Professional Information for SUNMATIN 100 / SUNMATIN 400

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SUNMATIN 100 film coated tablets

SUNMATIN 400 film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SUNMATIN 100: Each film coated tablet contains imatinib mesilate equivalent to 100 mg imatinib.

SUNMATIN 400: Each film coated tablet contains imatinib mesilate equivalent to 400 mg imatinib.

Excipient with known effect:

Contains sugar.

SUNMATIN 100: Contains 100 mg mannitol per film coated tablet.

SUNMATIN 400: Contains 400 mg mannitol per film coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

SUNMATIN 100: Yellow coloured, round shaped, biconvex film coated tablets debossed with “472” on one side and a break line on the other side.

SUNMATIN 400: Yellow coloured, capsule shaped, biconvex film coated tablets debossed with “475” on one side and a break line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Therapy should be initiated by a medical practitioner experienced in the treatment of patients with chronic myeloid leukaemia or GIST respectively.

The prescribed dose should be administered orally, once daily 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).

Adult dosage in CML:

The recommended dosage of SUNMATIN is 400 mg daily for patients in chronic phase CML and 600 mg daily 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 (given as 400 mg twice 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 haematological response after at least 3 months of treatment; failure to achieve a cytogenic response after 12 months of treatment; or a loss of a previously achieved haematological and/or cytogenic response.

Dosage for CML in children:

Dosing in children should be on the basis of body surface area (mg/m^2). A dose of 340 mg/m^2 daily is recommended for children with chronic phase CML and advanced phases 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. There is no experience with the use of SUNMATIN in children under the age of 2 years.

Dosage in Ph+ ALL:

The recommended dose of SUNMATIN is 600 mg daily for patients with Ph+ ALL.

Dosage in MDS/MPD:

The recommended dose of SUNMATIN is 400 mg daily for patients with MDS/MPD.

Dosage in SM:

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

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

Dosage in GIST:

The recommended dose of SUNMATIN is 400 mg daily 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 side effects if assessments demonstrate an insufficient response to therapy.

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

Dosage in DFSP:

The recommended dose of SUNMATIN is 800 mg daily for patients with DFSP.

Dose adjustments for side effects:

Non-haematological adverse reactions:

If a severe non-haematological adverse reaction develops with SUNMATIN 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, SUNMATIN should be withheld until bilirubin levels have returned to < 1,5 x IULN and transaminase levels to < 2,5 x IULN. Treatment with SUNMATIN 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 is recommended as indicated in the table below.

Dose adjustments for neutropenia and thrombocytopenia:

SM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1,0 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop SUNMATIN until ANC ≥ 1,5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with SUNMATIN at previous dose (i.e. before severe side effect).
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 SUNMATIN until ANC ≥ 1,5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with SUNMATIN 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 SUNMATIN at reduced dose of 300 mg.

Paediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1,0 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop SUNMATIN until ANC ≥ 1,5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with SUNMATIN 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 SUNMATIN at a reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg [c])	[a] ANC < 0,5 x 10^9/L and/or platelets < 10 x 10^9/L	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of SUNMATIN 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 SUNMATIN until ANC ≥ 1 x10^9/L and platelets ≥ 20 x 10^9/L, then resume treatment at 300 mg [d].
DFSP (starting dose 800 mg)	ANC < 1,0 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop SUNMATIN until ANC ≥ 1,5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with SUNMATIN 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

Sign:

		SUNMATIN at reduced dose of 400 mg.
ANC = absolute neutrophil count [a] = occurring after at least 1 month of treatment [b] = or 260 mg/m^2 in children [c] = or 340 mg/m^2 in children [d] = or 200 mg/m^2 in children		

Special populations

Children:

There is very limited experience with the use of SUNMATIN in children for other indications.

Hepatic insufficiency:

Cases of hepatic failure including fatal outcome have occurred in patients treated with SUNMATIN (see section 4.8).

SUNMATIN is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if the patient develops unacceptable toxicity.

Renal insufficiency:

Imatinib and its metabolites are not significantly excreted via the kidney. However, in severe renal insufficiency caution is recommended. Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as a starting dose. The dose can be reduced if not tolerated. If tolerated it can be increased for lack of efficacy.

Elderly patients:

No specific dose recommendation is necessary in the elderly.

Sign:

Method of administration

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

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

4.3 Contraindications

- Hypersensitivity to imatinib, the metabolite *N*-demethylated piperazine deriviative, or to any of the excipients of SUNMATIN (see section 6.1).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Exposure to SUNMATIN may be increased if hepatic function is impaired and peripheral blood counts and liver enzymes should be carefully monitored (see sections 4.2 and 4.8).

Concomitant use of imatinib and medicines that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) may significantly reduce exposure to SUNMATIN, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and imatinib should be avoided (see section 4.5).

Live attenuated vaccination is not recommended (see section 4.5).

SUNMATIN should be taken with food and a full glass of water to minimise the risk of gastrointestinal irritation.

Fluid retention

Severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites and superficial oedema) has been reported in patients taking SUNMATIN. It is therefore recommended that patients be weighed regularly. An unexpected 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 the elderly and cardiac patients. Therefore, caution should be exercised in patients with cardiac dysfunction.

Patients with 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 occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of SUNMATIN therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding SUNMATIN.

Myelodysplastic/myeloproliferative diseases with PDGFR gene re-arrangements and systemic mastocytosis, might 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 before SUNMATIN is administered. If either is abnormal, follow-up with a cardiology specialist and the prophylactic use of systemic steroids (1 – 2 mg/kg)

for one to two weeks concomitantly with SUNMATIN should be considered at the initiation of therapy.

Hepatotoxicity

Metabolism of SUNMATIN is mainly hepatic, and only 13 % of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see section 4.2). It should be noted that GIST patients may have hepatic metastases which could lead to hepatic impairment.

Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When SUNMATIN is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia can be observed. Monitoring of liver function is recommended in circumstances where SUNMATIN is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.8).

Gastrointestinal haemorrhage

In GIST patients, gastrointestinal (GI) haemorrhage and haemorrhages at the site of tumours were reported (see section 4.8). Patients should therefore be monitored for gastrointestinal symptoms at the start of therapy.

Patients with unresectable and/or metastatic GIST, both gastrointestinal and intratumoural haemorrhages were reported (see section 4.8). Based on the available data, no predisposing factors (e.g. tumour size, tumour location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of haemorrhage. Since increased vascularity and propensity for bleeding is a part of the nature and clinical course of GIST, standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied.

In addition, gastric antral vascular ectasia (GAVE), a rare cause of gastrointestinal haemorrhage, has been

reported in patients with CML, ALL and other diseases (see section 4.8). When needed, discontinuation of SUNMATIN treatment may be considered.

Tumour lysis syndrome

Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of SUNMATIN (see section 4.8).

Hypothyroidism

Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement therapy during treatment with SUNMATIN (see section 4.5). Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.

Laboratory tests:

Regular complete blood counts must be performed during therapy with SUNMATIN. Treatment of CML patients with SUNMATIN has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is dependent on the stage of the disease being treated. SUNMATIN treatment may be interrupted or the dose reduced, as recommended in section 4.2.

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

In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated (see section 4.2).

Long-term treatment with imatinib may be associated with a clinically significant decline in renal function. Renal function should, therefore, be evaluated prior to the start of imatinib therapy and closely monitored during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction. If renal dysfunction is observed, appropriate management and treatment should be prescribed in accordance with standard treatment guidelines.

As recommended under section 4.2, Non-haematological adverse reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with SUNMATIN. SUNMATIN 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 SUNMATIN kinetics.

Hepatitis B reactivation:

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with SUNMATIN. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with SUNMATIN should be closely monitored for signs and symptoms of active HBV infection (fever, chills, weakness, confusion, vomiting and jaundice) throughout therapy and for several months following termination of therapy (see section 4.8).

Class effects of tyrosine kinase inhibitors (TKIs) such as contained in SUNMATIN:

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

Phototoxicity

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

Thrombotic microangiopathy

BCR-ABL tyrosine kinase inhibitors (TKIs) have been associated with thrombotic microangiopathy (TMA) (see section 4.8). If laboratory or clinical findings associated with TMA occur in a patient receiving SUNMATIN, treatment should be discontinued and thorough evaluation for TMA, including ADAMTS13 activity and anti-ADAMTS13-antibody determination, should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with SUNMATIN should not be resumed.

Paediatric population

There have been case reports of growth retardation occurring in children and preadolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under SUNMATIN treatment is recommended (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Medicines that may increase SUNMATIN plasma concentrations:

- Cytochrome P450 (isoenzyme CYP3A4) enzyme inhibitors, including protease inhibitors (such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir); azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as clarithromycin, erythromycin and telithromycin and grapefruit juice.

Caution should be taken when administering SUNMATIN with inhibitors of the CYP3A4 family.

Medicines that may decrease SUNMATIN plasma concentrations:

- Cytochrome P450 (isoenzyme CYP3A4) enzyme inducers, including carbamazepine, dexamethasone, phenobarbitone, phenytoin, rifampicin, fosphenytoin, primidone or *Hypericum perforatum* (also known as St John's wort) may significantly reduce exposure to SUNMATIN. Caution should be taken when administering SUNMATIN with inhibitors of CYP3A4.

In patients where rifampicin or other CYP3A4 inducers are indicated, alternative therapeutic medicines with less enzyme induction potential should be considered. Concomitant use of rifampicin or other strong CYP3A4 inhibitors and SUNMATIN should be avoided.

Medicines that may have their plasma concentration altered by SUNMATIN:

- SUNMATIN increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3,5-fold, respectively, indicating an inhibition of the CYP3A4 by SUNMATIN. Therefore, caution is recommended when administering SUNMATIN with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine).
- SUNMATIN may increase plasma concentrations of other CYP3A4 metabolised medicines (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMGCoA reductase inhibitors, i.e. statins, etc.).
- SUNMATIN 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 the end of SUNMATIN therapy and when altering the dosage. Alternatively, the use of low molecular weight heparin should be considered.

- Cytochrome P450 (isoenzyme CYP2D6) enzyme substrates, including beta-blockers, cyclophosphamide, morphine, oxycodone and serotonin antagonists.
- SUNMATIN inhibits the cytochrome P450 isoenzyme CYP2D6 *in vitro*. Systemic exposure to substrates of CYP2D6 is therefore potentially increased when co-administered with SUNMATIN. No specific studies have been performed however and caution is recommended. Dose adjustments do not seem to be necessary when imatinib is co- administrated with CYP2D6 substrates, however caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol clinical monitoring should be considered.
- SUNMATIN inhibits paracetamol *O*-glucuronidation. Patients should be warned to avoid or restrict the use of over-the-counter and prescription medicines containing paracetamol.
- In Ph+ ALL patients, there is clinical experience of co-administering imatinib with chemotherapy (see section 5.1), but medicine-medicine interactions between imatinib and chemotherapy regimens are not well characterised. Imatinib adverse events, i.e. hepatotoxicity, myelosuppression or others, may increase and it has been reported that concomitant use with L-asparaginase could be associated with increased hepatotoxicity (see section 4.8). Therefore, the use of SUNMATIN in combination requires special precaution.

Other medicines:

- Other bone marrow depressants or radiation therapy: Additive bone marrow depression may occur; dosage reduction may be required with concomitant use.
- Live/killed virus vaccines: Because normal defence mechanisms may be suppressed by SUNMATIN therapy, the patient's antibody response to the vaccine may be decreased (see warnings and special precautions).
- In thyroidectomy patients receiving levothyroxine, the plasma exposure to levothyroxine may be

decreased when SUNMATIN is co-administered (see warnings and special precautions). Caution is therefore recommended.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUNMATIN. If the patient becomes pregnant while receiving SUNMATIN, the potential hazard to the foetus must be explained. An effective method of contraception should be used during treatment and for 6 months after the last dose of SUNMATIN.

Based on genetic toxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of imatinib mesilate.

Pregnancy

SUNMATIN should not be taken during pregnancy (see section 4.3).

Breastfeeding

SUNMATIN should not be taken when breastfeeding (see section 4.3)

Patients should not breastfeed during treatment and for at least 15 days after stopping treatment with SUNMATIN. Both imatinib and its active metabolite can be distributed into human milk.

Fertility

Studies on patients receiving imatinib and its effect on fertility and gametogenesis have not been performed. Patients concerned about their fertility on SUNMATIN treatment should consult with their medical practitioner.

4.7 Effects on ability to drive and use machines

No specific reports have been received but patients should be advised that they may experience undesirable effects such as dizziness or blurred vision during treatment with SUNMATIN. Caution should therefore be recommended when driving a car or operating machinery.

4.8 Undesirable effects

Patients with advanced stages of malignancies may have numerous confounding medical conditions that make causality of adverse reactions difficult to assess due to the variety of symptoms related to the underlying disease, its progression and the co-administration of numerous medicines.

More myelosuppression can be seen in CML patients than in GIST, which is probably due to the underlying disease. In patients with unresectable and/or metastatic GIST, CTC grade ¾ bleeds were experienced, intratumoural bleeds or both. GI tumour sites may be the source of the GI bleeds (see section 4.4). GI and tumoural bleeding may be serious and sometimes fatal.

Most frequently reported medicine-related adverse events are nausea, vomiting, diarrhoea, myalgia, muscle cramps and rash. Superficial oedemas are a frequent finding and are described primarily as periorbital or lower limb oedemas. However, these oedemas are rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of SUNMATIN.

When SUNMATIN is combined with high dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of transaminase elevation and hyper bilirubinaemia are observed.

A mix of side effects represents local or general fluid retention, including pleural effusion, ascites, pulmonary oedema and rapid weight gain (with or without superficial oedema). These side effects can be managed by withholding SUNMATIN temporarily and with diuretics or other supportive care measures. Some of these events may be serious or life-threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure.

Tabulated summary of adverse reactions

System organ class	Frequent	Less frequent	Frequency not known
Infections and infestations		Sepsis, pneumonia[1], herpes simplex, nasopharyngitis, herpes zoster, upper respiratory tract infection, gastroenteritis, sinusitis, cellulitis, influenza, urinary tract infections, fungal infection	Hepatitis B reactivation*
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Tumour lysis syndrome	Tumour haemorrhage/ tumour necrosis*
Blood and lymphatic system disorders	Neutropenia, thrombocytopenia, anaemia, pancytopenia, febrile neutropenia	Bone marrow depression, eosinophilia, lymphadenopathy, thrombocythaemia, lymphopenia, haemolytic anaemia, thrombotic microangiopathy	
Immune system disorders		Anaphylactic shock	
Metabolism and nutrition disorders	Anorexia	Dehydration, hyperuricaemia, hypokalaemia, increased appetite, decreased appetite, gout,	

		hypophosphataemia, hyperkalaemia, hyponatraemia, hyperglycaemia, hypercalcaemia, hypomagnesaemia	
Psychiatric disorders	Insomnia	Depression, anxiety, decreased libido, confusion	
Nervous system disorders	Headache[2], dizziness, paraesthesia, taste disturbances, hypoaesthesia	Cerebral haemorrhage, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, cerebral oedema, increased intracranial pressure, convulsions, sciatica, restless leg syndrome, tremor, optic neuritis	
Eye disorders	Conjunctivitis, increased lacrimation, blurred vision, eyelid oedema, conjunctival haemorrhage, dry eye	Eye irritation, orbital oedema, macular oedema, papilloedema, retinal and scleral haemorrhage, vitreous haemorrhage, glaucoma, blepharitis, cataract, eye pain	
Ear and labyrinth disorders		Vertigo, tinnitus, hearing loss	
Cardiac disorders		Congestive cardiac failure[3]/arrest, pulmonary oedema, tachycardia,	

		pericardial effusion, pericarditis, cardiac tamponade, angina pectoris, myocardial infarction, atrial fibrillation, palpitations, dysrhythmia	
Vascular disorders[4]	Flushing, haemorrhage	Haematoma, subdural haematoma, hypertension, hypotension, peripheral coldness, thrombosis/ embolism, Raynaud's phenomenon,	
Respiratory system, thoracic and mediastinal disorders	Epistaxis, dyspnoea, cough	Pleural effusion[5], pharyngolaryngeal pain, acute respiratory failure[11], pulmonary fibrosis, interstitial pneumonitis/lung disease, pharyngitis, pleuritic pain, pulmonary hypertension, pulmonary haemorrhage	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain[6], abdominal distension, flatulence, constipation, gastro-oesophageal reflux, mouth ulceration, dry mouth, gastritis	Gastrointestinal haemorrhage[7], melaena, ascites, gastric ulcer, eructation, colitis, diverticulitis, ileus/ intestinal obstruction, gastrointestinal perforation, pancreatitis and oropharyngeal pain, colitis, inflammatory bowel disease, gastric antral vascular	

Sign:

		ectasia (GAVE), cheilitis, stomatitis, oesophagitis, haematemesis, dysphagia	
Hepatobiliary disorders	Increased hepatic enzymes	Jaundice, hepatitis, hyperbilirubinaemia, hepatic failure[8], hepatic necrosis	
Skin and subcutaneous tissue disorders	Periorbital oedema, dermatitis, eczema, rash, face oedema, pruritus, erythema, dry skin, alopecia, night sweats, photosensitivity reaction	Petechiae, contusion, increased sweating, urticaria, onychoclasis, purpura, hypotrichosis, skin hyperpigmentation, skin hypopigmentation, psoriasis, exfoliative dermatitis and bullous eruptions, angioedema, vesicular rash, Stevens-Johnson syndrome, acute febrile neutrophilic dermatosis (Sweet's syndrome), rash pustular, ecchymosis, increased tendency to bruise, folliculitis, nail discolouration, angioneurotic oedema, erythema multiforme, leukocytoclastic vasculitis, acute generalised exanthematous pustulosis (AGEP), panniculitis (including erythema nodosum), pemphigus	Palmoplantar erythrodysaesthesia syndrome, lichenoid keratosis, lichen planus, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), pseudoporphyria*

Musculoskeletal and connective tissue disorders	Muscle spasm and cramps, musculoskeletal pain, joint pain, including myalgia[9], arthralgia, bone pain[10], joint swelling	Sciatica, joint and muscle stiffness, avascular necrosis/hip osteonecrosis, muscular weakness, arthritis, rhabdomyolysis/myopathy	Growth retardation in children
Renal and urinary disorders		Renal failure acute, renal pain, increased urinary frequency, haematuria	Renal failure chronic
Reproductive system and breast disorders		Gynaecomastia, breast enlargement, scrotal oedema, menorrhagia, nipple pain, sexual dysfunction, erectile dysfunction, menstruation irregular, haemorrhagic corpus luteum/haemorrhagic ovarian cyst	
General disorders and administration site conditions	Fluid retention and oedema, fatigue, pyrexia, weakness, rigors, anasarca, chills	Malaise, chest pain	
Investigations	Increased weight, decreased weight	Increased blood alkaline phosphatase, increased blood creatinine, increased blood creatine phosphokinase, increased blood lactate dehydrogenase, blood amylase increased	

Sign:

* Reported mainly from post-marketing experience with imatinib. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

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

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

[3] 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.

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

[5] Pleural effusion was reported more frequently 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 frequently observed in GIST patients.

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

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

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

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

Post-marketing reported adverse events:

Class-related cerebrovascular events may occur in patients on treatment with TKIs, with or without risk factors, and may occur at any time during treatment with TKIs (see section 4.4).

During post-marketing use of SUNMATIN seven cases of cerebrovascular events were reported. These events were cerebral infarction, transient ischaemic attack, moyamoya disease, cerebrovascular accident and cerebrovascular disorder.

Sign:

Spontaneous reports form post-marketing experience with other TKIs included cerebrovascular accident, transient ischaemic attack and ischaemic stroke.

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. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms:

Severe muscle cramps, elevations of serum creatinine, ascites and elevated liver transaminase levels, and elevations of bilirubin. A general exacerbation of symptoms listed as side effects may be seen in the event of overdosage (see section 4.8).

Events that have been reported at different dose ranges are as follows:

Adult population

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

Paediatric population

- With a single dose of 400 mg, a patient may experience vomiting, diarrhoea and anorexia.
- 980 mg (single dose): decreased white blood cell count and diarrhoea.

Treatment:

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, BCR-ABL tyrosine kinase inhibitors

ATC code: L01EA01

Imatinib is a protein-tyrosine kinase inhibitor that inhibits the breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukaemia (CML). It also inhibits the tyrosine kinases for platelet-derived growth factor and stem cell factor, c-kit, which is expressed in gastrointestinal stromal tumours (GIST).

5.2 Pharmacokinetic properties

Absorption

Mean absolute bioavailability is about 98 %. The coefficient of variation for plasma imatinib AUC is in the range of 40 to 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 hours), with a small reduction in AUC (7,4 %) compared to fasting conditions.

Distribution

Imatinib is reported to be about 95 % bound to plasma proteins.

Metabolism

The major enzyme responsible for metabolism of imatinib is cytochrome P450 isoenzyme CYP3A4. Isoenzymes CYP1A2, CYP2D6, CYP2C9, and CYP2C19 also play a minor role in the metabolism of imatinib. The major active metabolite is the *N*-demethylated piperazine derivative. It shows in vitro potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15 % of the AUC of imatinib.

Elimination

About 81 % of a dose is eliminated within 7 days in faeces (68 % of dose) and urine (13 % of dose). It is excreted mainly as metabolites with only 25 % of the dose (5 % urine, 20 % faeces) as unchanged imatinib.

Plasma pharmacokinetics

Following oral administration in healthy volunteers, the $t_{½}$ was approximately 18 hours.

Organ function impairment:

Imatinib is mainly metabolised through the liver. Exposure to imatinib may be increased if liver function is impaired. Imatinib should be used with caution in patients with liver impairment and patients should be closely monitored (see section 4.8).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone

Crospovidone

Magnesium stearate

Mannitol

Opadry Yellow (containing FD&C Yellow, hypromellose, iron oxide red, iron oxide yellow, macrogol, titanium dioxide)

Polyethylene glycol

Silicified microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Do not remove from outer carton until required for use.

6.5 Nature and contents of container

SUNMATIN 100: Aluminium foil laminated with 150 g/m^2 poly layer blister strips containing 10 tablets each.

Sixty (6 x 10) tablets per carton.

SUNMATIN 400: Aluminium foil laminated with 150 g/m^2 poly layer blister strips containing 10 tablets each.

Thirty (3 x 10) tablets per carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd.

Sign:

14 Lautre Road, Stormill, Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBERS

SUNMATIN 100: 44/26/0886

SUNMATIN 400: 44/26/0887

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 December 2013

10. DATE OF REVISION OF THE TEXT

04 October 2024

Sign: