NOVARTIS

GLEEVEC

(imatinib)

100 and 400 mg film-coated tablet

Professional Information

Document status: Final

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SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

GLEEVEC ® FC (film-coated tablet)

GLEEVEC ® 400 (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GLEEVEC FC: Each film-coated tablet contains 119,5 mg imatinib mesilate equivalent to 100 mg imatinib base

GLEEVEC 400: Each film-coated tablet contains 478,00 mg imatinib mesilate equivalent to 400 imatinib base

Sugar free

3. PHARMACEUTICAL FORM

GLEEVEC FC: Very dark yellow to brownish orange, round, biconvex, film-coated tablets with bevelled edges. Debossed with "NVR" on one side and "SA" and a score on the other side, with an approximate diameter of 9.3 mm.

GLEEVEC 400: Very dark yellow to brownish orange, ovaloid, biconvex, film-coated tablets with bevelled edges. Debossed with "400" on one side and score on the other side and "SL" on each side of the score, with an approximate length of 18.2 mm and width 7.3 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

GLEEVEC is indicated for:

- treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML).
- treatment of adult and paediatric patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

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

The effectiveness of GLEEVEC is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph + ALL, MDS/MPD, on haematological response rates in SM, HES/CEL, on objective response rates and progression-free survival in unresectable and/or metastatic GIST, on recurrence free survival in adjuvant GIST, and on objective response rates in DFSP (see section 5- Pharmacological Properties). 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.

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

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 ml for a 100 mg tablet, and 200 ml for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Dosage in CML in Adults:

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

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

Dose increase from 400 mg to 600 mg, or to 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg daily in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse 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.

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 (see Pharmacological action and Pharmacokinetics). There is no experience with the use of GLEEVEC in children below 2 years of age.

Dosage in Ph+ ALL in Adults:

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

Dosage in MDS/MPD:

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

Dosage in SM:

The recommended dose of GLEEVEC is 400 mg/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/day is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Dosage in HES/CEL

The recommended dose of GLEEVEC 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 drug reactions if assessments demonstrate an insufficient response to therapy.

Dosage in GIST:

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

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

The recommended dose of GLEEVEC 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 GLEEVEC is not known.

Dosage in DFSP

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

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

Haematological adverse reactions:

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

Table 1: Dose adjustments for neutropenia and thrombocytopenia

Dose adjustments for neutropenia and thrombocytopenia		
SM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1,0 $x10^9$/L and/or platelets < 50 $x10^9$/L	1. Stop GLEEVEC until ANC ≥ 1,5 $x10^9$/L and platelets ≥ 75 $x10^9$/L. 2. Resume treatment with GLEEVEC at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, MDS/MPD, SM, HES/CEL and GIST (starting dose 400 mg).	ANC < 1,0 $x10^9$/L and/or platelets < 50 $x10^9$/L	1. Stop GLEEVEC until ANC ≥ 1,5 $x10^9$/L and platelets ≥ 75 $x10^9$/L. 2. Resume treatment with GLEEVEC 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 GLEEVEC 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 GLEEVEC until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with GLEEVEC 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 GLEEVEC at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg[c])	[a]ANC < 0,5 x10^9/L and/or platelets < 10 x10^9/L	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of GLEEVEC 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 GLEEVEC until ANC 1 x10^9/L and platelets ≥ 20 x10^9/L, then resume treatment at 300 mg[d].

DFSP (starting dose 800 mg)	ANC < 1,0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop GLEEVEC until ANC ≥ 1,5 x10^9/L and platelets ≥ 75 x10^9/L. 2. Resume treatment with GLEEVEC at 600 mg 3. In the event of recurrence of ANC < 1,0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume GLEEVEC 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 paediatric patients [c] or 340 mg/m^2 in paediatric patients [d] or 200 mg/m^2 in paediatric patients		

Special populations

Paediatric patients (below 18 years):

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

Dosing in paediatric patients 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 impairment

Imatinib is mainly metabolised through the liver. Patients with liver impairment 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 GLEEVEC (see sections 4.4, 4.8 and 5.2).

Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidney. Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy (see sections 4.4 and 5.2).

Geriatric patients (65 years and above)

No significant age-related pharmacokinetic differences have been observed in adult patients in clinical trials, which included over 20 % of patients aged 65 and older. No specific dose recommendation is necessary in the elderly.

4.3. Contraindications

Hypersensitivity to imatinib or to any of the excipients of GLEEVEC.

Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

Hepatitis B reactivation

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

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as GLEEVEC. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.8).

Patients currently on GLEEVEC should have baseline testing for hepatitis B infection 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 disease) and for patients who test positive for hepatitis B infection during treatment. Carriers of hepatitis B virus who require treatment with GLEEVEC should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

When GLEEVEC is co-administered with other medicines, there is a potential for interactions (see section 4.5). Caution should be used when taking GLEEVEC 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).

Hypothyroidism

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

Hepatotoxicity

In patients with hepatic dysfunction, peripheral blood counts and liver enzymes should be carefully monitored (see section 4.2, 4.8 and 5.2).

When GLEEVEC is combined with high dose chemotherapy regimens, liver toxicity in the form of transaminase elevation and hyperbilirubinaemia have been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended in circumstances where GLEEVEC is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.5 and 4.8).

Fluid retention

Severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial oedema) have been reported in approximately 2,5 % of newly diagnosed CML patients taking GLEEVEC. 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.

Patients with cardiac disease or renal failure

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 occult infiltration of HES cells within the myocardium, cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. Myelodysplastic/myeloproliferative diseases 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 GLEEVEC should be considered at the initiation of therapy.

Gastrointestinal haemorrhage

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 intra-hepatic, 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 GLEEVEC therapy. When needed, GLEEVEC discontinuation may be considered (see section 4.8).

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

Tumour Lysis Syndrome

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

Class effects

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in GLEEVEC.

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 GLEEVEC should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with GLEEVEC should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

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 or renal failure should be evaluated and treated.

Laboratory tests

Haematology

Full blood counts must be performed regularly during therapy with GLEEVEC.

Treatment of CML patients with GLEEVEC has been associated with neutropenia and/ or thrombocytopenia. However, the occurrence of these cytopenias is also related to the stage of the disease being treated and they were more frequent in patients with accelerated phase CML, or blast crisis as compared to patients with chronic phase CML. Treatment with GLEEVEC may be interrupted or the dose be reduced, as recommended in section 4.2.

Liver function

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

Renal function

GLEEVEC 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 GLEEVEC 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 GLEEVEC can be reduced if not tolerated.

Long-term treatment with GLEEVEC may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of GLEEVEC 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 initiated in accordance with standard treatment guidelines.

4.5. Interaction with other medicines and other forms of interaction

Observed interactions resulting in a concomitant use not recommended

*Medicines that may **decrease** GLEEVEC plasma concentrations:*

Medicines that are inducers of CYP3A4 activity could increase metabolism and decrease GLEEVEC plasma concentrations. Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbitone and *hypericum perforatum* (also known as St. John's Wort) may significantly reduce exposure to GLEEVEC. Pre-treatment of 14 healthy volunteers with multiple doses of rifampicin, 600 mg daily for 8 days, followed by a single 400 mg dose of GLEEVEC, increased GLEEVEC oral-dose clearance by 3,8-fold (90 % confidence interval = 3,5 to 4,3-fold), which represents mean decreases 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 GLEEVEC while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, 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 St. John's wort led to a 30-32 % reduction in the AUC of GLEEVEC.

In patients where rifampicin or other CYP3A4 inducers are indicated, alternative medicines with less enzyme induction potential should be considered.

Other interactions that may affect exposure to GLEEVEC or other medicines

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

Medicines that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) could decrease metabolism and increase GLEEVEC concentrations. There was a significant increase in exposure to GLEEVEC (the mean C_{max} and AUC of imatinib rose by 26 % and 40 %, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be exercised when administering GLEEVEC with inhibitors of the CYP3A4 family.

Medicines that may have their plasma concentration altered by GLEEVEC:

GLEEVEC increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3,5-fold, respectively, indicating an inhibition of the CYP3A4 by GLEEVEC.

Therefore, caution is recommended when administering GLEEVEC with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin or pimozide). GLEEVEC may increase plasma concentration of other CYP3A4 metabolised medicines (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors i.e. statins, etc.).

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

In vitro, GLEEVEC inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. GLEEVEC 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 interactions and dose adjustment may not be necessary.

In vitro, GLEEVEC inhibits paracetamol O-glucuronidation (Ki value of 58,5 MicroM at therapeutic levels) (see section 4.4).

Co-administration of GLEEVEC (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.

GLEEVEC pharmacokinetics was not altered in the presence of single-dose paracetamol.

There is no PK or safety data on the concomitant use of GLEEVEC at doses > 400 mg/day or the chronic use of concomitant paracetamol and GLEEVEC.

4.6. Fertility, pregnancy and lactation

Pregnancy:

GLEEVEC is contraindicated in Pregnancy and Lactation (see section 4.3). GLEEVEC can cause foetal harm when administered to a pregnant woman based on findings from animal reproduction studies. 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. There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken GLEEVEC during pregnancy. GLEEVEC should therefore not be used during pregnancy.

Lactation:

Both imatinib and its active metabolite are transferred into human milk. The effects of low-dose exposure of the infant to imatinib are unknown. Because of the potential for serious adverse drug reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least 15 days after stopping treatment with GLEEVEC.

Fertility:

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 GLEEVEC and for at least 15 days after stopping treatment with GLEEVEC.

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

Males using GLEEVEC should use barrier contraceptives (condoms) for at least 15 days after stopping treatment with GLEEVEC. 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 sperm were observed in the high dose male rats. In pre- and postnatal study in rats, fertility in the first-generation offspring was also not affected by GLEEVEC.

4.7. Effects on ability to drive and use machines

Patients should be advised that they may experience undesirable effects such as dizziness, syncope, somnolence or blurred vision or other eye disorders during treatment with GLEEVEC (see section 4.8). Therefore, caution is recommended when driving a car or operating machinery.

4.8. Undesirable effects

a. Summary of the safety profile

During clinical development, the majority of patients experienced adverse events at some point in time. The most frequently reported ADRs (>10 %) were neutropenia, thrombocytopenia, anaemia, headache, dyspepsia, oedema, weight increased, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhoea, rash, fatigue, and abdominal pain. Events were of mild to moderate grade; 2 % to 5 % of patients permanently discontinued therapy due to medicine-related events.

The safety profile of GLEEVEC in adult and paediatric patients with Ph+ leukaemias is similar.

The differences in the safety profile between Ph+ leukaemias and solid tumours are a higher incidence and severity of myelosuppression in Ph+ leukaemias, 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.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000), including isolated reports. Adverse reactions and their frequencies reported in Table 2 are based on the registration studies for CML and GIST.

b. Tabulated summary of adverse reactions

Table 2 Adverse reactions in clinical studies for CML and GIST

Infections and infestations	
Uncommon	Sepsis, pneumonia[1], herpes simplex, herpes zoster, nasopharyngitis upper respiratory tract infection, gastroenteritis, sinusitis, cellulitis, influenza, urinary tract infection
Rare	Fungal infection
Blood and lymphatic system disorders	
Very common	Neutropenia, thrombocytopenia, anaemia
Common	Febrile neutropenia, pancytopenia
Uncommon	Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
Rare	Haemolytic anaemia
Metabolism and nutrition disorders	
Common	Anorexia

Uncommon	Dehydration, hyperuricaemia, hypokalaemia, increased appetite, decreased appetite, gout, hypophosphataemia, hypercalcaemia, hyperglycaemia, hyponatraemia
Rare	Hyperkalaemia, hypomagnesaemia
Psychiatric disorders	
Common	Insomnia
Uncommon	Depression, anxiety, decreased libido
Rare	Confusion
Nervous system disorders	
Very common	Headache[2]
Common	Dizziness, taste disturbance, paraesthesia, hypoaesthesia
Uncommon	Cerebral haemorrhage, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, sciatica, restless leg syndrome, tremor
Rare	Optic neuritis, increased intracranial pressure, convulsions
Eye disorders	
Common	Conjunctivitis, increased lacrimation, blurred vision, eyelid oedema, conjunctival haemorrhage, dry eye
Uncommon	Eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema
Rare	Cataract, papilloedema, glaucoma
Ear and labyrinth disorders	

Uncommon	Vertigo, tinnitus, hearing loss
Cardiac disorders	
Uncommon	Cardiac failure congestive[3], pulmonary oedema, palpitations, tachycardia.
Rare	Pericardial effusion, arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris
Vascular disorders	
Common	Flushing, haemorrhage[4]
Uncommon	Haematoma, hypertension, hypotension, peripheral coldness, Raynaud`s phenomenon.
Respiratory, thoracic and mediastinal disorders	
Common	Epistaxis, dyspnoea, cough
Uncommon	Pleural effusion[5], pharyngolaryngeal pain, pharyngitis
Rare	Pulmonary fibrosis, pleuritic pain, pulmonary hypertension, pulmonary haemorrhage
Gastrointestinal disorders	
Very common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain[6]
Common	Abdominal distension, flatulence, constipation, gastro-oesophageal reflux, dry mouth, gastritis
Uncommon	Gastrointestinal haemorrhage[7], eructation, melaena, oesophagitis, ascites, gastric ulcer, mouth ulceration, stomatitis, haematemesis, cheilitis, dysphagia, pancreatitis
Rare	Colitis, ileus/inflammatory bowel disease

Hepato-biliary disorders	
Common	Increased hepatic enzymes
Uncommon	Jaundice, hepatitis, hyperbilirubinaemia
Rare	Hepatic failure, hepatic necrosis
Skin and subcutaneous tissue disorders	
Very common	Periorbital oedema, dermatitis / eczema / rash
Common	Facial oedema, pruritus, erythema, dry skin, alopecia, night sweats, photosensitivity reaction
Uncommon	Pustular rash, petechiae, contusion, increased sweating, urticaria, ecchymosis, increased tendency to bruise, onychoclasis, folliculitis, purpura, hypotrichosis, skin hyperpigmentation, psoriasis, exfoliative dermatitis and bullous eruptions, skin hypopigmentation. Panniculitis (including Erythema Nodosum).
Rare	Nail discolouration, vesicular rash, Stevens-Johnson syndrome, acute febrile neutrophilic dermatosis (Sweet's syndrome), erythema multiforme, leucocytoclastic vasculitis, angioneurotic oedema, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, connective tissue and bone disorders	
Very common	Muscle spasm and cramps, musculoskeletal pain, including myalgia, arthralgia, bone pain[8]
Common	Joint swelling
Uncommon	Joint and muscle stiffness
Rare	Muscular weakness, arthritis

Renal and urinary disorders	
Uncommon	Renal failure, renal pain, increased urinary frequency, haematuria
Reproductive system and breast disorders	
Uncommon	Gynaecomastia, erectile dysfunction, breast enlargement, scrotal oedema, menorrhagia, irregular menstruation, nipple pain, sexual dysfunction
General disorders and administration site conditions	
Very common Common Uncommon	Fluid retention and oedema, fatigue. Pyrexia, weakness, rigors, anasarca, chills Malaise, chest pain
Investigations	
Very common Common Uncommon Rare	Increased weight Decreased weight Increased blood alkaline phosphatase, increased blood creatinine, increased blood creatine phosphokinase, increased blood lactate dehydrogenase Increased blood amylase
[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]Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.

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

The following types of reactions have been reported from post-marketing experience and from additional clinical studies with GLEEVEC. 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	
Not known	Hepatitis B reactivation
Nervous system disorders	
Uncommon	Cerebral oedema
Eye disorders	
Rare	Vitreous haemorrhage

Cardiac disorders	
Rare	Pericarditis, pericardial effusion, cardiac tamponade
Vascular disorders	
Uncommon	Thrombosis/embolism
Very rare	Anaphylactic shock
Respiratory, thoracic and mediastinal disorders	
Uncommon	Acute respiratory failure[1], interstitial lung disease
Gastrointestinal disorders	
Uncommon	Ileus/intestinal obstruction, tumour haemorrhage/tumour necrosis, gastrointestinal perforation[2]
Rare	Diverticulitis, gastric antral vascular ectasia (GAVE)
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain, spinal pain)
Uncommon	Osteonecrosis
Rare	Rhabdomyolysis/myopathy
Not known	Growth retardation in children

Skin and subcutaneous tissue disorders	
Uncommon	Palmar-plantar erythrodysaesthesia syndrome, panniculitis (including erythema nodosum)
Rare	Lichenoid keratosis, lichen planus, pemphigus
Very rare	Toxic epidermal necrolysis
Not known	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Pseudoporphyria
Reproductive disorders	
Very rare	Haemorrhagic corpus luteum / haemorrhagic ovarian cyst
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Rare	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 GLEEVEC. Myelosuppression, thrombocytopenia, neutropenia and anaemia were the most frequently reported Grade 3 and 4

laboratory abnormalities. The myelosuppression experienced with GLEEVEC 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 GLEEVEC. The incidence of haematologic toxicities is less in patients with solid tumours (i.e. GIST) than in patients with Ph+ leukaemias, 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 GLEEVEC 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 GLEEVEC 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, GLEEVEC 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 mellitus 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 GLEEVEC 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. GLEEVEC 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 GLEEVEC. 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 month 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 GLEEVEC treatment is possible (see section 4.4).

Growth retardation in paediatric patients

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

Severe respiratory adverse drug reaction

Severe respiratory events, sometimes fatal, have been observed with GLEEVEC 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:

In CML cytopenias, particularly neutropenia and thrombocytopenia, there have been a consistent finding in all studies, 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 were less frequent than in the other CML patients. The frequency of Grade 3 or 4 neutropenias (ANC < 1,0 x 10^9/L) and thrombocytopenias (platelet count < 50 x 10^9/L) being between 4 and 6 times higher in blast crisis and accelerated phase (59 - 64 % and 44 – 63 % for neutropenia and thrombocytopenia, respectively) as compared to newly diagnosed patients in chronic phase CML (16,7 % neutropenia and 8,9 % thrombocytopenia). In newly diagnosed chronic phase CML Grade 4 neutropenia (ANC < 0,5 x 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 ranged from 2 to 3 weeks and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with GLEEVEC, but may need 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 were seen in 7,5 % and 2,7 % of patients, respectively, and Grade 3 thrombocytopenia in 0,7 % of patients. No patient developed Grade 4 thrombocytopenia.

The decreases in WBC and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.

Biochemistry

Severe elevation of transaminases (< 5 %) or bilirubin (< 1 %) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1 % of CML patients. In GIST patients, 6,8 % of Grade 3 or 4 SGPT (serum glutamic pyruvic transferase) elevations and 4,8 % of Grade 3 or 4 SGOT (serum glutamic oxaloacetic transferase) elevations were observed. Bilirubin elevation was below 3 %.

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

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.

4.9. Overdose

In overdose, side effects will be elicited and exacerbated (see section 4.8). Experience with doses greater than 800 mg is limited. Isolated cases of GLEEVEC overdose have been reported. In such an event of overdosage, the patient should be observed and appropriate supportive treatment given.

Adult overdose

1,200 mg to 1,600 mg (duration varying between 1 to 10 days) resulted in: Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite. 1,800 mg to 3,200 mg (as high as 3,200 mg daily for 6 days): Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain. 6,400 mg (single dose): One case in the literature reported one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increased transaminases.

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

Paediatric overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: BCR-ABL tyrosine kinase inhibitor, ATC code: L01EA01

Mechanism of action (MOA)

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 KIT proto-oncogene, the discoidin domain receptors (DDR1) and DDR2), the

colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.

Pharmacodynamic effects

Imatinib is a protein-tyrosine kinase inhibitor, which potently inhibits the breakpoint cluster region-Abelson (Bcr-Abl) tyrosine kinase at the *in vitro* cellular and *in vivo* levels. *In vitro*, the compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemia cell cultures from patients with Philadelphia chromosome positive chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL) patients.

In colony transformation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows selective inhibition of Bcr-Abl positive colonies from CML patients.

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

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), KIT, and inhibits PDGF- and SCF- mediated cellular events.

In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumour (GIST) cells, which express an activating KIT mutation. Constitutive activation of the platelet-derived growth factor receptor (PDGFR) or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of myelodysplastic syndrome / myeloproliferative disorder (MDS/MPD), hypereosinophilic syndrome / chronic eosinophilic leukaemia (HES/CEL) and dermatofibrosarcoma protuberans (DFSP). In addition, constitutive activation of 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

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

Absorption:

Mean absolute bioavailability is 98 %. The coefficient of variation for plasma imatinib AUC is in the range of 40 % - 60 % after an oral dose. When given with a high fat meal, the rate of absorption of imatinib was minimally reduced (11 % decrease in C_{max} and prolongation of t_{max} by 1,5 h), with a small reduction in AUC (7,4 %) compared to fasting conditions.

Distribution:

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

Biotransformation/Metabolism:

CYP3A4 is the major enzyme responsible for metabolism for imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative (CGP 71588), formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent compound. The plasma AUC for this metabolite is about 15 % of the AUC of imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the parent compound.

Elimination:

Elimination is predominantly in the faeces, mostly as metabolites. Based on the recovery of compound(s) after an oral ^{14}C-labelled dose of imatinib, approximately 81 % of the dose was eliminated within 7 days, in faeces (68 % of dose) and urine (13 % of dose).

Unchanged imatinib accounted for 25 % of the dose (5 % urine, 20 % faeces), the remainder being metabolites.

The mean apparent elimination half-life estimated from the single dose PK study was 13,5 hours. The half-life of all ^{14}C-labelled components in plasma was from 41-72 hours.

Plasma pharmacokinetics:

Following oral administration in healthy volunteers, the $t_{½}$ was approximately 18 h, suggesting that once-daily dosing is appropriate.

The increase in mean AUC with increasing dose was linear and dose proportional in the range of 25 – 1 000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1,5 – 2,5-fold at steady state when dosed once daily.

Special populations:

Based on population pharmacokinetic analysis, there was a small effect of age on the volume of distribution (12 % increase in patients > 65 years old). This change is not thought to be clinically significant. The effect of body weight on the clearance of imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8,5 L/h, while for a patient weighing 100 kg the clearance will rise to 11,8 L/h. These changes are not considered sufficient to warrant dose adjustment based on kg bodyweight. There is no effect of gender on the kinetics of imatinib.

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

Pharmacokinetics in paediatric patients (below 18 years):

As in adult patients, imatinib was rapidly absorbed after oral administration in paediatric patients in both phase I and phase II studies. Dosing in children at 260 mg/m^2 and 340 mg/m^2 achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients. The comparison of $AUC_{(0-24)}$ on Day 8and Day 1 at 340 mg/m^2 dose level revealed a 1,7-fold drug accumulation after repeated once daily dosing.

Based on pooled population pharmacokinetic analysis in paediatric patients with haematological disorders (CML, Ph+ ALL, or other haematological disorders treated with imatinib), clearance of imatinib increases with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and body mass index did not have clinically significant effects on the exposure of imatinib. The analysis confirmed that exposure of imatinib in paediatric patients receiving 260 mg/m^2 once daily (not exceeding 400 mg once daily) or 340 mg/m^2 once daily (not exceeding 600 mg once daily) were similar to those in adult patients who received imatinib 400 mg or 600 mg once daily.

Organ function impairment:

Although, 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 alpha-acid glycoprotein (AGP), to which imatinib binds strongly. However, renal excretion represents only a minor elimination pathway for imatinib (see section 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, 4.8 and 5).

5.3. Preclinical safety data

Imatinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity studies. Target organs associated with the pharmacological action of imatinib include bone marrow, peripheral blood, lymphoid tissues, gonads and gastrointestinal tract. Multiple dose toxicity studies revealed mild to moderate haematological changes in rats, dogs and monkeys, accompanied by bone marrow changes in rats and dogs.

Other target organs include the liver and the kidney.

Animal data

In embryo-foetal development studies in rats and rabbits, pregnant animals received oral doses of imatinib mesylate up to 100 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, imatinib mesylate was teratogenic at 100 mg/kg/day (approximately equal to the maximum human dose of 800 mg/day based on body surface area), the number of foetuses with encephalocoele and exencephaly was higher than historical control values and these findings were associated with missing or underdeveloped cranial bones. Lower mean foetal body weights were associated with retarded skeletal ossifications. In rabbits, at doses 1,5 times higher than the maximum human dose of 800 mg/day based on body surface area, no effects on the reproductive parameters with respect to implantation sites, number of live foetuses, sex ratio or foetal weight were observed. The examinations of the foetuses did not reveal any drug related morphological changes. In a pre- and postnatal development study in rats, pregnant rats received oral doses of imatinib mesylate during gestation (organogenesis) and lactation up to 45 mg/kg/day. Five animals developed a red vaginal discharge in the 45 mg/kg/day group on Days 14 or 15 of gestation, the significance of which is unknown since all females produced viable litters and none had increased post-implantation loss. Other maternal effects noted only at the dose of 45 mg/kg/day (approximately one-half the maximum human dose of 800

mg/day based on body surface area) included increased numbers of stillborn pups and pups dying between postpartum Days 0 and 4. In the F1 offspring at this same dose level, mean body weights were reduced from birth until terminal sacrifice and the number of litters achieving criterion for preputial separation was slightly decreased. There were no other significant effects in developmental parameters or behavioural testing. F1 fertility was not affected but reproductive effects were noted at 45 mg/kg/day including an increased number of resorptions and a decreased number of viable foetuses. The NOEL for both maternal animals and the F1 generation was 15 mg/kg/day.

No new target organs were identified in the rat juvenile development toxicology study (day 10 to 70 post-partum). In the juvenile toxicology study, transitory effects upon growth and delay in vaginal opening and preputial separation were observed at approximately 0,3 to 2 times the average paediatric exposure at the highest recommended dose of 340 mg/m^2. Also, mortality was observed in juvenile animals (around weaning phase) at approximately 2-times the average paediatric exposure at the highest recommended dose of 340 mg/m /day. The are no observed effect level (NOEL) was 15 mg/kg/day.

In the 2-year rat carcinogenicity study administration of imatinib at 15, 30 and 60 mg/kg/day resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/day and females at ≥30 mg/kg/day. Histopathological examination of decedents revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Target organs for neoplastic changes were the kidneys, urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach. The no observed effect levels (NOEL) for the various target organs with neoplastic lesions were established as follows: 30 mg/kg/day for the kidneys, urinary bladder, urethra, small intestine, parathyroid glands, adrenal glands and non-glandular stomach, and 15 mg/kg/day for the preputial and clitoral gland.

The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day, representing approximately 0,5 to 4 or 0,3 to 2,4 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0,4 to 3,0 times the daily exposure in children (based on AUC) at 340 mg/m^2/day. The renal adenoma/carcinoma, the urinary bladder and urethra papilloma, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumours of the adrenal glands and the non-glandular stomach papillomas/ carcinomas were noted at 60 mg/kg/day, representing approximately 1,7 or 1 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 1,2 times the daily exposure in children (based on AUC) at 340 mg/m^2/day.

The relevance of these findings in the rat carcinogenicity study for humans is not yet known. An analysis of the safety data from clinical trials and spontaneous adverse event reports did not provide evidence of an increase in overall incidence of malignancies in patients treated with imatinib compared to that of the general population.

Non-neoplastic lesions not identified in earlier preclinical studies were the cardiovascular system, pancreas, endocrine organs and teeth. The most important changes included cardiac hypertrophy and dilatation, leading to signs of cardiac insufficiency in some animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Film coated tablets:

Tablet content: Cellulose microcrystalline, Crospovidone, Hypromellose, Magnesium stearate, Silica colloidal anhydrous.

Coating content: Iron oxide, red (E 172), Iron oxide, yellow (E 172), Hypromellose, Polyethylene Glycol, Talc.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

GLEEVEC FC: Store at or below 30° C in the original pack.

GLEEVEC 400: Store at or below 30° C in the original pack

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

Keep out of the reach of children.

6.5. Nature and contents of container

GLEEVEC 100 mg tablets

20, 30 or 60 film-coated tablets in colourless, transparent PVC/PE/PVDC (polyvinylchloride/polyethylene/polyvinylidene chloride) blisters with an aluminium foil backing, or PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with an aluminium foil backing.

The outer carton is a printed cardboard box.

GLEEVEC 400

20, 30 or 60 film-coated tablets in colourless, transparent PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with an aluminium foil backing.

The outer carton is a printed cardboard box.

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with legislative requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

NOVARTIS SOUTH AFRICA (Pty) Ltd

Magwa Crescent West

Jukskei View

Waterfall City

Johannesburg

South Africa

Telephone number: +27 (0) 11 347 6600

8. REGISTRATION NUMBER(S)

GLEEVEC® FC: 38/34/0143

GLEEVEC® 400: 38/34/0144

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

GLEEVEC FC: 25 November 2005

GLEEVEC 400: 25 November 2005

10. DATE OF REVISION OF THE TEXT

03 February 2026

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