriasis, exfoliative dermatitis, bullous eruptions, nail discoloration, vesicular rash, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP), acute febrile neutrophilic dermatosis (Sweet's syndrome), erythema multiforme, leucocytoclastic vasculitis. panniculitis**(including erythema nodosum)**, skin hyperpigmentation
	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

MedDRA system organ class	Frequency	Side effects
	Less frequent	• joint and muscle stiffness, osteonecrosis* muscular weakness, arthritis, rhabdomyolysis/myopathy
	Frequency unknown	• avascular necrosis/hip necrosis*, growth retardation in children*
Renal and urinary disorders	Less frequent	• acute renal failure, renal pain, increased urinary frequency, haematuria
	Frequency unknown	• chronic renal failure
Reproductive system and breast disorders	Less frequent	• gynaecomastia, erectile dysfunction, breast enlargement, scrotal oedema, menorrhagia, irregular menstruation, nipple pain, sexual dysfunction haemorrhagic corpus luteum/haemorrhagic ovarian cysts.
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 alkaline phosphatase, increased blood creatinine, increased blood creatine phosphokinase, increased blood lactate dehydrogenase, increased blood amylase.

*These types of reactions have been reported mainly from post-marketing experience with IMAVEC. 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.

The following types of reactions have been reported from post-marketing experience and from additional clinical studies with imatinib. They include spontaneous case reports as well as serious adverse events from smaller or ongoing clinical studies and the expanded access programmes. 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.

Table 3 Adverse reactions from post-marketing reports

Infections and infestations	Hepatitis B reactivation
Nervous system disorders	Cerebral oedema
Eye disorders	Vitreous haemorrhage
Cardiac disorders	Pericarditis, pericardial effusion, cardiac tamponade
Vascular disorders	Thrombosis/embolism, anaphylactic shock
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure[1], interstitial lung disease
Gastrointestinal disorders	Ileus/intestinal obstruction, tumour haemorrhage/tumour necrosis, gastrointestinal perforation[2], diverticulitis, gastric antral vascular ectasia (GAVE)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain, spinal pain), avascular necrosis/hip osteonecrosis, rhabdomyolysis/ myopathy, growth retardation in children
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome, Lichenoid keratosis, lichen planus, toxic epidermal

	necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Pseudoporphyria
Reproductive disorders	Haemorrhagic corpus luteum / haemorrhagic ovarian cyst
Neoplasm benign, malignant and unspecified (including cysts and polyps)	Tumour lysis syndrome
[1] Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions. [2] Some fatal cases of gastrointestinal perforation have been reported.	

Description of selected adverse drug reactions

Myelosuppression

Myelosuppression is very common in cancer patients treated with imatinib. Myelosuppression, thrombocytopenia, neutropenia and anaemia were the most frequently reported Grade 3 and 4 laboratory abnormalities. The myelosuppression experienced with imatinib in CML patients was generally reversible and, in most patients, did not result in dose interruption or dose reduction, but some patients required treatment discontinuation. Other events of pancytopenia, lymphopenia, and bone marrow depression have also been reported.

Haematologic depression appeared greatest at the highest doses and also appeared to be dependent on the stage of CML disease, with Grade 3 or 4 neutropenia and thrombocytopenia between 4 and 6 times higher in blast and accelerated phase (44 % and 63 %, respectively) as compared to newly diagnosed patients in CP CML (16,7 % and 8,9 %, respectively). These events can usually be managed with either a dose reduction or interruption, but may require discontinuation of treatment with imatinib.

The incidence of haematologic toxicities is less in patients with solid tumours (i.e. GIST) than in

patients with Ph+ leukaemia, with Grade 3/4 neutropenia and thrombocytopenia occurring approximately 10 % and 1 %, respectively.

Haemorrhage

CNS and GI haemorrhages are not uncommon in CML patients with compromised marrow function at baseline. Haemorrhages are well-recognized part of the disease complications in an acutely ill population of leukaemic patients, and may result from thrombocytopenia, or less commonly, platelet dysfunction. However, not all patients experiencing CNS and GI haemorrhages during therapy with imatinib are thrombocytopenic.

The most common manifestation of clinically significant bleeding was GI haemorrhage, which occurred most commonly in advanced CML patients and in metastatic GIST patients, where bleeding might occur as part of the underlying disease due to tumour bleeding from tumour haemorrhage/tumour necrosis. In first line CML and in adjuvant GIST setting, the observed frequencies of GI haemorrhage were generally the lowest. Gastric antral vascular ectasia (GAVE) is also rarely reported with imatinib use in the post-marketing setting.

Oedema and Fluid Retention

Oedema is a common toxicity of imatinib appearing in greater than 50 % of all patients across all indications. Oedema is dose-related and there appears to be a correlation with its occurrence and plasma levels. The most common manifestation is periorbital oedema and somewhat less common is lower extremity oedema. Specific therapy may be required. The most frequent fluid retention event was pleural effusion, most commonly observed in advanced CML and metastatic GIST patients. The frequency of cardiac failure was generally low in patients with oedema and fluid retention. It was higher in advanced CML than in other groups. The same trend was observed for renal failure in patients with oedema and fluid retention. Most patients with oedema and fluid retention were elderly (> 65 years old). There are reports of pericardial effusion and cardiac

tamponade.

In a clinical study, the frequency of events suggesting congestive heart failure was 1,5 % on imatinib in patients with newly-diagnosed CML. The frequency was appreciably higher in patients with transformed CML (accelerated phase or blast crisis), higher age, or with a baseline haemoglobin of less than 8 g/dL. Congestive Heart Failure (CHF) and left ventricular dysfunction have since been continuously monitored in the PSUR. Across all indications a higher frequency of CHF events are observed in patients with CML than in patients with GIST. In a safety analysis of cardiac events within the EORTC study of 942 patients with unresectable or metastatic GIST concluded that imatinib does not induce left ventricular failure in GIST patients where the rate was approximately 0,2 % while it can be up to 2 % in a population with pre-existing cardiac disease.

Although rare, imatinib induced cardiac CHF have been observed. Severe CHF and reduction of left ventricular ejection fraction (LVEF) have been reported in patients taking imatinib mesylate. Although several of these patients had pre-existing conditions including hypertension, diabetes and prior coronary artery disease, they were subsequently diagnosed with CHF. Patients with known cardiac disease or risk factors for cardiac failure should be monitored carefully and those with symptoms or signs consistent with CHF should be evaluated and treated.

Skin Rashes and Severe Cutaneous Adverse Reactions

Skin rashes have been observed in up to one third of patients treated with imatinib across all indications. A generalised erythematous, maculopapular, pruritic skin rash has been reported that may fade despite continued therapy. Some patients may have pruritus without accompanying rash, and sometimes there is an exfoliative component. Re-exposure in some patients has resulted in reappearance of rash. These eruptions generally respond to antihistamines and topical steroids. Occasionally, systemic steroids are required.

Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur. LFT abnormalities usually consisted of elevations in transaminases, although a minority of patients had elevated levels of bilirubin. Onset is generally within the first two months of therapy, but has occurred as late as 6 to 12 months after commencing therapy. The levels generally normalise after withholding therapy for 1 to 4 weeks.

Hypophosphataemia

Low serum phosphate and hypophosphataemia (up to Grade 3 or 4) has been observed across all indications, however the origin and the clinical significance of this finding have not been established. Imatinib has been shown to inhibit the differentiation of human monocytes into osteoclasts. The decrease was accompanied by a decrease in the resorptive capacity of these cells. A dose-dependent decrease of RANK-L was observed in osteoclasts in the presence of Imatinib. Sustained inhibition of osteoclastic activity may lead to counter-regulatory responses resulting in increased levels of PTH. The clinical relevance of the preclinical findings is yet unclear and an association with skeletal AEs such as bone fractures has not been demonstrated. In the clinical development program serum phosphate was not routinely measured in all studies. Although it was initially hypothesised that hypophosphataemia might be dose-dependent, 24 months interpretable results from a Phase III study designed to investigate dose dependency of safety endpoints in patients with newly diagnosed CML, have shown that Grade 3 or 4 decreased serum phosphate or serum calcium has been experienced by 19,1 % vs.15,5 % and 5,1 % vs. 0,9 % of patients receiving 400 mg and 800 mg, respectively.

Gastrointestinal (GI) Obstruction, Perforation or Ulceration

GI ulceration, which may represent in extreme cases local irritation by imatinib, has been observed in a small proportion of patients across all indications. Tumour haemorrhage/tumour necrosis, obstruction and GI perforation seem to be disease-related and have occurred more frequently amongst GIST patients. In the case of metastatic GIST, tumour necrosis may occur in

the context of tumour response, which may lead to perforation. GI obstruction/ileus occurred most commonly in the GIST population where it may be caused by tumour obstruction from metastatic GIST and in the adjuvant setting by adhesions from previous GI surgery.

Tumour lysis syndrome

A causal relationship between tumour lysis syndrome and IMAVEC treatment is possible (see **section 4.4**).

Growth retardation in children

Imatinib appears to affect the stature of children especially children who are pre-pubertal. A causal relationship between growth retardation in children and imatinib treatment could not be ruled out (see **section 4.4**).

Severe respiratory adverse drug reaction

Severe respiratory events, sometimes fatal, have been observed with imatinib treatment, including acute respiratory failure, pulmonary hypertension, interstitial lung disease, and pulmonary fibrosis. Pre-existing cardiac or pulmonary conditions that may be associated with severe respiratory events have been reported in many of these cases.

Class related adverse events

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is evidence that the TKIs share to a variable degree, class-related cerebrovascular adverse events such as: cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction (see **section 4.4**). Other TKI class-related adverse events are HBV activation and hepatic events, including acute liver failure (see **section 4.4**).

Laboratory test abnormalities:

Haematology

In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding, with the suggestion of a higher frequency at high doses ≥ 750 mg (phase I study) .However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. In patients with newly diagnosed CML, cytopenias are less frequent than in the other CML patients. The frequency of Grade 3 or 4 neutropenias (ANC < 1,0 x 10^9/l) and thrombocytopenia (platelet count < 50 x 10^9/l) being between 4 and 6 times higher in blast crisis and accelerated phase (59 to 64% and 44 to 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 10^9/l) and thrombocytopenia (platelet count < 10 x 10^9/l) were observed in 3,6% and < 1% of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes usually ranges from 2 to 3 weeks and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction in the dose or an interruption of treatment with IMAVEC 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 or metastatic malignant GIST, Grade 3 and 4 anaemia were 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 were observed in 0,7% of patients.No patient developed Grade 4 thrombocytopenia. The decreases in 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 (study B2222) 6,8 % of Grade 3 or 4 ALT elevations and 4,8% of Grade 3 or 4 AST elevations were observed. Bilirubin elevations was below 3 %. However, one patient with accelerated phase died of acute liver failure in which a medicine interaction with high doses of paracetamol could not be formally ruled out (see **section 4.5**).

There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some the 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 the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd by email: drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9 Overdose

Experience with doses greater than 800 mg is limited. Isolated cases of imatinib overdose have been reported spontaneously and in the literature. In the event of overdosage, the patient should be observed and appropriate supportive treatment given. Generally the reported outcome in these cases was “improved” or “recovered”. Events that have been reported at different dose ranges are as follows:

Adult population

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

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

6400 mg (single dose): One case reported in the literature of one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, decreased neutrophil count, increased transaminases.

8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

Paediatric population

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 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 (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, a protein-tyrosine kinase inhibitor, inhibits the Bcr-Abl tyrosine kinase at the *in vitro,* cellular as well as *in vivo* levels. *In vitro* imatinib selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines and in fresh leukaemic cell cultures obtained from patients with Philadelphia chromosome positive chronic myeloid leukaemia (CML) and from patients with acute lymphoblastic leukaemia (ALL).

In vivo, imatinib demonstrates anti-tumour activity as a single agent in animal models that made use of Bcr-Abl positive tumour cells.

Imatinib furthermore inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, as well as PDGF- and SCF-mediated cellular events.

In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stomal tumour (GIST) cells, which express an activating kit mutation.

Constitutive activation of the platelet-derived growth factor receptor (PDGFR) or the Abl protein kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of myelodysplastic syndrome/ myeloproliferative disorder (MDS/MPD), hypereosinophilc syndrome/ chronic eosinophilic leukemia (HES/CEL) and dermatofibrosarcoma protuberans (DFSP). In addition, constitutive activation of c-Kit or the PDGFR has been implicated in the pathogenesis of SM. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR, Kit and Abl kinase activity.

5.2 Pharmacokinetic properties

Imatinib pharmacokinetics have been assessed over a dosage range of 25 to 1000 mg. Plasma pharmacokinetic profiles were studied on day 1 and on either day 7 or day 28, by which time plasma concentrations had achieved steady state.

Absorption

Imatinib has a mean absolute bioavailability of 98 %. Following an oral dose, the coefficient of variation for plasma imatinib AUC falls in the range of 40 to 60 %. When administered with a high fat meal, imatinib's rate of absorption 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 %) in comparison with fasting conditions.

Distribution

At clinically relevant concentrations of imatinib, plasma protein binding is about 95 %, mainly to albumin and alpha-acid-glycoprotein, with little binding to lipoprotein.

Biotransformation

CYP3A4 is the principle enzyme responsible for imatinib metabolism. Other cytochrome P450 enzymes, for example CYP1A2, CYP2D6, CYP2C9, and CYP2C19, have a minor role in its metabolism. The N-demethylated piperazine derivative is the chief circulating active metabolite in humans and it is formed predominantly by CYP3A4. It demonstrates *in vitro* potency analogous to the parent imatinib. This metabolite's plasma AUC is approximately 15 % of the AUC of imatinib.

Approximately 65 % of the circulating radioactivity (AUC(0-48h), was accounted for by Imatinib and the N-demethyl metabolite together. The remaining circulating radioactivity consisted of a number of minor metabolites.

Elimination

Imatinib is predominantly eliminated via the faecal route, mostly as metabolites. About 81 % of the dose is eliminated within 7 days, with 68 % eliminated faecally and 13 % in the urine. Unchanged imatinib accounts for 25 % of the dose (5 % in urine, 20 % in faeces), the remainder is excreted in the form of metabolites.

Plasma pharmacokinetics:

Imatinib's $t_{½}$ was approximately 18 h after oral administration in healthy volunteers. There is a linear increase in mean AUC with increasing dose and this increase is dose-proportional in the range of 25 to 1000 mg imatinib following oral administration. The kinetics of imatinib do not change with repeated dosing and accumulation is 1,5- to 2,5-fold at steady state when

administered 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 age has a small effect on the volume of distribution (12 % increase in patients over 65 years). This change is not considered to be clinically significant. Body weight affects clearance to the extent that, for a patient who weighs 50 kg, the expected mean clearance is 8,5 L/h, while for a patient who weighs 100 kg, the clearance will increase to 11,8 L/h. These changes are not thought sufficient to warrant dose adjustment based on kg bodyweight. Gender has no effect on imatinib pharmacokinetics.

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

Similar to adult patients, imatinib was rapidly absorbed following oral administration in paediatric

patients. Children who received doses of 260 and 340 mg/m^2 achieved the same exposure, respectively, as adult patients who received doses of 400 mg and 600 mg. Comparing the AUC_{0-24} on day 8 and day 1 at the 340 mg/m^2 dose level, showed 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 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 However, 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 **section 4.2, 4.4 and 4.8**).

5.3. Preclinical safety data

No information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Crospovidone

Magnesium stearate

Microcrystalline cellulose (IMAVEC).

Capsule shells:

IMAVEC: brilliant blue FCF, gelatin, M.P.S, P.P.S, silicon dioxide, sodium lauryl sulphate, sunset yellow and titanium dioxide.

IMAVEC 400: gelatin, purified water, sodium lauryl sulphate, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172).

Contains sugar (159, 64 mg lactose per capsule)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C in the original pack.

Protect from moisture. The blisters should not be removed from the carton until required for use.

6.5 Nature and contents of container

IMAVEC: Carton containing 60 capsules in PVC / Alu blister strips.

IMAVEC 400: Carton containing three Alu/ PVC blister strips of 10 capsules each.

6.6 Special precautions for disposal and other handling

Any unused medicines or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

7530

RSA

Customer Care: 080 222 6662

8. REGISTRATION NUMBERS

IMAVEC: 42/34/0496

IMAVEC 400: 50/34/0118

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 20 April 2017

Latest renewal: Not Applicable

10. DATE OF REVISION OF THE TEXT

03 June 2026