MODULE 1.3.1.1: Professional Information for IMAVEC/IMAVEC 400 (capsules)

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

IMAVEC CAPSULES

IMAVEC 400 CAPSULES

COMPOSITION:

IMAVEC:

Each capsule contains imatinib mesylate equivalent to imatinib 100 mg.

The other inactive ingredients include colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose.

The capsule shells are made of brilliant blue FCF, gelatin, M.P.S, P.P.S, silicon dioxide, sodium lauryl sulphate, sunset yellow and titanium dioxide.

IMAVEC 400:

Each capsule contains imatinib mesylate equivalent to imatinib 400 mg.

The other inactive ingredients include colloidal silicon dioxide, crospovidone, and magnesium stearate.

The capsule shells are made of gelatin, purified water, sodium lauryl sulphate, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (172).

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

PHARMACOLOGICAL CLASSIFICATION:

A.34 Other.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 colony transformation assays making use of *ex vivo* peripheral blood and bone marrow samples, imatinib demonstrates selective inhibition of Bcr-Abl positive colonies obtained from CML patients.

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 signaling and proliferation of cells driven by dysregulated PDGFR, Kit and Abl kinase activity.

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.

Metabolism:

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.

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 $t_{½}$ is 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.

Population pharmacokinetics:

Based on population pharmacokinetic analysis, 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 is 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.

Organ function impairment:

Imatinib and its metabolites are not excreted via the kidney to a siginificant extent. Patients with mild and moderate impairment of renal fuction have a higher plasma exposure than patients with normal renal function. The increase is approximately 1,5- to 2-fold, correspeonding to a 1,5-fold elevation of plamsa AGP, to which imatinib binds strongly. However, renal excretion represents only a minor elimination pathway for imatinib (see "**DOSAGE AND DIRECTIONS FOR USE**" and "**WARNINGS AND SPECIAL PRECAUTIONS**").

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 "**DOSAGE AND DIRECTIONS FOR USE**" and "**WARNINGS AND SPECIAL PRECAUTIONS**").

INDICATIONS:

IMAVEC is indicated for adult patients:

- The treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML).
- The treatment of adult 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.

CONTRAINDICATIONS:

IMAVEC is contraindicated in:

- Patients with hypersensitivity to imatinib or to any of the excipients of **IMAVEC**.
- Pregnancy and lactation, since safety has not been established (see "**PREGNANCY AND LACTATION**").

WARNINGS AND SPECIAL PRECAUTIONS:

Co-administration of **IMAVEC** with other medicines may potentially cause drug interactions. Caution should be used when taking **IMAVEC** with rifampicin or other strong CYP3A4 inducers, or ketoconazole or other CYP3A4 substrates with a narrow therapeutic window (such as ciclosporin) or CYP2C9 substrates with a narrow therapeutic window (such as warfarin (see "**INTERACTIONS**").

One patient, who took paracetamol regularly to reduce fever, died of acute hepatic failure. Although the aetiology is currently unknown, special caution is required when using paracetamol concomitantly with **IMAVEC** as acute liver failure may be precipitated.

*Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in **IMAVEC*****:**

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events (e.g. cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction). These 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.

Viral reactivation:

Hepatitis B reactivation, including fatal outcomes have occurred in patients treated with **IMAVEC**. Hepatitis B virus status should be established before initiating treatment with **IMAVEC**. Patients should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Hypothyroidism:

Cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib. TSH levels should be closely monitored in such patients.

Hepatic dysfunction:

In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see “**DOSAGE AND DIRECTIONS FOR USE**”, “**SIDE EFFECTS**” and “**Pharmacokinetic properties**”).

When **IMAVEC** is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia has been observed. However less frequent reports of acute liver failure were reported. Monitoring of hepatic function is recommended in circumstances where **IMAVEC** is combined with chemotherapy regimens also known to be associated with hepatic dysfuction (see "**SIDE EFFECTS**").

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.

Cardiac disease:

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

In patients with hypereosinophilic syndrome (HES) with ocult infiltration of HES cells into the myocardium, isolated cases of cardiogenic shock/ left ventricular dysfunction with HES cells degranulation have been reported following the initiation of imatinib therapy such as in **IMAVEC**. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. Myelodysplastic/

myeloproliferative disease and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/ CEL, and in patients with MDS/ MPD or SM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1–2 mg/kg for one to two weeks concomitantly with **IMAVEC** should be considered at the initiation of therapy).

Gastrointestinal haemorrhage:

In studies in patients with unresectable or metastatic malignant GIST 12,9 % of patients reported Grade 3/ 4 haemorrhage at any site. In clinical trials 5,4 % of GIST patients with unresectable or metastatic malignant GIST were reported to have had gastrointestinal haemorrhage and 2,7 % of patients were reported to have had haemorrhages at the site of tumour deposits. The tumour haemorrhages have been either intra-abdominal or intra-hepatic, depending on the anatomical location of tumour lesions. Gastrointestinal sites of tumour may have contributed to reports of gastrointestinal bleeding in this patient population (see **"Side-Effects"**). Patients should therefore be monitored for gastrointestinal symptoms at the start of therapy.

Tumour lysis syndrome (TLS):

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**.

Hepatitis B reactivation:

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 such as in **IMAVEC**. HBV reactivation may occur at any time during treatment with **IMAVEC**. An increase in viral load or positive serology occurred upon HBV reactivation.

Patients should be tested for HBV infection before initiating treatment with **IMAVEC**. Patients already on treatment with **IMAVEC** should be tested for hepatitis B infection in order to identify chronic carriers of the virus. Initiation of treatment in patients with positive serology (including those with active diseases) as well as continuation of treatment in patients who tested positive for HBV infections during treatment should be done in consultation with medical practitioners experienced in oncology and hepatology.
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 **"SIDE EFFECTS"**).

Children and pre-adolescents:
There have been reports of growth retardation occurring in children and pre-adolescents receiving **IMAVEC**. The long-term effects of prolonged treatment with **IMAVEC** on growth in children are unknown. Therefore, close monitoring of growth in children under **IMAVEC** treatment is recommended.

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, as recommended under **"DOSAGE AND DIRECTIONS FOR USE"**.

Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored regularly in patients receiving **IMAVEC**. As recommended under **"DOSAGE AND DIRECTIONS FOR USE"**, *"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 is known to decrease with age, and age did not significantly affect **IMAVEC** kinetics (see "**PHARMACOLOGICAL ACTION**").

Lactose:

IMAVEC 400 contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus and should not be used by patients with rare hereditary galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption.

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 **IMAVEC**. Therefore, caution should be recommended when driving a car or operating machinery.

INTERACTIONS:

Medicines that may alter IMAVEC plasma concentrations:

*Medicines that may **increase** imatinib plasma concentrations:*

Substances that inhibit the activity of the cytochrome P450 isoenzyme CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, erythromycin, and clarithromycin) could reduce metabolism and increase imatinib concentrations. 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.
Grapefruit juice may also cause increases in the plasma concentrations of imatinib, as in **IMAVEC**, and should be avoided.

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

In healthy volunteers administration of multiple doses of rifampicin, 600 mg daily for 8 days, followed by a single 400 mg dose of imatinib, increased imatinib oral-dose clearance by 3,8-fold (90 % confidence interval, 3,5- to 4,3-fold), which represents mean decreases in C_{max}, AUC_{0-24} 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. Concomitant administration of imatinib and a product containing Hypericum perforata (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.

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), and patients should be warned to avoid or restrict the use of over-the-counter and prescription medicines containing paracetamol. *In vitro*, imatinib inhibits paracetamol/ acetaminophen O-glucuronidation (Ki value of 58,5 µmol/ℓ at therapeutic levels) (see **"Warnings and Special Precautions"**). **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.).

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.

In vitro, imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. imatinib at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23 %. 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.

Systemic exposure to substrates of CYP2D6 is therefore potentially increased when co-

administered with **IMAVEC**. No specific studies have been performed, however, and caution is recommended.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (see "**CONTRAINDICATIONS**"). Women of child-bearing potential must be advised to use highly effective contraception during treatment.

Studies in animals have shown reproductive toxicity. Both imatinib and its active metabolite can be distributed into human milk. Mothers should not breastfeed their infants while on treatment with **IMAVEC**.

DOSAGE AND DIRECTIONS FOR USE:

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

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) a 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.

Dosage in CML:

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 discontinued 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 reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances:

- Disease progression (at any time);
- Failure to achieve a satisfactory 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.

Dosage in Ph+ ALL:

The recommended dose is 600 mg per day.

Dosage in MDS. MPD:

The recommended dose is 400 mg per day.

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 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:

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 i**s 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 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. 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.

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.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg)	[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. 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.
DFSP (at dose 800 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 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		

Special populations:

Children:

There is no experience with the use of imatinib in children with CML below 2 years of age. There is very limited to no experience with the use of **IMAVEC** in children below 3 years of age in other indications.

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 (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"Pharmacokinetics"**). Cases of hepatic failure including fatal outcome have occurred in patients treated with **IMAVEC**. (see **Side Effects**).

Renal insufficiency:

Imatinib and its metabolites are not significantly excreted via the kidneys. Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. The dose can be reduced if not tolerated. If tolerated the dose may be increased for lack of efficacy (see **"WARNINGS" AND "SPECIAL PRECAUTIONS"**). 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.

SIDE EFFECTS:

The majority of adult patients experienced adverse events at some point in time during treatment, but most were of mild to moderate. In clinical trials, 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.

Fluid retention – oedema:

Superficial oedema was a common finding in all studies and were described primarily as periorbital or lower limb oedema. Oedema may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of **IMAVEC**.

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

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.

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 and/ or with diuretics and/ or 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.

The following side effects have been reported:

Infections and infestations:

Less frequent: Sepsis, pneumonia (most frequently in patients with transformed CML and in patients with GIST), herpes simplex, herpes zoster, nasopharyngitis, upper respiratory tract infection, gastroenteritis, sinusitis, cellulitis, influenza, urinary tract infection, fungal infection.
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 lymphatic system disorders:

Frequent: Neutropenia, thrombocytopenia, anaemia, febrile neutropenia, pancytopenia.
Less frequent: Thrombocythaemia, lymphopenia, bone marrow suppression, eosinophilia, lymphadenopathy, haemolytic anaemia.

Immune system disorders:

Frequency unknown: anaphylactic shock, angioedema.

Metabolism and nutrition disorders:

Frequent: Anorexia, decreased weight.
Less frequent: Dehydration, hyperuricaemia, hypokalaemia, increased appetite, decreased appetite, gout, hypophosphataemia, hypercalcaemia, hyperglycaemia, hyponatraemia, hyperkalaemia, hypomagnesaemia.
Frequency unknown: Growth retardation in children.

Psychiatric disorders:

Frequent: Insomnia.

Less frequent: Depression, anxiety, decreased libido, confusion.

Nervous system disorders:

Frequent: Headache (most frequently observed in GIST patients), dizziness, taste disturbance, paraesthesia, hypoaesthesia.

Less frequent: Cerebral haemorrhage, subdural haematoma, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, sciatica, restless leg syndrome, tremor, increased intracranial pressure, convulsions, cerebral oedema.

Eye disorders:

Frequent: Conjunctivitis, increased lacrimation, blurred vision, periorbital oedema, conjunctival haemorrhage, dry eye.

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

Frequency unknown: Vitreous haemorrhage.

Ear and labyrinth disorders:

Less frequent: Vertigo, tinnitus, hearing loss.

Cardiac disorders:

Less frequent: Cardiac failure, congestive pulmonary oedema (on a patient-year basis, cardiac events, including congestive heart failure were more frequently observed in patients with transformed CML than in patients with chronic CML), palpitations, tachycardia, pericardial effusion, dysrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris.

Frequency unknown: Pericarditis, cardiac tamponade.

Vascular disorders:

Frequent: Flushing, haemorrhage.

Less frequent: Haematoma, hypertension, hypotension, peripheral coldness, Raynaud's phenomenon, subdural haematoma, thrombosis embolism, vasculitis.

Respiratory, thoracic and mediastinal disorders:

Frequent: Epistaxis, dyspnoea, cough.

Less frequent: Pleural effusion pharyngolaryngeal pain, pharyngitis, pulmonary fibrosis, pleuritic pain, pulmonary hypertension, pulmonary haemorrhage, chest pain.

Frequency unknown: Acute respiratory failure, interstitial lung disease.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain abdominal distension, flatulence, constipation, gastro-oesophageal reflux, dry mouth, gastritis.

Less frequent: Gastrointestinal haemorrhage melaena, oesophagitis, ascites, gastric ulcer, eructions, mouth ulceration, stomatitis, haematemesis, cheilitis, dysphagia, pancreatitis, colitis, ileus/ inflammatory bowel disease.

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

Hepatobiliary disorders:

Frequent: Increased hepatic enzymes.

Less frequent: Jaundice, hepatitis, hyperbilirubinaemia, hepatic failure, hepatic necrosis.

Skin and subcutaneous tissue disorders:

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

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, angioedema.

Frequency unknown: Lichenoid keratosis, lichen planus, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS).

Musculoskeletal, connective tissue and bone disorders:

Frequent: Muscle spasm and cramps, musculoskeletal pain, including myalgia, arthralgia, bone pain, joint swelling.

Less frequent: Joint and muscle stiffness, muscular weakness, arthritis.

Frequency unknown: Avascular necrosis/ hip osteonecrosis.

Renal and urinary disorders:

Less frequent: Acute or chronic renal failure, renal pain, increased urinary frequency, haematuria.

Reproductive system and breast disorders:

Less frequent: Gynaecomastia, erectile dysfunction, breast enlargement, scrotal oedema,

menorrhagia, irregular menstruation, nipple pain, sexual dysfunction, haemorrhagic ovarian cysts.

General disorders and administration site conditions:

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

Less frequent: Malaise.

Investigations:

Frequent: Increased weight.

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

Post-marketing reported side effects:

Hepatic failure, including fatal events and hepatitis B reactivation, including fatal events.

Class related side effects:

Class related side effects reported are cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction.

Side effects from clinical trials:

Hepatic failure, including fatal events and hepatitis B reactivation, including fatal events.

Laboratory test abnormalities:

In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding,

with the suggestion of a higher frequency at high doses ≥ 750 mg. However, the occurrence of cytopenias is 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 is between 4 and 6 times higher in blast crisis and accelerated phase as compared to newly diagnosed patients in chronic phase. In newly diagnosed chronic phase CML Grade 4 neutropenia and thrombocytopenia were observed. The median duration of the neutropenic and thrombocytopenic episodes usually range 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 patients with unresectable or metastatic malignant GIST, Grade 3 and 4 anaemia were reported and may have been related to gastrointestinal or intra-tumoural bleeding. Grade 3 and 4 neutropenia and Grade 3 thrombocytopenia were observed. 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. Treatment was discontinued permanently because of liver laboratory abnormalities in CML patients. In GIST patients Grade 3 or 4 ALT elevations and 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 **"INTERACTIONS"**).

There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some the outcome was fatal.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Events that have been reported with doses greater than 800 mg are nausea, vomiting, diarrhoea, rash, erythema, oedema, selling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite, weakness, myalgia, increased creatine, phosphokinase, increased bilirubin, gastrointestinal pain, pyrexia, facial swelling, decreased neutrophil count, and increased transaminases.

IDENTIFICATION:

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 can and brown body.

PRESENTATION:

IMAVEC:

Carton containing 60 capsules in PVC / ALU blister strips.

IMAVEC 400:

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

STORAGE INSTRUCTIONS:

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.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

IMAVEC: 42/34/0496

IMAVEC 400: 50/34/0118

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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