New Zealand Datasheet

1 PRODUCT NAME
Imatinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Imatinib 100 mg and 400 mg as Imatinib mesilate.

3 PHARMACEUTICAL FORM
Imatinib Capsules 100 mg consist of light-yellow granules in a size 3 hard gelatin capsule with a brown cap and white body.

Imatinib Capsules 400 mg consist of light-yellow granules filled in a size 00EL hard gelatin capsule with a brown cap and brown body.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Imatinib is indicated for the

- Treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (Ph+CML) (Please refer to section 4.2 Dose and Method of Administration for paediatric use).
- Treatment of adult and paediatric patients with Ph+CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy (Please refer to section 4.2 Dose and Method of Administration for paediatric use).
- 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 hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL).
- Treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

4.2 Dose and method of administration

Imatinib treatment should only be initiated by a physician who is specialised in haematological malignancies and malignant sarcomas treatment.

The therapeutic dose of imatinib should be taken orally with a large glass of water and with food or immediately after a meal to reduce the possibility of gastrointestinal problems.

Prescribed doses of 400 mg or 600 mg are to be taken once per day, while 800 mg per day should be taken as 400 mg twice per day, once in the morning and once at night.

For patients who have difficulty swallowing, the capsules can be opened and the capsule contents emptied into a glass of still water or apple juice at room temperature (50 mL for 100 mg capsule or 200 mL for a 400 mg capsule) and mixed with a spoon. The mixture should

be taken immediately after stirring of the capsule contents is complete in the water or apple juice.

Imatinib treatment should resume for as long as the patient benefits from the medication.

Regular monitoring of Ph+ CML patients should be completed to observe their response to imatinib treatment. Monitoring is important in the following circumstances: when treatment has been adjusted, there is a loss in response to treatment, when there are potential drug to drug interactions, where less than optimal responses are achieved or when there is inadequate patient compliance. The results from monitoring these circumstances should help influence the appropriate CML treatment.

Dose for Chronic Myeloid Leukaemia (CML)

Description	**Recommended Dosage**
Adult Patient – Chronic phase CML	400 mg per day (An increase to 600 mg or 800 mg per day may be considered)*
Adult Patient – Accelerated Phase or Blast Crisis	600 mg per day (An increase to 800 mg per day may be considered)*

*A dose increase may be considered only if there is an absence of severe non-leukaemia-related neutropenia or thrombocytopenia and an absence of severe adverse drug reactions:

- Loss of a formerly attained haematological and/or cytogenetic response;
- Progression of the disease at any stage;
- Unable to attain an adequate haematological response after more than three months of imatinib treatment; and/or
- Unable to attain a cytogenetic response after 12 months of imatinib treatment.

Dose for Philadelphia Chromosome Positive (Ph-positive ALL)

Description	**Recommended Dosage**
Adult Patient – Ph+ ALL	600 mg per day

Dose for Myelodysplastic / Myeloproliferative Diseases (MDS/MPD)

Description	**Recommended Dosage**
Adult Patient – MDS/MPD	400 mg per day

Dose for Hypereosinphilic Syndrome and/or Chronic Eosinophilic Leukaemia (HES/CEL)

Description	**Recommended Dosage**
Adult Patient – HES/CEL	400 mg per day
Adult Patient – HES/CEL with FIP1L1-PDGFR-alpha fusion kinase	Initial dose of 100 mg per day. A dose increase to 400 mg per day may be contemplated only in the absence of adverse events and if monitoring of treatment shows an inadequate treatment response.

Imatinib treatment should resume for as long as the patient benefits from the medication.

Dose for Dermatofibrosarcoma Protuberans (DFSP)

Description	Recommended Dosage
Adult Patient – DFSP	800 mg per day

Guidelines for Dose Management

Non-haematological adverse drug reactions

Imatinib treatment must be withdrawn in the event of a severe non-haematological adverse drug reaction until it has been resolved. Dependent on the seriousness of the event, imatinib treatment can be restarted, as appropriate.

If increases in liver transaminases >5 x institutional upper limit of normal (IULN) or increases in bilirubin >3 x IULN arise, imatinib treatment should be withdrawn until the liver transaminase levels return to <2.5 x IULN and bilirubin levels return to <1.5 x IULN.

Imatinib treatment can then be reinstated at a decreased daily dose.

For adults, the dosage should be decreased from either 400 mg to 300 mg per day, 600 mg to 400 mg per day, or from 800 mg to 600 mg per day. In children the dosage should be decreased from 340 mg/m^2/day to 260 mg/m^2/day.

Haematological adverse drug reactions

Severe neutropenia and thrombocytopenia require a reduction in dose or treatment to be withheld as shown in the table below:

Table 1: Guidelines for Dosage Ddjustments for Neutropenia and Thrombocytopenia

Indication	Adverse Drug Reaction	Recommended Dosage Adjustments
CML Accelerated Phase and Blast Crisis and Ph+ ALL (initial dose 600 mg[c])	[a]ANC <0.5 x 10^9/L And/or Platelets <10 x 10^9/L	1. Assess whether cytopenia is associated with leukaemia (marrow aspirate or biopsy). 2. If unrelated – decrease the imatinib dosage to 400 mg[b]. 3. If cytopenia continues for two weeks – decrease the imatinib dosage further to 300 mg[d]. 4. If cytopenia continues for four weeks (and is still not associated with leukaemia) – withdraw imatinib treatment until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L. Then recommence treatment at 300 mg[d].
Chronic phase CML – MDS/MPD, HES/CEL (initial dose 400 mg)	ANC <1.0 x 10^9/L And/or Platelets <50 x 10^9/L	1. Withdraw imatinib treatment until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Recommence imatinib treatment at the starting dose (for example, before the drug reaction). 3. If severe adverse drug

		reaction reoccurs, repeat step 1 and recommence imatinib treatment at the decreased dosage of 300 mg.
Chronic phase CML – paediatric (dose 340 mg/m^2)	ANC <1.0 x 10^9/L And/or Platelets <50 x 10^9/L	1. Withdraw imatinib treatment until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Recommence imatinib treatment at the starting dose (for example, before the drug reaction). 3. If severe adverse drug reaction reoccurs, repeat step 1 and recommence imatinib treatment at the decreased dosage of 260 mg/m^2.
HES/CEL with FIP1L1PDGFR-alpha fusion kinase (initial dose 100 mg)	ANC <1.0 x 10^9/L And/or Platelets <50 x 10^9/L	1. Withdraw imatinib treatment until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Recommence imatinib treatment at the starting dose (for example, before the drug reaction).
DFSP (initial dose 800 mg)	ANC <1.0 x 10^9/L And/or Platelets <50 x 10^9/L	1. Withdraw imatinib treatment until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Recommence imatinib treatment at 600 mg. 3. If severe adverse drug reaction reoccurs, repeat step 1 and recommence imatinib treatment at the decreased dosage of 400 mg.

ANC = absolute neutrophil count
[a] appearing after imatinib treatment of one month or more
[b] or 260 mg/m^2 in children
[c] or 340 mg/m^2 in children
[d] or 200 mg/m^2 in children

Children
For children under the age of two, there is no experience with the use of imatinib with CML.

For all other indications, there is inadequate experience in children.

The imatinib dose for children must be calculated on their body surface area (mg/m^2). For children with advanced phase and chronic phase CML, the recommended dose is 340 mg/m^2 per day (maximum dose is not to exceed 600 mg per day). This can be taken as one dose per day or split into two doses to be taken once in the morning and once at night (Please refer to section 5.2 Pharmacokinetic Properties).

Elderly Patients
For elderly patients, there is no change of dose required. In clinical studies, there were no significant pharmacokinetic differences that were related to age observed in patients where 20% were 65 years and older.

Hepatically Impaired Patients
Patients with liver dysfunction (mild, moderate or severe), should be prescribed the minimum dosage recommended of 400 mg per day as the majority of imatinib is metabolised by the liver. If the dose is not tolerated it may be decreased (Please refer to sections 4.4 Special Warnings and Precautions for Use, 4.8 Undesirable Effects, 5.1 Pharmacodynamic Properties and 5.2 Pharmacokinetic Properties).

Renally Impaired Patients
Patients with renal dysfunction (or on dialysis), should be prescribed the minimum dosage recommended of 400 mg per day as the initial treatment dose (Please refer to sections 5.1 Pharmacodynamic Properties and 5.2 Pharmacokinetic Properties), as imatinib and its metabolites are not extensively eliminated through the kidneys. However, it is still recommended that caution is taken with renally impaired patients. If the dose is not tolerated, it may be decreased and if the dose is tolerated, it may be increased on the basis of lack of efficacy (Please refer to sections 4.4 Special Warnings and Precautions for Use).

4.3 Contraindications

Imatinib is not to be used in individuals with identified hypersensitivity to imatinib or to any of the excipients (Please refer to section 6.1 Pharmaceutical Particulars, List of Excipients).

4.4 Special warnings and precautions for use

There is a risk of drug interactions when imatinib is given alongside other medications.

Caution should be taken particularly when using imatinib with strong CYP3A4 inducers (for example, rifampicin), strong CYP3A4 inhibitors (for example, ketoconazole), CYP3A4 substrates with a limited therapeutic window (for example, pimozide or cyclosporin) and CYP2C9 substrates with a limited therapeutic window (for example, coumarin derivatives or warfarin) (Please refer to section 4.5 Interaction with Other Medicines and Other Forms of Interaction).

Cardiac Disease or Renal Failure
Patients should be carefully monitored if they have cardiac disease, are at risk of cardiac failure, or have renal failure history. Patients that exhibit symptoms that may indicate cardiac disease or renal failure must be assessed and treated.

The introduction of imatinib treatment in patients with hypereosinophilic syndrome (HES) (with occult infiltration of HES cells inside the myocardium), has in rare cases presented with cardiogenic shock and/or left ventricular dysfunction associated with HES degradation of cells. With the use of circulatory support measure, systemic steroids and temporarily halting imatinib treatment, the disorder was reported to be reversible.

There may be an association of myelodysplastic/myeloproliferative (MDS/MPD) diseases with increased eosinophil levels. In patients with increased eosinophil levels who have MDS/MPD an echocardiogram should be considered as well as the measurement of serum troponin. If either of these are irregular, prophylactic use should be considered using systemic steroids when therapy is initiated over the course of 1-2 weeks (1 to 2 mg/kg) alongside imatinib treatment.

Fluid Retention
In 2.5% of patients newly diagnosed with CML and taking imatinib, there have been incidences of severe fluid retention. Reports have included ascites, oedema, pleural effusion, pulmonary oedema and superficial oedema. Any sudden weight gain that is not

expected must be investigated and if required, therapeutic measures and suitable supportive care put into place. Patients should be weighed frequently to monitor the risk of fluid retention. Clinical studies have shown an increase in frequency of these events particularly in patients with a previous history of cardiac disease or in elderly patients.

Reactivation of Hepatitis B
Hepatitis B reactivation may arise in patients who are chronic virus carriers and have received a BCR-ABL tyrosine kinase inhibitor (TKI), for example, imatinib. In some circumstances, this has caused acute hepatic failure or fulminant hepatitis which has led to liver transplant or death (Please refer to section 4.8 Undesirable Effects).

Prior to imatinib treatment, patients should be assessed for hepatitis B infection.

Hepatitis B infection baseline testing should be completed in patients already having imatinib treatment to identify chronic virus carriers. Hepatitis B treatment and liver disease specialists must be consulted for patients that have tested hepatitis B positive for infection whilst being treated with imatinib and patients with serology that is positive for hepatitis B (also includes patients with the active disease). Close monitoring is required for patients starting imatinib treatment and who are hepatitis B virus carriers. For the duration of imatinib treatment and several months after treatment termination, the patient should be observed for any symptoms or indications of an active hepatitis B infection.

Hepatotoxicity
It is recommended that liver enzymes and peripheral blood counts are monitored carefully in patients with mild, moderate or severe hepatic dysfunction (Please refer to sections 4.2 Dose and Method of Administration, 4.8 Undesirable Effects and 5.1 Pharmacodynamic Properties).

There have been reports of transient liver toxicity in the form of hyperbilirubinemia and transaminase elevation when imatinib treatment is combined with chemotherapy treatments at a high dose. There have also been rare reports of acute liver failure. In treatments where imatinib is given in combination with other chemotherapy treatments linked with hepatic dysfunction, careful monitoring is recommended (Please refer to section 4.8 Undesirable Effects).

Hypothyroidism
TSH levels are to be monitored carefully in thyroidectomy patients having treatment with imatinib and levothyroxine replacement as there have been clinical reports of hypothyroidism in these patients.

Tumour Lysis Syndrome
There have been cases reported of tumour lysis syndrome (TLS) in patients having imatinib treatment. It is recommended, prior to the start of imatinib treatment, that the treatment of high uric acid levels and the correction of clinically significant dehydration is completed, due to the potential risk of TLS (Please refer to section 4.8 Undesirable Effects).

Laboratory Tests

Haematology
Regular complete blood counts must be completed whilst having imatinib treatment. Neutropenia and/or thrombocytopenia has been connected with CML patients on imatinib therapy. The existence of neutropenia and/or thrombocytopenia is related to the disease stage being treated. There is a higher incidence in patients with blast crisis or accelerated phase CML in comparison to patients in the chronic phase of CML. In this case, imatinib

treatment may be suspended or the dose decreased (Please refer to section 4.2 Dose and Method of Administration).

Liver Function
Regular monitoring of liver function (alkaline phosphatase, bilirubin and transaminases) is required in patients on imatinib treatment. Laboratory deviations should be managed by imatinib treatment being suspended or the dose decreased (Please refer to section 4.2 Dose and Method of Administration - Non-haematological Adverse Drug Reactions).

Renal Function
Imatinib (and its metabolites) are not eliminated to a significant extent via the kidneys. It is known that with age creatinine clearance (CrCL) decreases, however the kinetics of imatinib were not significantly affected with age. The plasma exposure of imatinib tends to be greater in patients with renal function that is impaired. In these patients, this is most likely due to the alpha-acid glycoprotein (AGP) plasma level being elevated (an imatinib binding protein). There is no association between the exposure of imatinib and the level of renal impairment as categorized by the CrCL measurement between patient with mild renal impairment and patients with severe renal impairment (CrCL: 40 to 59 mL/min and <20 mL/min, respectively). The initial dose of imatinib can be decreased if not tolerated (Please refer to section 4.2 Dose and Method of Administration).

A clinically significant deterioration in renal function may be related to imatinib treatment, long-term. Prior to imatinib treatment initiation, renal function should be assessed. During treatment renal function should also be closely monitored, especially in patients that exhibit renal dysfunction risk factors. If renal dysfunction is detected, suitable management and imatinib treatment introduced in relation to standard treatment guidelines.

Children and Adolescents
The occurrence of growth retardation has been reported in children and adolescents having imatinib treatment. It is unknown what the long term effects of imatinib treatment are on the growth of children. It is recommended that the growth of children is closely monitored while having imatinib treatment (Please refer to section 4.8 Undesirable Effects).

4.5 Interaction with other medicines and other forms of interaction

Other medicines that may change imatinib plasma concentrations

Medicines that may raise imatinib plasma concentrations

The concentration of imatinib may be increased and metabolism decreased with medicines that constrain the activity of the cytochrome P450 isoenzyme CYP3A4, for example, clarithromycin, erythromycin, itraconazole and ketoconazole. When imatinib was co-administered with an individual dose of ketoconazole (a CYP3A4 inhibitor) in healthy individuals, there was a significant increase in imatinib exposure (the mean C_{max} increased by 26% and AUC of imatinib increased by 40%). Therefore, when co-administering imatinib with CYP3A4 inhibitors, caution must be taken.

Medicines that may reduce imatinib plasma concentrations

Exposure to imatinib may be significantly decreased when co-administered with medicines that induce CYP3A4 activity, for example, carbamazepine, dexamethasone, hypericum perforatum (St. John's Wort), phenobarbital, phenytoin and rifampicin. Fourteen healthy individuals were pretreated with several 600 mg rifampicin doses over eight days, followed by a 400 mg imatinib single dose, which resulted in an increase of oral-dose clearance of

imatinib by 3.8-fold (90% CI = 3.5 to 4.3-fold). This signifies decreases of the mean C_{max} by 54%, $AUC_{(0-24)}$ by 68% and $AUC_{(0-\infty)}$ by 74% of the separate values without treatment of rifampicin.

Patients with malignant gliomas and who had imatinib treatment, showed comparable results while receiving enzyme-inducing anti-epileptic drugs (EIAEDs), for example, carbamazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin and primidone. The imatinib plasma AUC reduced by 73% in comparison to individuals who were not taking EIAEDs. The co-administration of imatinib with products containing St. John's wort showed a 30 to 32% decrease in the imatinib AUC in two studies that have been published. Other therapeutic medications (with a lower enzyme induction potential) should be deliberated in patients whose treatment plan discusses taking imatinib and other CYP3A4 inducers (for example, rifampicin).

Medicines that may have a change in their plasma concentration due to imatinib

Imatinib inhibits CYP3A4 when used with simvastatin (a CYP3A4 substrate) as the mean C_{max} is increased by 2-fold and AUC 3.5-fold for simvastatin. Caution should be taken when giving imatinib with CYP3A4 substrates (with a limited therapeutic window), for example, pimozide or cyclosporin. The plasma concentrations may be increased by imatinib in other CYP3A4 metabolised medicines, for example, dihydropyridine calcium channel blockers, particular HMP-CoA reductase inhibitors, such as statins and triazolo-benzodiazepines.

In vitro, CYP2C9 and CYP2C19 activity is inhibited by imatinib. When warfarin was co-administered with imatinib, PT prolongation was seen. When administering coumarins with imatinib treatment, short-term PT monitoring is required at the start and end when modifying the dosage. As an alternative, consideration should be given to low-molecular weight heparin.

In vitro, cytochrome P450 isoenzyme CYP2D6 is inhibited by imatinib, at strengths comparable to those that influence the activity of CYP3A4. Imatinib administered at 400 mg twice per day, exhibited a low inhibitory effect on the metabolism of CYP2D6-medicated metoprolol, with both C_{max} and AUC of metoprolol being increased by 23% approximately. When imatinib is co-administered with CYP2D6 substrates (for example, metoprolol), there does not appear to be a high possibility for drug-drug interactions. Therefore, an adjustment to the dosage may not be required.

In vitro, the acetaminophen O-glucuronidate pathway is inhibited by imatinib (Ki 58.5 microM).

Imatinib of 400 mg per day (over 8 days), co-administered with paracetamol (1,000 mg individual dose on day 8), in CML patients showed no changes in the paracetamol pharmacokinetics.

Paracetamol (single dose) did not alter the pharmacokinetics of imatinib.

There is no safety data or PK on the chronic use of imatinib and paracetamol concomitantly at doses of imatinib more than 400 mg per day.

4.6 Fertility, pregnancy and lactation

Summary of Risk
Imatinib treatment when given to women who are pregnant, may cause harm to the foetus based on observations seen in animal reproductive reports. There have been no clinical

studies conducted on pregnant women having imatinib treatment. In women who have taken imatinib treatment, there are post-marketing reports of infant congenital anomalies and spontaneous abortions. Reproductive trials completed in rats have revealed induced teratogenicity from imatinib mesilate (having an increase of congenital abnormality incidence), which was observed at treatment doses the equivalent to the maximum recommended dose for humans of 800 mg per day (on the basis of body surface area). If imatinib is used in pregnancy (only if the potential risk to the foetus is less than the benefit expected), or if the patient using imatinib becomes pregnant, the patient must be informed of the likely risks to the foetus.

Data
Pregnant rabbits and rats were given imatinib mesilate orally up to 60 mg/kg/day in rabbits and 100 mg/kg/day in rats, throughout the organogenesis period in an embryo-foetal development study.

In rats, the dose of 100 mg/kg/day of imatinib mesilate was considered teratogenic. This dosage was the equivalent to the human dosage maximum of 800 mg per day (on the basis of body surface area). Encephalocoele and exencephaly were reported more, in comparison to the historical control values and were related to underdeveloped or missing cranial bones. Retarded skeletal ossifications were correlated with a reduction in the mean foetal body weights.

In rabbits, there were no influences on the parameters of reproduction with respect to foetal weight, implantation locations, amount of live foetuses or the sex ratio when the dose was administered at 1.5 times greater than the human dose maximum of 800 mg per day. There were no morphological changes that were drug related when the foetuses were examined.

In rats, a prenatal and postnatal development study was completed where pregnant rats received imatinib mesilate oral doses up to 45 mg/kg/day during organogenesis (gestation) and lactation. On Days 14 to 15 of gestation, 5 rats were observed to have a vaginal discharge that was red while taking 45 mg/kg/day imatinib mesilate in which the implication is unknown as all female rats yielded litters and there was no increase of post-implantation loss. Other observations of maternal effects at the dosage of 45 mg/kg/day was an increase in the total of pups that were stillborn and pups that died postpartum between Days 0 to 4, (this dose being approximately one half the human dose maximum of 800 mg per day, on the basis of body surface area). The F1 offspring showed a minor decrease in the amount of litters attaining the criteria for preputial separation and a reduction of mean body weights from birth until terminal sacrifice at the same dosage. In behavioural testing and development parameters there were no other significant conclusions. Fertility in the F1 offspring was not influenced, however the reproductive effects (at 45 mg/kg/day) involved a reduction in viable foetus numbers and an increase number of resorptions. The NOEL was 15 mg/kg/day for both the maternal animals and the F1 group.

Fertility
There have been no clinical studies conducted on human male patients having imatinib treatment and the effect of imatinib on male fertility and spermatogenesis. Male patients taking or about to have imatinib treatment and who are worried about fertility should discuss this with their physician (Please refer to section 5.3 Pre-clinical safety data).

Contraception
Appropriate contraceptive measures that are highly effective should be taken from both males and females whilst on imatinib treatment and until more than 15 days have passed since treatment was withdrawn. When used properly and consistently, highly effective contraception should have a low failure rate of fewer than 1% per year.

Use in Lactation

Summary of Risk
Women should be advised to not breastfeed when completing imatinib treatment as it is known that imatinib (and its active metabolite) are passed through into the breast milk.

The consequences of an infant being exposed to low-dose imatinib is not known and because of the possibility of a severe adverse drug reaction in the infant being breastfed, it is not recommended that the woman breastfeeds during imatinib treatment and until more than 15 days have passed since treatment was withdrawn.

Human Research
It is believed that the combined total exposure of imatinib (and its active metabolite) to the infant would be low (approximately 10% of the dose), however there are no reports on the effects of low-dose exposure in infants and therefore breastfeeding is not recommended.

For imatinib and its active metabolite the milk plasma ratio was established to be 0.5 and 0.9, respectively. This indicated that the metabolite would have greater distribution.

4.7 Effects on ability to drive and use machines

Imatinib is known to cause blurred vision, dizziness and/or somnolence. Patients should be instructed to not drive or operate machinery if these side effects occur. There are reports of accidents when driving with patients on imatinib treatment, however the majority are not thought to have been directly caused by imatinib treatment.

4.8 Undesirable effects

Imatinib Safety Profile Summary
The overall imatinib safety profile in a clinical capacity with humans has been developed from over 12 years of imatinib research and experience. Most patients, at some point throughout the clinical development of imatinib, experienced an adverse event. The most commonly reported adverse events (more than 10%) were abdominal pain, anaemia, diarrhoea, dyspepsia, oedema, fatigue, headache, increase in weight, muscle cramps, musculoskeletal pain, nausea, neutropenia, rash, thrombocytopenia and vomiting. These adverse events were mild to moderate and due to this the number of patients who discontinued imatinib treatment permanently was only 2-5%.

There is an increased severity and incidence of myelosuppression in the safety profile of Ph+ leukemias in comparison to solid tumours. This is most likely due to disease associated factors. Oedema, gastrointestinal adverse reactions, myelosuppression and rashes are regularly reported in these populations. Other gastrointestinal disorders, for example, gastrointestinal perforation, ulceration and obstruction tend to be indication exclusive.

Acute renal failure, hepatotoxicity, hypophosphataemia, slower than normal growth in children, severe respiratory adverse events and tumour lysis syndrome are other adverse events that have been reported following imatinib exposure. These potentially are causally related.

Adjustment to dosage may be essential, dependent on the adverse event severity. Imatinib may be required to be discontinued in few occasions due to an adverse reaction.

Adverse reactions are graded under the title of frequency using the following principle: very common ≥ 10%; common ≥ 1% to < 10%; uncommon ≥ 0.1% to 0.01%; rare ≥ 0.01% to < 0.1% and very rare < 0.01%, including one-off reports.

Table 2: Adverse Drug Reactions in Chronic Myeloid Leukaemia Clinical Studies

Frequency	**Description of Adverse Reaction**
Blood and Lymphatic System Disorders	
Very Common:	Anaemia, neutropenia and thrombocytopenia.
Common:	Febrile neutropenia and pancytopenia.
Uncommon:	Bone marrow depression, eosinophilia, lymphopenia, lymphadenopathy and thrombocythaemia.
Rare:	Haemolytic anaemia.
Cardiac Disorders	
Uncommon:	Cardiac failure congestive[1], palpitations, pulmonary oedema and tachycardia.
Rare:	Angina pectoris, arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction and pericardial effusion.
Ear and Labyrinth Disorders	
Uncommon:	Loss of hearing, tinnitus and vertigo.
Eye Disorders	
Common:	Conjunctival haemorrhage, conjunctivitis, dry eyes, eyelid oedema, increase of lacrimation and vision blurred.
Uncommon:	Blepharitis, eye pain, irritation of the eyes, macular oedema, orbital oedema, retinal haemorrhage and scleral haemorrhage.
Rare:	Cataracts, glaucoma and papilloedema.
Gastrointestinal Disorders	
Very Common:	Abdominal pain, diarrhoea, dyspepsia, nausea and vomiting.
Common:	Abdominal distension, constipation, dry mouth, flatulence, gastritis and gastro-oesophageal reflux.
Uncommon:	Ascites, cheilitis, dysphagia, eructation, gastric ulcers, gastrointestinal haemorrhage, haematemesis, melaena, mouth ulceration, oesophagitis, pancreatitis and stomatitis.
Rare:	Colitis, ileus and inflammatory bowel disease.
General Disorders and Administration Site Conditions	
Very Common:	Fatigue, fluid oedema and fluid retention.
Common:	Anasarca, chills, pyrexia, rigors and weakness.
Uncommon:	Chest pain and malaise.
Hepatobiliary Disorders	
Common:	Hepatic enzymes increased.
Uncommon:	Hepatitis, hyperbilirubinaemia and jaundice.
Rare:	Hepatic failure[2] and hepatic necrosis[2].
Infections and Infestations	

Uncommon:	Cellulitis, gastroenteritis, herpes simplex, herpes zoster, influenza, nasopharyngitis, pneumonia[3], upper respiratory tract infection, urinary tract infection, sepsis and sinusitis.
Rare:	Fungal infection.
Investigations	
Very common:	Increase in weight.
Common:	Decrease in weight.
Uncommon:	Increase in blood alkaline phosphatase, increase in blood creatine phosphokinase, increase in blood creatinine and an increase in blood lactate dehydrogenase.
Rare:	Increase in blood amylase.
Metabolism and Nutrition Disorders	
Common:	Anorexia.
Uncommon:	Appetite decreased, appetite increased, dehydration, gout, hypercalcaemia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia and hypophosphataemia.
Rare:	Hyperkalaemia and hypomagnesaemia.
Musculoskeletal and Connective Tissue Disorders	
Very Common:	Arthralgia, bone pain[4], muscle cramps and spasms and musculo-skeletal pain (including myalgia).
Common:	Swelling of the joints.
Uncommon:	Stiffness of the joints and muscles.
Rare:	Arthritis and muscle weakness.
Nervous System Disorders	
Very Common:	Headache.
Common:	Disturbance of taste, feeling dizzy, hypoaesthesia and paraesthesia.
Uncommon:	Cerebral haemorrhage, impaired memory, migraine, peripheral neuropathy, restless leg syndrome, sciatica, somnolence, syncope and tremor.
Rare:	Convulsions, increase in intracranial pressure and optic neuritis.
Psychiatric Disorders	
Common:	Insomnia.
Uncommon:	Anxiety, decrease in libido and depression.
Rare:	Confusion.
Renal and Urinary Disorders	
Uncommon:	Haematuria, increase in urinary frequency, renal acute failure and renal pain.
Reproductive System and Breast Disorders	
Uncommon:	Breast enlargement, erectile dysfunction, gynaecomastia, irregular menstruation, menorrhagia, nipple pain, scrotal oedema and sexual dysfunction.
Respiratory, Thoracic and Mediastinal Disorders	
Common:	Cough, dyspnoea and epistaxis.
Uncommon:	Pharyngitis, pharyngolaryngeal pain and

	pleural effusion[5].
Rare:	Pleuritic pain, pulmonary fibrosis, pulmonary haemorrhage and pulmonary hypertension.
Skin and Subcutaneous Tissue Disorders	
Very Common:	Dermatitis, eczema, periorbital oedema and rash.
Common:	Alopecia, dry skin, erythema, face oedema, night sweats, photosensitivity reaction and pruritis.
Uncommon:	Bullous eruptions, contusion, dermatitis exfoliative, ecchymosis, folliculitis, hypotrichosis, increase in sweating, onychoclasis, petechiae, psoriasis, purpura, rash pustular, skin hyperpigmentation, skin hypopigmentation, tendency to bruise increased and urticaria.
Rare:	Acute febrile neutrophilic dermatosis (Sweet's syndrome), acute generalised exanthematous pustulosis (AGEP), angioneurotic oedema, discolouration of the nails, erythema multiforme, leucocytoclastic vasculitis, rash vesicular and Stevens-Johnson syndrome.
Vascular Disorders[6]	
Common:	Flushing and haemorrhage.
Uncommon:	Haematoma, hypertension, hypotension, subdural haematoma, peripheral coldness and Raynaud's phenomenon.

[1] Individuals with transformed CML were more likely to experience cardiac events (as well as congestive heart failure) in comparison to individuals with chronic CML, on a patient to year observation.

[2] There have been some reports of fatalities due to hepatic failure and hepatic necrosis.

[3] Pneumonia was most regularly reported in individuals with transformed CML.

[4] Musculoskeletal pain (and other related occurrences) were most regularly reported in individuals with CML.

[5] Pleural effusion was most regularly reported in individuals with transformed CML (CML-AP and CML-BS) in comparison to individuals with chronic CML.

[6] Haematoma and Haemorrhage (bleeding) was most regularly reported in individuals with transformed CML (CML-AP and CML-BC).

Table 3 shows adverse reactions that have been observed from post-marketing reports and from additional imatinib clinical studies which include unexpected case reports and serious adverse events from research that was yet to be completed or studies of a smaller scale. It is difficult to determine a causal relationship with imatinib or to evaluate the adverse reactions frequency as this information is extracted from a population of an undefined size.

Table 3: Post-marketing Adverse Drug Reactions Reported

Frequency	**Description of Adverse Reaction**
Cardiac Disorders	
Rare:	Cardiac tamponade and pericarditis.
Eye Disorders	
Rare:	Vitreous haemorrhage.
Gastrointestinal Disorders	
Uncommon:	Gastrointestinal perforation[1], ileus/intestinal obstruction and tumour haemorrhage/tumour

	necrosis.
Rare:	Diverticulitis and gastric antral vascular ectasia (GAVE).
Musculoskeletal and Connective Tissue Disorders	
Rare:	Avascular necrosis, hip osteonecrosis, myopathy and rhabdomyolysis.
Unknown:	Growth retardation in children/adolescents.
Neoplasm benign, malignant and undetermined (incorporating cysts and polyps)	
Rare:	Tumour lysis syndrome.
Nervous System Disorders	
Uncommon:	Cerebral oedema.
Reproductive Disorders	
Very Rare:	Haemorrhagic corpus luteum and haemorrhagic ovarian cyst.
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon:	Acute respiratory failure[2] and interstitial lung disease.
Skin and Subcutaneous Tissue Disorders	
Uncommon:	Palmar-plantar erythrodysaesthesia syndrome.
Rare:	Lichenoid keratosis and lichen planus.
Very Rare:	Toxic epidermal necrolysis.
Unknown:	Drug rash with eosinophilia and systemic symptoms (DRESS).
Vascular Disorders	
Uncommon:	Embolism or thrombosis.
Very Rare:	Anaphylactic shock.

[1] There have been some reports of fatalities from gastrointestinal perforation.

[2] There are reports of fatalities in individuals with advanced disease, who have severe infections, neutropenia that is severe and severe concomitant conditions.

Further Information on Specific Adverse Drug Reactions

Fluid Retention and Oedema

A common toxicity to imatinib treatment is oedema, which appears in more than 50% of patients in all indications. It appears that the circumstance of oedema is directly related with plasma levels and therefore is related to the dosage of imatinib. Periorbital oedema is the most frequent type and lower extremity oedema is less frequent. Treatment is not usually necessary. Whilst other events of fluid retention are not as common, they may be serious due to the anatomic site location. Pleural effusion was the most common fluid retention incident, and this was mainly observed in patients with CML that was advanced. Patients experiencing fluid retention and oedema generally had low frequency of cardiac failure in comparison to advanced CML where cardiac failure was higher. An explanation for this may be due to patients with advanced CML having a more severe medical condition. Patients with renal failure experienced the same trend with fluid retention and oedema.

The frequency of events in a clinical study showed that patients with CML that had been recently diagnosed were 1.5% more likely to experience congestive heart failure on imatinib, in comparison to 1.1% on IFN-alpha.

For patients who were older, had a hemoglobin baseline of <8 g/dL, or with transformed CML in the blast crisis or accelerated phase, the frequency was significantly higher. In CML patients, a higher event frequency was observed of CHF events, in comparison to other indications, indicating disease-related risk factor differences.

Gastrointestinal Ulceration
Gastrointestinal ulceration has been reported in a small number of patients over all indications. In some severe circumstances, gastrointestinal ulceration may signify local irritation by imatinib.

Growth Development in Children
Imatinib treatment appears to influence children's stature (particularly in pre-pubertal children). It has not been excluded that imatinib treatment has a causal relationship with growth retardation in children. In some circumstances information on growth retardation was limited (Please refer to section 4.4 Special Warnings and Precautions for Use).

Haemorrhage
It is not uncommon for patients with CML who have compromised marrow function at baseline to experience CNS and GI haemorrhages. In leukaemic patients who are acutely ill, disease events such as haemorrhages are well-documented. They may ensue from thrombocytopenia, or in some cases, platelet dysfunction. However, not every patient being treated with imatinib who experience CNS and GI haemorrhages are thrombocytopenic.

In patients with progressive CML, GI haemorrhage was the most common form of bleeding that was clinically significant. This may occur as part of the primary disease, from bleeding of tumours due to haemorrhage or tumour necrosis. In patients with first line CML, the frequency of GI haemorrhages was usually the lowest.

Hepatotoxicity
Severe hepatotoxicity may occasionally happen and has been both studied clinically and preclinically. This typically involved LFT abnormalities with slight transaminase increases. A small number of patients had increased bilirubin levels. Hepatotoxicity usually occurs in the initial two months of treatment however this has also occurred at later stages (up to six to twelve months after the commencement of treatment). The discontinuation of treatment over one to four weeks generally will regulate the levels.

Hypophosphataemia
Hypophosphataemia (< Grade 3 or 4) and low serum phosphate is moderately common throughout all indications. The clinical significance or source of this observation is yet to be established. It has been observed that imatinib inhibits human monocyte differentiation into osteoclasts. It was also observed that the resorptive capacity had decreased in these cells. With imatinib treatment, a dose-dependent reduction of RANK-L was reported in osteoclasts. Prolonged inhibition of the activity of osteoclasts, may result in an increase of PTH levels from a counter regulatory response. It is not known what the clinical relevance of the preclinical observations and a correlation with skeletal adverse reactions (for example, bone fractures) has yet to be established.

Serum phosphate was not regularly evaluated in all studies of the clinical development program. It was assumed at first that hypophosphataemia may be dependent on the dosage, however, results from the Phase III TOPS study over 24 months (aimed to investigate safety endpoints and dose dependency in recently diagnosed CML patients), revealed that 19.1% of patients receiving 400 mg imatinib had a reduction in serum phosphate and a 15.5% reduction in serum calcium, in comparison to patients receiving 800 mg imatinib who had a 5.1% reduction in serum phosphate and a 0.9% reduction in serum calcium (Grade 3 or 4).

Myelosuppression
It is very common for cancer patients who have had imatinib treatment to have myelosuppression. Anaemia, myelosuppression, neutropenia and thrombocytopenia were the Grade 3 and 4 most repeatedly reported laboratory abnormalities. In CML patients who

experienced myelosuppression when on imatinib treatment, most did not require any dose modification or disruption. Very few individuals required imatinib treatment to be discontinued. There have also been reports of other adverse events of bone marrow depression, lymphopenia and pancytopenia.

In higher doses of imatinib treatment, haematologic depression appeared greater. However, it also seemed to be directly related to the CML stage of the disease with neutropenia reported in 44% of patients and thrombocytopenia in 63% of patients (Grade 3 or 4), which was 4 to 6 times greater in the accelerated and blast phase in comparison to patients who had recently been diagnosed with chronic phase CMP (neutropenia 16.7% and thrombocytopenia 8.9%). These adverse events seldom require imatinib discontinuation and can be controlled typically with either a decrease in the dosage or an interruption to treatment. In individuals with solid tumours, hematologic toxicity incidence is less, in comparison to individuals with Ph+ leukemias, with Grade 3 and 4 neutropenia reported approximately in 10% of patients and thrombocytopenia in 1% of patients.

Severe Cutaneous Adverse Reactions and Skin Rashes
There are reports of a generalised skin rash that is pruritic, erythematous and maculopapular that can diminish even with continued treatment. Pruritus can occur in some patients without an associating rash, however, in some cases there may be an exfoliative element. Patients who have imatinib treatment restarted have had the rash reappear, but this has not been observed in every patient. Antihistamines and topical steroids generally help well with these eruptions, and at times systemic steroids are necessary.

For patients on imatinib treatment up to 1/3 of individuals within all indications have been reported to experience skin rashes. These skin rashes most frequently emerge as erythematous, exfoliative lesions or a maculopapular rash on the face, forearms, body or generalised with systemic expression and tend to be pruritic. In biopsies of the skin, harmful drug reactions with a mixed cellular infiltrate have been discovered. Most skin rashes are self-limiting and considered mild, however, rare cases that are severe may need a break in treatment or withdrawal of the medication.

Severe Respiratory Adverse Drug Reaction
There have been reports of severe respiratory events (including fatal reports) with imatinib treatment. This includes acute respiratory failure, interstitial lung disease, pulmonary fibrosis and pulmonary hypertension. In numerous cases, there have been reports of pre-existing pulmonary or cardiac disorders that may be linked with a severe respiratory adverse drug reaction.

Tumour Lysis Syndrome
There is a potential causal relationship between imatinib treatment and tumour lysis syndrome, however, several cases have been compromised by other risks independent of the imatinib treatment or concomitant medicines (Please refer to section 4.4 Special Warnings and Precautions for Use).

Laboratory Test Abnormalities

Haematology

A constant result over all studies is the occurrence of CML related cytopenias (thrombocytopenia and neutropenia, in particular). It is indicated that a higher frequency of cytopenias was observed in imatinib treatment given at higher doses (≥ 750 mg). Furthermore, evidence showed the incidence of cytopenias was directly linked to the stage of the CML disease. Cytopenias were infrequent in patients with CML that were newly diagnosed, in comparison to other CML patients. The occurrence of Grade 3 or 4

neutropenias (ANC <1.0 x10^9/L) and thrombocytopenias (platelet count <50 x10^9/L) were 59% to 64% for neutropenia and 44% to 63% for thrombocytopenia. This record is between four and six times greater in the accelerated phase or blast crisis in comparison to newly chronic phase CML diagnosed patients who had neutropenia 16.7% and thrombocytopenia 8.9%. In newly chronic phase CML diagnosed patients Grade 4 neutropenia (ANC <0.5 x10^9/L) was reported in 3.6% of patients and thrombocytopenia (platelet count <10x 10^9/L) in <1% of patients. The median episode for neutropenia ranged from two to three weeks and for thrombocytopenia from three to four weeks. These occurrences can typically be controlled with either a reduction in the dosage or a temporary break in imatinib treatment. In exceptional cases a permanent discontinuation of imatinib treatment may be required. In paediatric patients with CML, the most common toxicities reported were Grade 3 or 4 cytopenias (including anaemia, neutropenia and thrombocytopenia anaemia). These commonly would occur within the first few months of imatinib treatment.

Biochemistry

Severe increases of transaminases or bilirubin (<5% and <1%, respectively) have been observed in patients with CML. These occurrences were typically controlled with either a reduction in the dose or a temporary break of imatinib treatment. The median episode was about one week. In the case of laboratory abnormalities in the liver, imatinib treatment was permanently discontinued in <1% of CML patients.

Occurrences of cytolytic and cholestatic hepatitis and hepatic failure have been reported with several outcomes being fatal.

Reporting of Suspected Adverse Reactions

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

4.9 Overdose

Overdose information is limited for higher than the recommended therapeutic doses. There are isolated reports of overdosage on a spontaneous basis and in the literature. The outcome of most of these reports was that the patient improved and recovered.

In the occurrence of an overdose, appropriate symptomatic care should be arranged, and the patient observed and monitored.

Adverse events that have occurred after an overdose are shown in the table below:

Table 4: Adverse Events Experienced with Imatinib Overdose.

Overdose in Adults	
Dosage Taken	**Adverse Events Experienced**
1,200 to 1,600 mg (overdose duration varied between one to ten days):	Appetite decreased, diarrhoea, erythema, fatigue, headache, muscle spasms, nausea, oedema, pain in the abdomen, pancytopenia, rash, swelling, thrombocytopenia and vomiting.
1,800 to 3,200 mg (up to 3,200 mg per day over a six-day period):	Gastrointestinal pain, increased bilirubin, increased CPK, myalgia and weakness.

6,400 mg (as a single dose):	One patient in the literature reported: decrease in neutrophil count, facial swelling, nausea, pain in the abdomen, pyrexia, transaminases increased and vomiting.
8 to 10 g (as a single dose):	Gastrointestinal pain and vomiting.
Overdose in Pediatrics	
400 mg (as a single dose) in a 3-year-old male:	Anorexia, diarrhoea and vomiting.
980 mg (as a single dose) in a 3-year-old male	Diarrhoea and white blood cell count decreased.

For information on overdose management, contact the **National Poisons Centre on 0800 POISON or 0800 764 766**.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

The small molecule imatinib is a potent protein-tyrosine kinase inhibitor that effectively inhibits BCR-ABL tyrosine kinase (TK) activity, as well as various receptor TKs (colony stimulating factor receptor (CSF-1R), discoidin domain receptors DDR1 and DDR2, KIT – the receptor for stem cell factor (SCF) which is coded for by the KIT proto-oncogene, and the platelet derived growth factor receptors PDGFR-alpha and PDGFR-beta). Cellular events facilitated by these receptor kinases being activated can also be inhibited by imatinib.

Pharmacodynamics

Imatinib is a protein-tyrosine kinase inhibitor, which works at the cellular *in vitro* and *in vivo* levels, by effectively inhibiting the breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase. Imatinib inhibits proliferation selectively and stimulates apoptosis in BCR-ABL positive cell lines and new leukaemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukaemia (ALL) individuals. Imatinib shows inhibition selective of BCR-ABL positive colonies from patients with CML in colony transformation assays using ex vivo peripheral blood and samples of bone marrow.

In vivo, imatinib is shown in animal models as a single agent with anti-tumour activity in BCR-ABL positive tumour cells.

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

It has been implicated in the pathogenesis of DFSP, HES/CEL and MDS/MPD that the constitutive activation of PDGFR or the Abl protein tyrosine kinases as a result of combination to diverse partner proteins or constitutive production of PDGF. Imatinib prevents the proliferation and signaling of cells guided by unregulated ABL, KIT and PDGFR kinase actions.

Clinical Studies
The use of Imatinib Capsules is established on the bioequivalence and the results presented by various studies completed by the innovator:

1) CML Indication - Complete cytogenetic and haematological response rates and progression-free survival;
2) MDS/MPD and Ph+ ALL Indication - Cytogenetic and haematological response rates;
3) HES/CEL Indication – Haematological response rates;
4) DFSP Indication – objective response rates (Please refer to section 5.1 Pharmacodynamic Properties)

In controlled studies, the increase of survival rate has only been established in chronic phase CML that has been newly diagnosed.

5.2 Pharmacokinetic properties

Imatinib pharmacokinetics have been assessed over a dose span of 25 mg to 1,000 mg. The profiles of the plasma pharmacokinetics were evaluated on day 1 and on day 7 or either day 28, where at this point the concentrations of the plasma had attained steady state.

Absorption
For imatinib, the mean absolute bioavailability is 98% and the amount of variation for plasma AUC following an oral dose is in the range of 40 to 60%. When imatinib is taken with a meal that is high in fat, the absorption rate was marginally reduced in comparison to conditions when fasting (C_{max} decreased by 11%, t_{max} prolonged by 1.5 hours and AUC was reduced by 7.4%).

Distribution
In vitro studies showed that at concentrations that were clinically relevant, imatinib binds generally to albumin and alpha-acid-glycoprotein 95% of the time and binds rarely to lipoprotein.

Metabolism
In humans, the key metabolite is N-demethylated piperazine derivative (CGP71588). This main metabolite shows comparable *in vitro* potency as the parent compound. For this metabolite, the plasma AUC was observed to be 16% of the imatinib AUC. The N-demethylated metabolite plasma protein binding is comparable to the parent compound.

Elimination
Following an oral ^{14}C-labelled imatinib dose, over seven days, 68% of the dose was eliminated in the faeces and 13% in the urine (total 81% of the dose). This was established on the compound(s) recovery. Imatinib that was unchanged was eliminated by 20% in the faeces and 5% in the urine with the balance being metabolites.

In the PK study, the mean noticeable elimination half-life from the single dose was estimated to be 13.5 hours. For all ^{14}C-labelled components in plasma, the half-life was between 41 to 72 hours.

Plasma Pharmacokinetics
In healthy individuals, after imatinib oral administration, the t½ was 18 hours approximately, which proposes that imatinib taken once per day is suitable. Following oral administration, the rise in mean AUC with an increase in imatinib dosage was proportional to the range of the dose (25 mg to 1,000mg) and the relationship was linear.

When the dosage of imatinib was repeated, there was no difference in the kinetics of imatinib, and when imatinib was taken once per day, the accumulation was 1.5- to 2.5-fold at steady state.

Population Pharmacokinetics
Pharmacokinetic analysis in the population showed there was a slight effect that is not clinically significant on the volume of distribution with age where patients who were older than 65 years had a 12% increase. The influence of body weight on imatinib clearance is not deemed to be significant enough to instigate a change in dosage (for a patient that weighs 50 kg the mean clearance is anticipated to be 8.5 L/h in comparison to a patient that weighs 100 kg where, the clearance increased to 11.8 L/h). Gender has no effect on the imatinib kinetics.

Additional population PK examination in the phase III study in patients who had been recently diagnosed with CML, indicated that the influence of co-medications and covariates seems to be slight on both the volume of distribution and clearance. Due to this, no dose modification is required.

Paediatric Pharmacokinetics
Imatinib is quickly absorbed following oral administration in children, as also seen in adult patients. This was observed in clinical studies phase I and phase II. In children, the imatinib dose of 260 mg/m^2 and 340 mg/m^2 attained the same exposure as the adult doses of 400 mg and 800 mg, respectively. A 1.7-fold accumulation of imatinib was shown after recurrent once per day dosing between $AUC_{(0-24)}$ on Day 8 and Day 1 at the dose level of 340 mg/m^2.

Impairment of Organ Function
Imatinib (and metabolites) are not eliminated to a significant degree via the kidneys. Individuals that have impaired renal function (of mild to moderate extent) have a greater plasma exposure in comparison to individuals with regular renal function. The increased plasma exposure is nearly 1.5 to 2 times more than patients with regular renal function and this corresponds to the plasma AGP being elevated by 1.5 times (which imatinib binds to strongly). The drug free clearance for imatinib is most likely comparable between individuals with regular renal function and individuals with renal function that is impaired as excretion of imatinib via the renal pathway in minimal (Please refer to sections 4.2 Dose and Method of Administration, 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties).

Even though the pharmacokinetic analysis results indicated that there is significant inter-subject differences, in individuals with different degrees of liver dysfunction in comparison to individuals with regular liver function, the mean exposure of imatinib did not escalate (Please refer to sections 4.2 Dose and Method of Administration, 4.4 Special Warnings and Precautions for Use, 4.8 Undesirable Effects, 5.1 Pharmacodynamic Properties and 5.2 Pharmacokinetic Properties).

5.3 Preclinical safety data

Evaluations of imatinib have been completed in dose toxicity repetition, genotoxicity, pharmacology safety, and reproductive toxicity studies. The organs focused on with imatinib pharmacological action includes the bone marrow, gastrointestinal tract, gonads, lymphoid tissues and peripheral blood. Other organs targeted are the kidneys and the liver.

In rats, imatinib was embryotoxic and teratogenic. In a preclinical fertility study and an early embryonic development study, fertility was not affected. However, a decreased amount of motile sperm and lower epididymal and testes weights, were detected in the male rats

given a high dose of imatinib. Imatinib did not affect the fertility in the rat offspring (first generation) in the preclinical pre and postnatal studies.

In the rat juvenile development toxicology study (postpartum, days 10-70), there were no additional target organs identified. In the juvenile toxicology study, at the maximum suggested dose of 340 mg/m^2 (0.3 to 2 times the average paediatric dosage), preputial separation and temporary outcomes on the growth and delay in vaginal opening were observed. Juvenile animals that were given the maximum suggested dose of 340 mg/m^2 (2 x the average pediatric dosage), around the weaning stage showed an increase in mortality.

Longevity was significantly reduced, statistically in both male and female rats at an imatinib dose of 60 mg/kg/day and ≥ 30 mg/kg/day, respectively, in a rat carcinogenicity study completed over two years with imatinib given at 15, 30 and 60 mg/kg/day. Histopathological examination showed the main reasons of death were cardiomyopathy (in both male and female rats), preputial gland papilloma and chronic progressive nephropathy in females. Organs targeted for neoplastic changes were the adrenal glands, kidneys, non-glandular stomach, parathyroid gland, preputial and clitoral gland, small intestine, urethra and urinary bladder. Several organs targeted with neoplastic lesions had the following no observed effect levels (NOEL) established: 30 mg/kg/day for the adrenal glands, kidneys, non-glandular stomach, parathyroid glands, small intestine, urethra, and urinary bladder and the NOEL for the preputial and clitoral gland was 15 mg/kg/day.

For the preputial and clitoral gland, the papilloma/carcinoma were observed at 30 and 60 mg/kg/day. This represents approximately 0.4 to 3 times the exposure of imatinib given to children at 340 mg/m^2 (based on AUC) and 0.5 to 4 or 0.3 to 2.4 times the exposure of imatinib given to adults daily at 400 mg per day or 800 mg per day, respectively (based on AUC).

For the adrenal glands, benign and malignant medullary tumours, non-glandular stomach papillomas/carcinomas, parathyroid glands adenomas, renal adenoma/carcinoma, small intestine adenocarcinomas, urethra papilloma and urinary bladder papilloma were all observed at 60 mg/kg/day.

The significance of these rat carcinogenicity study results for humans is unknown. Clinical trials safety data and adverse event reports (spontaneous) analysis did not impart any evidence of malignancies being observed more in individuals given imatinib in comparison to the general population.

In preclinical research, non-neoplastic lesions that were not recognised were the cardiovascular system, endocrine organs, pancreas and teeth. The most significant changes lead to observations of cardiac insufficiency in a few animals which incorporated cardiac hypertrophy and dilatation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, crospovidone, silica-colloidal anhydrous, magnesium stearate.

Capsule cap and body contains gelatin, purified water, iron oxide red (CI 77491), iron oxide yellow (CI 77492), titanium dioxide (CI 77891) and sodium lauryl sulfate.

Does not contain gluten. Does contain lactose.

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf life is 24 months (2 years) from manufacture.

6.4 Special precautions for storage
Store at or below 30°C, protect from moisture.

6.5 Nature and contents of container
100 mg capsules: PVC/PE/PVdC/Al blister packs of 60.
400 mg capsules: PVC/PE/PVdC/Al blister packs of 30 and 60's.

6.6 Special precautions for disposal
No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1	Updated therapeutic indications
4.2	Updated dose and method of administration
4.6	Further information added on section for Fertility, Pregnancy and Lactation