Arwan

SAGITTA®

Imatinib Mesilate

Sagitta 100 mg hard capsules
Sagitta 400 mg hard capsules

Composition

Each 100 mg capsule contains:
Active ingredients: 100 mg imatinib (as mesilate).
Excipients: Capsule filling: Crospovidone (type A), Lactose monohydrate, Magnesium stearate.
Capsule shell: Gelatin, Yellow iron oxide (E172), Titanium dioxide (E171), Red iron oxide (E172).
Each 400 mg capsule contains:
Active ingredients: 400 mg imatinib (as mesilate).
Excipients: Capsule filling: Crospovidone (type A), Lactose monohydrate, Magnesium stearate.
Capsule shell: Gelatin, Yellow iron oxide (E172), Titanium dioxide (E171), Red iron oxide (E172).

Indications

Sagitta is indicated for the treatment of
- Adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- Adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- 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 advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL).

The effect of imatinib on the outcome of bone marrow transplantation has not been determined.
Sagitta is indicated for:
- The treatment of adult patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- The adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117) positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- The treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and paediatric patients, the effectiveness of imatinib 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 HES/CEL and on objective response rates in adult patients with unresectable and/or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST.

Dosage and Administration

Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.
The prescribed dose should be administered orally with a meal and a large glass of water to minimize the risk of gastrointestinal irritations. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.
For patients unable to swallow the capsules, their content may be dispersed in a glass of either still water or apple juice.

Dosage in CML

- *In adult patients:* The recommended dosage of **Sagitta** is 400 mg/day for adult patients in chronic phase CML, and 600 mg/day for adult patients in accelerated phase or blast crisis.
Treatment duration: In clinical trials, treatment with imatinib was continued until disease progression. The effect of stopping treatment after the achievement of a complete cytogenetic response has not been investigated.
- *In children:* Dosing for children should be on the basis of body surface area (mg/m²). The doses of 340 mg/m² daily is recommended for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 800 mg). Treatment can be given as a once daily dose or alternatively the daily dose may be split into two administrations – one in the morning and one in the evening. The dose recommendation is currently based on a small number of paediatric patients.
There is no experience with the treatment of children below 2 years of age.

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 cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response, an increase of doses can be considered as given:
- A dose increases from 400 mg to 600 mg or 800 mg in adult patients with chronic phase disease,
- from 600 mg to a maximum of 800 mg (given as 400 mg twice daily) in patients with accelerated phase or blast crisis,
- from 340 mg/m² daily to 570 mg/m² daily for pediatric population (not to exceed the total dose of 800 mg).

Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

Dosage in Ph+ ALL

The recommended dose of **Sagitta** is 600 mg/day for adult patients with Ph+ ALL. Haematological experts in the management of this disease should supervise the therapy throughout all phases of care.
Treatment schedule: On the basis of the existing data, imatinib has been shown to be effective and safe when administered at 600 mg/day in combination with chemotherapy in the induction phase, the consolidation and maintenance phases of chemotherapy for adult patients with newly diagnosed Ph+ ALL. The duration of **Sagitta** therapy can vary with the treatment programme selected, but generally longer exposures to imatinib have yielded better results.
For adult patients with relapsed or refractory Ph+ALL **Sagitta** monotherapy at 600 mg/day is safe, effective and can be given until disease progression occurs.

Dosage in MDS/MPD

The recommended dose of **Sagitta** is 400 mg/day for adult patients with MDS/MPD.
Treatment duration: In the only clinical trial performed up to now, treatment with imatinib was continued until disease progression. At the time of analysis, the treatment duration was a median of 47 months (24 days - 60 months).

Dosage in HES/CEL

The recommended dose of **Sagitta** is 100 mg/day for adult patients with HES/CEL.
Dose increase from 100 mg to 400 mg may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.
Treatment should be continued as long as the patient continues to benefit.

Dosage in GIST

The recommended dose of **Sagitta** is 400 mg/day for adult patients with unresectable and/or metastatic malignant GIST.
Limited data exist on the effect of dose increases from 400 mg to 600 mg or 800 mg in patients progressing at the lower dose.
Treatment duration: In clinical trials in GIST patients, treatment with **Sagitta** was continued until disease progression. At the time of analysis, the treatment duration was a median of 7 months (7 days to 13 months). The effect of stopping treatment after achieving a response has not been investigated.
The recommended dose of **Sagitta** is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. Optimal treatment duration is not yet established. Length of treatment in the clinical trial supporting this indication was 36 months.

Dosage in DFSP

The recommended dose of **Sagitta** is 800 mg/day for adult patients with DFSP.

Dose adjustment for adverse reactions

Non-haematological adverse reactions
If a severe non-haematological adverse reaction develops with **Sagitta** 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 > 3x institutional upper limit of normal (IULN) or in liver transaminases > 5x IULN occur, **Sagitta** should be withheld until bilirubin levels have returned to < 1.5x IULN and transaminase levels to < 2.5x IULN. Treatment with **Sagitta** may then be continued at a reduced daily dose. In adults the dose should be reduced from 600 mg to 400 mg or from 800 mg to 600 mg.
In children the dose should be reduced from 340 mg/m²/day to 260 mg/m²/day.
Haematological adverse reactions
Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.

Dose adjustments for neutropenia and thrombocytopenia:

HES/CEL (starting dose 100 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop **Sagitta** until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with **Sagitta** at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, MDS/MPD and GIST (starting dose 400 mg) HES/CEL (at dose 400 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop **Sagitta** until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with **Sagitta** 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 **Sagitta** at reduced dose of 300 mg.
Paediatric chronic phase CML (at dose 340 mg/m²)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop **Sagitta** until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with **Sagitta** 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 **Sagitta** at reduced dose of 260 mg/m².
Paediatric accelerated phase CML and blast crisis (starting dose 340 mg/m²)	[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 **Sagitta** to 260 mg/m². 3. If cytopenia persists for 2 weeks, reduce further to 200 mg/m². 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop **Sagitta** until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 200 mg/m².
Adult patients with CML in blast crisis (starting dose 600 mg)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of **Sagitta** to 400 mg. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop **Sagitta** until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 300 mg.
DFSP (at dose 800 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop **Sagitta** until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with **Sagitta** 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 **Sagitta** at reduced dose of 400 mg.

ANC = absolute neutrophil count
[a] occurring after at least 1 month of treatment

Special populations

Paediatric use: There is no experience in children with CML below 2 years of age. There is limited experience in children with Ph+ ALL and very limited experience in children with MDS/MPD and DFSP. There is no experience in children or adolescents with GIST and HES/CEL.
Hepatic insufficiency: Imatinib is mainly metabolized through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated.
Liver dysfunction classification:

Liver dysfunction	Liver function tests
Mild	Total bilirubin: = 1.5 ULN AST: >ULN (can be normal or <ULN if total bilirubin is >ULN)
Moderate	Total bilirubin: >1.5–3.0 ULN AST: any
Severe	Total bilirubin: >3–10 ULN AST: any

ULN = upper limit of normal for the institution
AST = aspartate aminotransferase
Renal insufficiency: Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy.
Elderly patients: imatinib pharmacokinetics has not been specifically studied in the elderly. No significant age-related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose recommendation is necessary in the elderly.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed above.

Warnings and Precautions

Sagitta should be taken with food and a large glass of water to minimize the risk of gastrointestinal disturbances.
When **Sagitta** is co-administered with other medicinal products, there is a potential for drug interactions.
Hypothyroidism: Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib. Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.
Hepatotoxicity: In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored.
When imatinib is combined with high dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia has been observed. Additionally, there have been uncommon reports of acute liver failure. Hepatic function should be carefully monitored in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction.
Fluid retention: Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial oedema) have been reported in approximately 2.5% of newly diagnosed CML patients taking imatinib. Therefore, it is highly recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.
Patients with cardiac disease: Patients with cardiac disease, risk factors for cardiac failure or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.
In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. As cardiac adverse events have been reported uncommonly with imatinib, a careful assessment of the benefit/risk of imatinib therapy should be considered in the HES/CEL population before treatment initiation. Myelodysplastic/myeloproliferative diseases with PDGFR gene re-arrangements could be associated with high eosinophil levels. Evaluation by a cardiology specialist, performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD associated with high eosinophil levels before imatinib is administered. If either is abnormal, follow-up with a cardiology specialist and the prophylactic use of systemic steroids (1–2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.
Gastrointestinal haemorrhage: In the study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoural haemorrhages were reported. Based on the available data, no predisposing factors (e.g. tumor size, tumor 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.
Laboratory tests: Complete blood counts must be performed regularly during therapy with **Sagitta**. Treatment of CML patients with imatinib has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is likely to be related to the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with **Sagitta** may be interrupted or the dose may be reduced, as recommended (see Dosage and Administration).
Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored regularly in patients receiving **Sagitta**.
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.
Paediatric population: There have been case reports of growth retardation occurring in children and pre-adolescents 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 imatinib treatment is recommended.

Pregnancy and Lactation

Pregnancy

There are limited data on the use of imatinib in pregnant women. Studies in animals have however shown reproductive toxicity and the potential risk for the foetus is unknown. **Sagitta** should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.
Women of childbearing potential must be advised to use effective contraception during treatment.

Breast-feeding

There is limited information on imatinib distribution on human milk. Studies in two breast-feeding women revealed that both imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio studied in a single patient was determined to be 0.5 for imatinib and 0.9 for the metabolite, suggesting greater distribution of the metabolite into the milk. Considering the combined concentration of imatinib and the metabolite and the maximum daily milk intake by infants, the total exposure would be expected to be low (~10% of a therapeutic dose). However, since the effects of low-dose exposure of the infant to imatinib are unknown, women taking imatinib should not breast-feed.

Driving and Using Machines

Patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with imatinib. Therefore, caution should be recommended when driving a car or operating machinery.

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 medicinal products.
In clinical trials in CML, drug discontinuation for drug-related adverse reactions was observed in 2.4% of newly diagnosed patients, 4% of patients in late chronic phase after failure of interferon therapy, 4% of patients in accelerated phase after failure of interferon therapy and 5% of blast crisis patients after failure of interferon therapy. In GIST the study drug was discontinued for drug-related adverse reactions in 4% of patients.
The adverse reactions were similar in all indications, with two exceptions. There was more myelosuppression seen in CML patients than in GIST, which is probably due to the underlying disease. In the study in patients with unresectable and/or metastatic GIST, 7 (5%) patients experienced CTC grade 3/4 GI bleeds (3 patients), intra-tumoural bleeds (3 patients) or both (1 patient). GI tumour sites may have been the source of the GI bleeds. GI and tumoural bleeding may be serious and sometimes fatal.
When imatinib was combined with high dose chemotherapy in Ph+ ALL patients, transient liver toxicity in the form of transaminase elevation and hyperbilirubinaemia were observed.
The most commonly reported (≥ 10%) drug-related adverse reactions were mild nausea, vomiting, diarrhoea, abdominal pain, fatigue, myalgia, muscle cramps and rash, which were easily manageable. Superficial oedemas were a common finding in all studies and were described primarily as periorbital or lower limb oedemas. However, these oedemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of imatinib.
Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as “fluid retention”. These reactions can usually be managed by withholding **Sagitta** temporarily and with diuretics and other appropriate supportive care measures. However, some of these reactions may be serious or life-threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure. There were no special safety findings in paediatric clinical trials.
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequency categories are defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).
Adverse reactions and their frequencies reported in Table 1 are based on the main registration studies.
Table 1: Adverse reactions in clinical studies

Infections and infestations	
Uncommon:	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1], sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis
Rare:	Fungal infection
Blood and lymphatic system disorders	
Very common:	Neutropenia, thrombocytopenia, anaemia
Common:	Pancytopenia, febrile neutropenia
Uncommon:	Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy
Rare:	Haemolytic anaemia
Metabolism and nutrition disorders	
Common:	Anorexia
Uncommon:	Hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia
Rare:	Hyperkalaemia, hypomagnesaemia
Psychiatric disorders	
Common:	Insomnia
Uncommon:	Depression, libido decreased, anxiety
Rare:	Confusional state
Nervous system disorders	
Very common:	Headache[2]
Common:	Dizziness, paraesthesia, taste disturbance, hypoaesthesia
Uncommon:	Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral haemorrhage
Rare:	Increased intracranial pressure, convulsions, optic neuritis
Eye disorders	
Common:	Eyelid oedema, lacrimation increased, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision
Uncommon:	Eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema
Rare:	Cataract, glaucoma, papilloedema
Ear and labyrinth disorders	
Uncommon:	Vertigo, tinnitus, hearing loss
Cardiac disorders	
Uncommon:	Palpitations, tachycardia, cardiac failure congestive[3], pulmonary oedema
Rare:	Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Vascular disorders[4]	
Common:	Flushing, haemorrhage
Uncommon:	Hypertension, haematoma, peripheral coldness, hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, epistaxis, cough
Uncommon:	Pleural effusion[5], pharyngolaryngeal pain, pharyngitis
Rare:	Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage
Gastrointestinal disorders	
Very common:	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain[6]
Common:	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis
Uncommon:	Stomatitis, mouth ulceration, gastrointestinal haemorrhage[7], eructation, melaena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis
Rare:	Colitis, ileus, inflammatory bowel disease
Hepatobiliary disorders	
Common:	Increased hepatic enzymes
Uncommon:	Hyperbilirubinaemia, hepatitis, jaundice
Rare:	Hepatic failure[8], hepatic necrosis
Skin and subcutaneous tissue disorders	
Very common:	Periorbital oedema, dermatitis/eczema/rash
Common:	Pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction
Uncommon:	Rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions
Rare:	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	
Very common:	Muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain[9]
Common:	Joint swelling
Uncommon:	Joint and muscle stiffness
Rare:	Muscular weakness, arthritis, rhabdomyolysis/myopathy
Renal and urinary disorders	
Uncommon:	Renal pain, haematuria, renal failure acute, urinary frequency increased
Reproductive system and breast disorders	
Uncommon:	Gynaecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema
Rare:	Haemorrhagic corpus luteum/haemorrhagic ovarian cyst
General disorders and administration site conditions	
Very common:	Fluid retention and oedema, fatigue
Common:	Weakness, pyrexia, anasarca, chills, rigors
Uncommon:	Chest pain, malaise
Investigations	
Very common:	Weight increased
Common:	Weight decreased
Uncommon:	Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased
Rare:	Blood amylase increased

[1]Pneumonia was reported most commonly in patients with transformed CML and in patients with GIST.
[2] Headache was the most common in GIST patients.
[3] On a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML.
[4] Flushing was most common in GIST patients and bleeding (haematoma, haemorrhage) was most common in patients with GIST and with transformed CML (CML-AP and CML-BC).
[5] Pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML.
[6+7]Abdominal pain and gastrointestinal haemorrhage were most commonly observed in GIST patients.
[8] Some fatal cases of hepatic failure and of hepatic necrosis have been reported.
[9] Musculoskeletal pain and related events were more commonly observed in patients with CML than in GIST patients.

The following types of reactions have been reported mainly from post-marketing experience with imatinib. This includes spontaneous case reports as well as serious adverse events from ongoing studies, the expanded access programs, clinical pharmacology studies and exploratory studies in unapproved indications. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to imatinib exposure.
Table 2: Adverse reactions from post-marketing reports

Nervous system disorders	
Not known:	Cerebral oedema
Eye disorders	
Not known:	Vitreous haemorrhage
Cardiac disorders	
Not known:	Pericarditis, cardiac tamponade
Vascular disorders	
Not known:	Thrombosis/embolism
Respiratory, thoracic and mediastinal disorders	
Not known:	Acute respiratory failure[1], interstitial lung disease
Gastrointestinal disorders	
Not known:	Ileus/intestinal obstruction, tumor haemorhage/ tumor necrosis, gastrointestinal perforation[2]
Rare	diverticulitis
Skin and subcutaneous tissue disorders	
Not known:	Palmoplantar erythrodysesthesia syndrome
Not known:	Lichenoid keratosis, lichen planus
Not known:	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Not known:	Avascular necrosis/hip necrosis
Not known:	Growth retardation in children
Reproductive disorders	
Very rare	Haemorragic corpus luteum/ Haemorragic ovarien cyst
Neoplasm benign mmalignant and unspecified (including cysts and polyps)	
Not known:	Tumor 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

Laboratory test abnormalities:

Haematology: In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses ≥ 750 mg (phase I study). However, the occurrence of cytopenias was also clearly dependent on the stage of the disease, the frequency of grade 3 or 4 neutropenias (ANC < 1.0 x 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 **Sagitta**, but can in rare cases leads to permanent discontinuation of treatment. In paediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.
Biochemistry: Severe elevation of transaminases (<5%) or bilirubin (<1%) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of CML patients. In GIST patients (study B2222), 6.8% of grade 3 or 4 ALT (alanine aminotransferase) elevations and 4.8% of grade 3 or 4 AST (aspartate aminotransferase) elevations were observed. Bilirubin elevation was below 3%. There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of them outcome was fatal, including one patient on high dose paracetamol.

Overdosage

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

Adult population

1200 to 1600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.
1800 to 3200 mg (as high as 3200 mg daily for 6 days): Weakness, myalgia, increased creatine phosphokinase, increased bilirubin, gastrointestinal pain.
6400 mg (single dose): One case reported in the literature of one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, decreased neutrophil count, increased transaminases.
8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

Paediatric population

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

Interactions

Active substances that may increase imatinib plasma concentrations:
Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) could decrease metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib (the mean Cmax and AUC of imatinib rose by 26% and 40%, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be taken when administering **Sagitta** with inhibitors of the CYP3A4 family.
Active substances that may decrease imatinib plasma concentrations:
Substances that are inducers of CYP3A4 activity could increase metabolism and decrease imatinib plasma concentrations. Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to **Sagitta**, potentially increasing the risk of therapeutic failure. Pretreatment with multiple doses of rifampicin 600 mg followed by a single 400 mg dose of imatinib resulted in decrease in Cmax and $AUC_{(0-24)}$ by at least 54% and 74%, of the respective values without rifampicin treatment. Similar results were observed in patients with malignant gliomas treated with imatinib while taking enzyme inducing anti-epileptic drugs (EIAEDs) such as carbazepine, oxcarbazepine and phenytoin. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. Concomitant use of rifampicin or other strong CYP3A4 inducers and **Sagitta** should be avoided.
Active substances that may have their plasma concentration altered by* imatinib*:
Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, indicating an inhibition of the CYP3A4 by imatinib. Therefore, caution is recommended when administering **Sagitta** with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide). Imatinib may increase plasma concentration of other CYP3A4 metabolized drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).
Imatinib also inhibits CYP2C9 and CYP2C19 activity in vitro. PT prolongation was observed following co- administration with warfarin. When giving coumarins, short term PT monitoring is therefore necessary at the start and the end of **Sagitta** therapy and when altering the dose. Alternatively, the use of low molecular weight heparin should be considered.
In vitro imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had an inhibitory effect on CYP2D6 mediated metoprolol metabolism, with metoprolol Cmax and AUC being increased by approximately 23%. Co- administration of **Sagitta** with CYP2D6 substrates, such as metoprolol, does not seem to be a risk factor for drug- drug interactions and dose adjustment may not be necessary.

Pharmacodynamics

Imatinib is a protein tyrosine kinase inhibitor which potently inhibits the Bcr-Abl tyrosine kinase at the in vitro, cellular and in vivo levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukaemia (ALL) patients.
In vivo the compound shows anti-tumor activity as a single agent in animal models using Bcr-Abl positive tumor cells.
Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), PDGF-R, and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating kit mutation. Constitutive activation of the PDGF receptor or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of MDS/MPD, HES/CEL and DFSP.
Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR and Abl kinase activity.

Pharmacokinetics

The pharmacokinetics of imatinib have been evaluated over a dosage range of 25 to 1000 mg. Plasma pharmacokinetic profiles were analyzed on day 1 and on either day 7 or day 28, by which time plasma concentrations had reached steady state.

Absorption

Mean absolute bioavailability for imatinib is 98%. There was high between patient variability in plasma imatinib AUC levels after an oral dose. When given with a high fat meal, the rate of absorption of imatinib was minimally reduced (11% decrease in Cmax and prolongation of tmax 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

The main circulating metabolite in humans is the N-demethylated piperazine derivative, which shows similar in vitro potency to the parent. The plasma AUC for this metabolite was found to be only 16% of the AUC for imatinib. The plasma protein binding of the N-demethylated metabolite is similar to that of the parent compound.

Elimination

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

Plasma pharmacokinetics

Following oral administration in healthy volunteers, the t½ 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 25–1000 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.

Population pharmacokinetics

Based on population pharmacokinetic analysis in CML patients, there was a small effect of age on the volume of distribution (12% increases in patients > 65 years old). This change is not thought to be clinically significant. The effect of bodyweight on the clearance of imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8.5 l/h, while for a patient weighing 100 kg the clearance will rise to 11.8 l/h. These changes are not considered sufficient to warrant dose adjustment based on kg bodyweight. There is no effect of gender on the kinetics of imatinib.

Pharmacokinetics in children

As in adult patients, imatinib was rapidly absorbed after oral administration in paediatric patients in both phase I and phase II studies. Dosing in children at 260 and 340 mg/m²/day achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients.
The comparison of $AUC_{(0-24)}$ on day 8 and day 1 at the 340 mg/m²/day dose level revealed a 1.7-fold drug accumulation after repeated once-daily dosing.

Organ function impairment

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Patients with mild and moderate impairment of renal function appear to have a higher plasma exposure than patients with normal renal function. The increase is approximately 1.5 to 2-fold, corresponding to a 1.5-fold elevation of plasma AGP, to which imatinib binds strongly.
The free drug clearance of imatinib is probably similar between patients with renal impairment and those with normal renal function, since renal excretion represents only a minor elimination pathway for imatinib.
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.

Expiry date and storage conditions

See the expiry date printed on the outer carton.
This date refers to the product correctly stored in unopened package.
Beware not to use **Sagitta** after this date.
Store below 30°C.
Keep all medicines out of reach of children.

Presentation

Sagitta 100 mg, hard capsule are gelatin capsules of size “3” with orange body and cap.
They are supplied in packs containing 60 capsules.
Sagitta 400 mg, hard capsule are gelatin capsules of size “00” with caramel body and cap.
They are supplied in packs containing 30 capsules.

Manufactured by: Pabianickie Zaklady Farmaceutyczne Polfa S.A.
Pabianice, Poland.
For: ARWAN Pharmaceutical Industries Lebanon s.a.l.
Jadra, Lebanon

THIS IS A MEDICAMENT
- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists

145294