NEW ZEALAND DATA SHEET

1. NAME OF MEDICINAL PRODUCT

IMATINIB-AFT 100 and 400 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance(s)

Imatinib-AFT 100 mg capsule

Each capsule contains 119.47 mg of imatinib mesilate, equivalent to 100 mg of imatinib free base.

Imatinib-AFT 400 mg capsule

Each capsule contains 477.88 mg of imatinib mesilate, equivalent to 400 mg of imatinib free base.

Excipients

For full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Imatinib-AFT 100 mg capsule

Hard gelatine capsules, orange body and cap, size no. 3

Imatinib-AFT 400 mg capsule

Hard gelatine capsules, caramel body and cap, size no. 00

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imatinib-AFT is indicated for the

• treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+CML) (for paediatric use see section 4.2 Dose and method of administration)

• treatment of adult and paediatric patients with Ph+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 or with c-Kit mutational status unknown.

• treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL).

• treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

The effectiveness of Imatinib-AFT is based on its bioequivalence to the innovator and the response rates shown by the innovator in various trials:

• overall haematological and cytogenetic response rates and progression-free survival in CML

• haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD

• haematological response rates in SM, HES/CEL

• objective response rates in DFSP (see section Pharmacodynamic properties)

Increased survival in controlled trials has been demonstrated only in newly diagnosed chronic phase CML.

4.2 Dose and method of administration

Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.

Dosage in CML

The recommended dosage of Imatinib-AFT 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 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 cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response.

Dosage in Ph+ ALL

The recommended dose of Imatinib-AFT is 600 mg/day for adult patients with Ph+ ALL.

Dosage in MDS/MPD

The recommended dose of Imatinib-AFT is 400 mg/day for adult patients with MDS/MPD.

Dosage in SM

The recommended dose of Imatinib-AFT is 400 mg/day for adult patients with SM without the D816V c-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-PDGFR-alpha, 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 Imatinib-AFT is 400 mg/day for adult patients with HES/CEL.

For HES/CEL patients with demonstrated FIP1L1-PDGFR-alpha 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.

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

Dosage in DFSP

The recommended dose of Imatinib-AFT is 800 mg/day for adult patients with DFSP.

Dose adjustments for adverse drug reactions

Non-haematological adverse drug reactions

If a severe non-haematological adverse drug reaction develops with Imatinib-AFT 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, Imatinib-AFT should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. Treatment with Imatinib-AFT 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/m2/day.

Haematological adverse drug 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

SM associated with eosinophilia [95] and HES/CEL with FIP1L1-PDGFR-alpha fusion kinase (starting dose 100 mg)	ANC <1.0 x10^9/L and/or platelets < 50x10^9/L	1. Stop Imatinib-AFT until ANC ≥1.5 x10^9/L and platelets ≥75 x10^9/L. 2. Resume treatment with Imatinib-AFT at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, MDS/MPD, SM, HES/CEL (starting dose 400 mg)	ANC <1.0 x10^9/L and/or platelets < 50x10^9/L	1. Stop Imatinib-AFT until ANC ≥1.5 x109/L and platelets ≥75 x10^9/L. 2. Resume treatment with Imatinib-AFT 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 Imatinib-AFT 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 < 50x10^9/L	1. Stop Imatinib-AFT until ANC ≥1.5 x10^9/L and platelets ≥75 x10^9/L. 2. Resume treatment with Imatinib-AFT 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 Imatinib-AFT at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg[c])	aANC <0.5 x10^9/L and/or platelets < 10x109/L	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of Imatinib-AFT 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 Imatinib-AFT 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 < 50x10^9/L	4. Stop Imatinib-AFT until ANC ≥ 1.5x10^9/L and platelets ≥ 75x10^9/L. 5. Resume treatment with Imatinib-AFT at 600 mg 6. In the event of recurrence of ANC < 1.0x10^9/L and/or platelets < 50x10^9/L, repeat step 1 and resume Imatinib-AFT at reduced dose of 400 mg.

ANC = absolute neutrophil count
[a] occurring after at least 1 month of treatment
[b] or 260 mg/m2 in children
[c] or 340 mg/m2 in children
[d] or 200 mg/m2 in children

Special Populations

Children

There is no experience with the use of Imatinib-AFT in children with CML below 2 years of age. There is very limited experience with the use of Imatinib-AFT in children in other indications.

Dosing in children should be on the basis of body surface area (mg/m2). The dose of 340 mg/m2 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 daily dose may be split into two administrations – one in the morning and one in the evening. Due to the non-divisibility of this product, not all dosings may be possible (see section 11 Clinical pharmacology).

Hepatic insufficiency

Imatinib is mainly metabolised by 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 (see sections 4.4 Special warnings and precautions for use and precautions, 4.8 Undesirable effects, 5. PHARAMCOLOGICAL PROPERTIES).

Renal insufficiency

Imatinib and its metabolites are not significantly excreted via the kidney. Patients with renal dysfunction or on dialysis could be given the minimum recommended dose of 400 mg daily as starting dose. (see sections 5. PHARAMCOLOGICAL PROPERTIES). 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 section 4.4 Special warnings and precautions for use).

Elderly patients

No significant age related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose

recommendation is necessary in the elderly.

Method of administration

The prescribed dose should be administered orally with a meal and a large glass of water to minimize 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 (children) unable to swallow the capsules, their content may be dispersed in a glass of water or apple juice. The entire content of the required number of capsules should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg capsule, and 200 mL for a 400 mg capsule) and stirred with a spoon. The suspension should be administered immediately after its preparation.

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

4.3 Contraindications

Use in patients with a hypersensitivity to the active substance or to any of the excipients is contraindicated.

4.4 Special warnings and precautions for use

When Imatinib-AFT is co-administered with other medications, there is a potential for drug interactions. Caution should be used when taking Imatinib-AFT with rifampicin or other strong CYP3A4 inducers, ketoconazole or other strong CYP3A4 inhibitors, CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide) or CYP2C9 substrates with a narrow therapeutic window (e.g. warfarin and other coumarin derivatives) (see section 4.5 Interaction with other medicines and other forms of interaction).

Hypothyroidism

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

Hepatotoxicity

In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections 4.2 Dose and method of administration, 4.8 Undesirable effects, 11 Clinical Pharmacology).

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. Monitoring of hepatic function is recommended in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section 4.8 Undesirable effects).

Fluid retention

Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, and superficial oedema) have been reported in approximately 2.5% of newly diagnosed CML patients taking Imatinib-AFT. 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.

Renal function

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.

Patients with cardiac disease or renal failure

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 degradation upon the initiation of Imatinib-AFT therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Imatinib-AFT. Myelodysplastic (MDS)/myeloproliferative (MPD) diseases 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. If either is abnormal, the prophylactic use of systemic steroids (1 to 2 mg/kg) for one to two weeks concomitantly with imatinib should be considered at the initiation of therapy.

Tumor lysis syndrome

Cases of tumor lysis syndrome (TLS) have been reported in patients treated with imatinib. Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of imatinib (see section 4.8 Undesirable effects).

Laboratory tests

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

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

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect imatinib kinetics. 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 Dose and method of administration, the starting dose of imatinib can be reduced if not tolerated.

Children and adolescents

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

4.5 Interaction with other medicines and other forms of interaction

Drugs that may alter imatinib plasma concentrations

Drugs 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 Imatinib-AFT with inhibitors of the CYP3A4 family.

Drugs that may decrease imatinib plasma concentrations

Substances that are inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or hypericum perforatum, also known as St.John's Wort) may significantly reduce exposure to imatinib. Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 8 days, followed by a single 400 mg dose of imatinib, increased imatinib oral-dose clearance by 3.8-fold (90%confidence interval = 3.5- to 4.3- fold), which represents mean decreases Cmax, AUC(0-24) and AUC(0-∞) by 54%, 68% and 74%, of the respective values without rifampin treatment. Similar results were observed in patients with malignant gliomas treated with imatinib while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, 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 to 32% reduction in the AUC of imatinib. In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Drugs 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 imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide). Imatinib may increase plasma concentration of other CYP3A4 metabolised 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 end of imatinib therapy and when altering the dosage. Alternatively, the use of low-molecular weight heparin should be considered.

In vitro, imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had a weak

inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol Cmax 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 drug-drug interactions and dose adjustment may not be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). There are no clinical trials on the use of imatinib in pregnant women. There have been post- market reports of spontaneous abortions and infant congenital anomalies from women who have taken imatinib. Imatinib should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

Women of child-bearing potential

Women of childbearing potential must be advised to use highly effective contraception during treatment. Highly effective contraception is a method of birth control which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

Breast-feeding

Both imatinib and its active metabolite can be distributed into human milk. The milk plasma ratio 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 of 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.

Fertility

Human studies on male patients receiving imatinib and its effect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on imatinib treatment should consult with their physician (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Reports of motor vehicle accidents have been received in patients receiving imatinib. While most of these reports are not suspected to be caused by imatinib, 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.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of imatinib in human clinical use has been well-characterized through more than 12 years of imatinib experience. During clinical development, the majority of patients experienced adverse events at some point in time. The most frequently reported ADRs (>10%) were neutropenia, thrombocytopenia, anemia, headache, dyspepsia, edema, weight increased,

nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and abdominal pain. Events were of mild to moderate grade, and only 2 to 5 % of patients permanently discontinued therapy due to drug-related events.

Myelosuppression, GI adverse events, edema, and rashes are common between 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 imatinib, and which may be causally related, include hepatotoxicity, acute renal failure, hypophosphatemia, severe respiratory adverse reactions, and tumor lysis syndrome and growth retardation in children.

Depending on severity of events, dose adjustment may be required. In very few cases will the medication have to be discontinued based on ADRs.

Adverse reactions (Table 1 and Table 2) are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000), including isolated reports.

Table 1: Adverse reactions

Infections and infestations	
Uncommon:	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia, 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
Common:	Dizziness, paraesthesia, taste disturbance, hypoesthesia

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 [1], pulmonary oedema Rare: Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion
Vascular disorders	
Common	Flushing, haemorrhage
Uncommon:	Hypertension, haematoma, peripheral coldness, hypotension, Raynaud`s phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, epistaxis, cough
Uncommon:	Pleural effusion [2], pharyngolaryngeal pain, pharyngitis
Rare:	Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage
Gastrointestinal disorders	
Very common:	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain
Common:	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis
Uncommon:	Stomatitis, mouth ulceration, gastrointestinal haemorrhage, 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 [3], 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, Musculo skeletal pain including myalgia, arthralgia, bone pain
Common:	Joint swelling
Uncommon:	Joint and muscle stiffness
Rare:	Muscular weakness, arthritis

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

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]*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.*

[2]*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*

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

The following types of ADRs have been reported from post-marketing experience and from
additional clinical studies with imatinib. They include spontaneous case reports as well as serious ADRs from smaller or ongoing clinical studies and the expanded access programmes. Because these ADRs 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
Uncommon: Cerebral oedema

Eye disorders
Rare: Vitreous haemorrhage

Cardiac disorders
Rare: Pericarditis, 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, tumor haemorrhage/tumor necrosis, gastrointestinal perforation [2]
Rare: Diverticulitis

Skin and subcutaneous tissue disorders
Uncommon: Palmar-plantar erythrodysaesthesia syndrome Rare:
Lichenoid keratosis, lichen planus
Very rare: Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Rare: Avascular necrosis/hip osteonecrosis, rhabdomyolysis/myopathy
Unknown: Growth retardation in children

Reproductive disorders
Very rare: Haemorrhagic corpus luteum / haemorrhagic ovarian cyst

Neoplasm benign, malignant and unspecified (including cysts and polyps)
Rare: 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

Description of selected Adverse Drug Reactions

Myelosuppression

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

Hematologic depression appeared greatest at the highest doses and also appeared to be dependent on 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 they rarely require discontinuation of treatment with imatinib. The incidence of hematologic toxicities is less in patients with solid tumors than in patients with Ph+ leukemias, with Grade 3/4 neutropenia and thrombocytopenia occurring approximately 10% and 1%, respectively.

Hemorrhage

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

The most common manifestation of clinically significant bleeding was GI hemorrhage, which occurred most commonly in advanced CML patients, where bleeding might occur as part of the underlying disease due to tumor bleeding from tumor hemorrhage/tumor necrosis. In first line CML, the observed frequencies of GI hemorrhage were generally the lowest.

Edema and Fluid Retention

Edema is a common toxicity of imatinib appearing in greater than 50% of all patients across all indications. Edema is dose-related and there appears to be a correlation with its occurrence and plasma levels. The most common manifestation is periorbital edema and somewhat less common is lower extremity edema. Specific therapy is not usually required. Other fluid retention events occur much less commonly, but due to the location of the anatomic site may be potentially serious. The most frequent fluid retention event was pleural effusion, most commonly observed in advanced CML patients. The frequency of cardiac failure was generally low in patients with edema and fluid retention. It was higher in advanced CML than in other groups. This could be explained by the worse medical condition of advanced CML patients. The same trend was observed for renal failure in patients with edema and fluid retention.

In a clinical study, the frequency of events suggesting congestive heart failure was 1.5%

on imatinib vs. 1.1% on IFN-alpha 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 hemoglobin of less than 8 g/dL. Across all indications a higher frequency of CHF events observed in patients with CML might indicate differences of some of these disease-related risk factors.

Skin Rashes and Severe Cutaneous Adverse Reactions

A generalized erythematous, maculopapular, pruritic skin rash that can fade despite continued therapy, has been reported. 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, but not in all patients. These eruptions generally respond to antihistamines and topical steroids. Occasionally, systemic steroids are required.

Skin rashes have been observed in up to one third of patients treated with imatinib across all indications. These are frequently pruritic and most commonly appear as erythematous, maculopapular lesions on the forearm, the trunk or the face. Skin biopsies have revealed a toxic drug reaction with a mixed cellular infiltrate. Although most rashes are mild and self limiting more severe cases may require interruption or discontinuation of treatment.

Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur, and has been observed preclinically and clinically. LFT abnormalities usually consisted of mild 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 normalize after withholding therapy for 1 to 4 weeks.

Hypophosphatemia

Low serum phosphate and hypophosphatemia (up to Grade 3/4) has been observed relatively commonly across all indications, however the origin and the clinical significance of this finding have not been established. Imatinib has been shown to inhibit the differentiation of human monocytes into osteoclasts. The decrease was accompanied by a decrease in the resorptive capacity of these cells. A dose-dependent decrease of RANK-L was observed in osteoclasts in the presence of imatinib. Sustained inhibition of osteoclastic activity may lead to counter regulatory response 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 hypothesized that hypophosphatemia might be dose dependent, 24 month interpretable results from the Phase III TOPS study designed to investigate dose dependency of safety endpoints in patients with newly diagnosed CML, have shown that Grade 3/4 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 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.

Tumor lysis syndrome

A causal relationship between tumor lysis syndrome and Imatinib treatment is deemed possible, although some cases were confounded by concomitant medications and other independent risks (see section 4.4 Special warnings and precautions).

Growth retardation in children

Imatinib appears to affect the stature of children, especially children who are pre-pubertal. A causal relationship between growth retardation in children and imatinib treatment could not be ruled out although for some cases of growth retardation there was limited information (see section 4.4 Special warnings and precautions).

Severe respiratory adverse drug reaction

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

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. 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 × 109/L) and thrombocytopenias (platelet count <50 × 109/L) being between 4 and 6 times higher in blast crisis and accelerated phase as compared to newly diagnosed patients in chronic phase CML. In newly diagnosed chronic phase CML Grade 4 neutropenia (ANC <0.5 × 109/L) and thrombocytopenia (platelet count <10 × 109/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 Imatinib, but can in rare cases lead to permanent discontinuation of treatment. In paediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anemia. 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.

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

Reporting of Suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/report/

4.9 Overdose

Experience with higher than therapeutic doses is limited. Isolated cases of Imatinib overdosage have been reported spontaneously and in the literature. Generally the reported outcome in these cases was

improvement or recovery. In the event of overdosage the patient should be observed and appropriate symptomatic treatment should be given.

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

Adult overdose

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 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 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 diarrhea.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: protein-tyrosine kinase inhibitor, ATC code: LO1XE01

Mechanism of action

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1) and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.

Pharmacodynamics

Imatinib is a protein-tyrosine kinase inhibitor, which potently inhibits the breakpoint cluster region-Abelson (Bcr-Abl) tyrosine kinase at the in vitro, cellular, 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 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), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. Constitutive activation of the 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 MDS/MPD, HES/CEL and DFSP. In addition, constitutive activation of c-Kit or the PDGFR has been implicated in the pathogenesis of SM. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR, Kit and Abl kinase activity.

5.2 Pharmacokinetic properties

The pharmacokinetics of Imatinib have been evaluated over a dosage range of 25 to 1,000 mg. Plasma pharmacokinetic profiles were analysed 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%. 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 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-acidglycoprotein, with little binding to lipoprotein.

Metabolism

The main circulating metabolite in humans is the N-demethylated piperazine derivative (CGP71588), which shows similar in vitro potency as the parent compound. 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 14C-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.

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 to 1,000 mg imatinib after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation was 1.5- to 2.5-fold at steady state when dosed once daily.

Population pharmacokinetics

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 PK analysis in the phase III study in newly diagnosed CML patients showed that the effect of covariates and co-medications on both clearance and volume appears to be small and is not sufficiently pronounced to warrant dose adjustment.

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 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 340 mg/m2 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 (see sections 4.2 Dose and method of administration,4.4 Special warnings and precautions, 5. PHARAMCOLOGICAL PROPERTIES).

Although the results of pharmacokinetic analysis showed that there is considerable intersubject 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 sections 4.2 Dose and method of administration,4.4 Special warnings and precautions, 4.8 Undesirable effects, 5. PHARAMCOLOGICAL PROPERTIES).

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. Other target organs include the liver and the kidney.

Imatinib was embryotoxic and teratogenic in rats. 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 males rats. In the preclinical pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by Imatinib.

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 pediatric exposure at the highest recommended dose of 340 mg/m2. Also, mortality was observed in juvenile animals (around weaning phase) at approximately 2-times the average pediatric exposure at the highest recommended dose of 340 mg/m2.

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/m2. 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.

The relevance of these findings in the rat carcinogenicity study for humans is not 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

Imatinib-AFT 100 mg capsule

Capsule content: crospovidone, lactose monohydrate, and magnesium stearate

Capsule shell: gelatin, yellow iron oxide (E172), titanium dioxide (E171), and red iron oxide (E172)

Imatinib-AFT 400 mg capsule

Capsule content: crospovidone, lactose monohydrate, and magnesium stearate

Capsule shell: gelatin, yellow iron oxide (E172), titanium dioxide (E171), red iron oxide (E172), and black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

Protect from moisture.

Store in the original package.

Imatinib-AFT must be kept out of reach and sight of children.

6.5 Nature and content of container

Imatinib-AFT 100 mg capsule: Packs containing 30, 60 and 120 capsules.

Imatinib-AFT 400 mg capsule: Packs containing 30 capsules.

6.6 Special precautions for disposal

No specific instructions for use

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

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