AUSTRALIAN PRODUCT INFORMATION
DASATINIB VIATRIS (DASATINIB) TABLETS

1 NAME OF THE MEDICINE

Dasatinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg, 50 mg, 70 mg or 100 mg dasatinib as the active ingredient.

Excipients with known effect

Sugars as lactose (monohydrate)

For the full list of excipients see section **6.1 List of Excipients**

3 PHARMACEUTICAL FORM

20 mg Tablet:

White to off-white, round, biconvex coated tablet. Engraved “APO” on one side, over “DA” over “20” on the other side.

50 mg Tablet:

White to off-white, oval, bevelled-edged, biconvex coated tablet. Engraved “APO” on one side, “DAS50” on the other side.

70 mg Tablet:

White to off-white, round, biconvex coated tablet. Engraved “APO” on one side, “DA” over “70” on the other side.

100 mg Tablet:

White to off-white, oval, bevelled-edged, biconvex coated tablet. Engraved “APO” on one side, “DAS100” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DASATINIB VIATRIS is indicated for the treatment of adults aged 18 years or over with:

- Newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase
- Chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib
- Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of Administration

To be administered orally. Tablets must not be crushed, cut or chewed in order to minimize risk of dermal exposure, they must be swallowed whole. Tablets can be taken with or without a meal and should be taken consistently either in the morning or the evening.

Dasatinib should not be taken with grapefruit or grapefruit juice (see section **4.5 Interactions with other medicines and other forms of interactions**).

Dosage

The recommended starting dosage of dasatinib for chronic phase CML is 100 mg administered orally once daily. The recommended starting dosage of dasatinib for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg/day administered orally once daily and should be taken consistently either in the morning or the evening.

In clinical studies, treatment with dasatinib was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment on long-term disease outcome after the achievement of a cytogenetic response (including complete cytogenetic response (CCyR) or major molecular response (MMR and MR4.5) has not been investigated.

To achieve the recommended dose, dasatinib is available as 20 mg, 50 mg, 70 mg and 100 mg tablets. Dose increase or reduction is recommended based on patient response and tolerability.

Dose Escalation

In clinical studies in adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a haematological or cytogenetic response at the recommended starting dosage.

Dose Adjustment for Adverse Reactions

<u>Myelosuppression</u>

In clinical studies, myelosuppression was managed by dose interruption, dose reduction or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Haematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications are summarized in Table 1.

Table 1: Dose Adjustments for Neutropenia and Thrombocytopenia

Chronic Phase CML (starting dose 100 mg once daily)	ANC* < 0.5 × 10^9/L and/or Platelets < 50 × 10^9/L	1. Stop dasatinib until ANC ≥ 1.0 x10^9/L and platelets ≥ 50 x 10^9/L. 2. Resume treatment with dasatinib at the original starting dose. 3. If platelets < 25 × 10^9/L and/or recurrence of ANC < 0.5 × 10^9/L for > 7 days, repeat step 1 and resume dasatinib at a reduced dose of 80 mg once daily for second episode. For third episode further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC* < 0.5 × 10^9/L and/or Platelets < 10 × 10^9/L	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, stop dasatinib until ANC ≥ 1.0 × 10^9/L and platelets ≥ 20 × 10^9/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat step 1 and resume dasatinib at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode). 4. If cytopenia is related to leukaemia, consider dose escalation to 180 mg once daily.

*ANC: absolute neutrophil count

Non-Haematological Adverse Reactions

If a moderate (Grade 2) non-haematologic adverse reaction develops with dasatinib, treatment should be interrupted until the adverse reaction has resolved or returned to baseline. The same dose should be resumed if this is the first occurrence and the dose should be reduced if this is a recurrent adverse reaction. If a severe (Grade 3 or 4) non-haematologic adverse reaction develops with dasatinib use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event.

For adult patients with chronic phase CML who received 100 mg once daily, dose reduction to 80 mg once daily with further reduction from 80 mg once daily to 50 mg once daily, if needed, is recommended. For adult patients with advanced phase CML or Ph+ ALL who received 140 mg once daily, dose reduction to 100 mg once daily with further reduction from 100 mg once daily to 50 mg once daily, if needed, is recommended.

Dose reduction for concomitant use of strong CYP3A4 inhibitors

The concomitant use of strong CYP3A4 inhibitors and grapefruit juice with dasatinib should be avoided (see **4.5 Interactions with other medicines and other forms of interactions**). If possible, an alternative concomitant medication with no or minimal enzyme inhibition potential should be selected. If dasatinib must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

• 40 mg daily for patients taking dasatinib 140 mg daily

• 20 mg daily for patients taking dasatinib 100 mg daily

• 20 mg daily for patients taking dasatinib 70 mg daily

For patients taking dasatinib 60 mg or 40 mg daily, consider interrupting dasatinib until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating dasatinib.

These reduced doses of dasatinib are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors. However, clinical data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If dasatinib is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or stop dasatinib until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the dasatinib dose is increased.

Paediatric Population

The safety and efficacy of dasatinib in children and adolescents below 18 years of age have not yet been established. No data are available (see section **4.4 Special warnings and precautions for use**).

Elderly Population

No clinically relevant age-related pharmacokinetic differences have been observed in these patients. No specific dose recommendation is necessary in the elderly (see section **4.4 Special warnings and precautions for use**).

Hepatic impairment

Patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. However, caution is recommended when dasatinib is administered to patients with hepatic impairment (see section **4.4 Special warnings and precautions for use**).

Renal impairment

No clinical trials were conducted with dasatinib in patients with decreased renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine > 3 times the upper limit of the normal range, and studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy excluded patients with serum creatinine concentration > 1.5 times the upper limit of the normal range). Since the renal clearance of dasatinib and its metabolites is < 4 %, a decrease in total body clearance is not expected in patients with renal insufficiency (see section **4.4 Special warnings and precautions for use**).

4.3 CONTRAINDICATIONS

Use of dasatinib is contraindicated in patients with hypersensitivity to dasatinib or to any of the ingredients in this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Myelosuppression

Treatment with dasatinib is associated with thrombocytopenia, neutropenia and anaemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML.

In patients with chronic phase CML, complete blood counts (CBCs) should be performed every two weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated.

In patients with advanced phase CML or Ph+ ALL, CBCs should be performed weekly for the first 2 months and then monthly thereafter or as clinically indicated.

Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily or dose reduction (see section **4.4 Special warnings and precautions, Effect on Laboratory Tests**, below, and section **4.2 Dose and method of administration, Dose adjustment for adverse reactions**). CTC Grade 3 or 4 (severe) cases of anaemia were managed with blood transfusions.

Bleeding

In the pooled population of Phase III studies in patients with chronic phase CML, 5 patients (1 %) receiving dasatinib at the recommended dose 100 mg daily (n = 548) had drug related Grade 3 or 4 haemorrhage. In the pooled population of clinical studies in patients with advanced phase CML or Ph+ ALL, severe (Grade 3–5) drug-related CNS haemorrhage, including fatalities, occurred in 1 % of patients receiving dasatinib at the recommended dose 140 mg daily (n = 304). Eight cases were fatal and 6 of them were associated with Common Toxicity Criteria (CTC) Grade 4 thrombocytopenia. Grade 3 or 4 drug-related gastrointestinal haemorrhage, including fatalities, occurred in 6 % of patients and generally required treatment interruptions and transfusions. Other cases of Grade 3 or 4 drug-related haemorrhage occurred in 2 % of patients treated with dasatinib 140 mg daily dose. Most bleeding reactions in clinical studies were typically associated with Grade 3 or 4 thrombocytopenia. Additionally, *in vitro* and *in vivo* platelet assays suggest that dasatinib treatment reversibly affects platelet activation.

Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

Fluid Retention

Dasatinib is associated with fluid retention. After 5 years of follow-up in the Phase III clinical study in patients with newly diagnosed chronic phase CML (n = 258), drug-related Grade 3 or 4 fluid retention was reported in 13 patients (5 %) receiving dasatinib compared to 2 patients (1 %) receiving imatinib (n = 258) (see section **4.8 Adverse effects (Undesirable effects)**). The cumulative incidence of drug-related pleural effusion (all Grades) in dasatinib-treated subjects increased over time; 7.8 % new adverse effects (AEs) of pleural effusion occurred in the first year of therapy followed by a smaller, yet consistent increase of ~5 % of subjects/year after 24, 36, 48 and 60 months of treatment, respectively. The majority were low grade. In the pooled population of patients with chronic phase CML (n = 548), severe (Grade 3–4) drug-related fluid retention occurred in 32 (6 %) patients receiving dasatinib at the 100 mg once daily recommended dose.

In clinical studies in patients with advanced phase CML or Ph+ ALL receiving dasatinib at the approved dose 140 mg daily (n = 304), Grade 3 or 4 drug-related fluid retention was reported in 8 % of patients, including severe pleural and pericardial effusion reported in 7 % and 1 % of patients, respectively. Severe congestive heart failure/cardiac dysfunction was reported in 1 % of patients. In these patients, severe pulmonary oedema and severe pulmonary hypertension were each reported in 1 % of patients.

Patients who develop symptoms suggestive of pleural effusion or other fluid retention such as new or worsened dyspnoea on exertion or at rest, pleuritic chest pain, or dry cough should be evaluated promptly with chest X-ray or additional diagnostic imaging as appropriate. Fluid retention reactions were typically managed with dasatinib dose interruption or reduction and supportive care measures that may include diuretics or short courses of steroids. Severe pleural effusion may require thoracentesis and oxygen therapy. Dose modification should be considered. While the safety profile of dasatinib in the elderly population was similar to that in the younger population, patients aged 65 years and older are more likely to experience pleural effusion, congestive heart failure, gastrointestinal bleeding and dyspnoea, and should be monitored closely.

Cases of chylothorax have also been reported in patients presenting with pleural effusion. Some cases of chylothorax resolved upon dasatinib discontinuation, interruption or dose reduction but most cases also required additional treatment (see section **4.8 Adverse effects (Undesirable effects)**).

QT Prolongation

In vitro data showing inhibition of the hERG K+ channel expressed in mammalian cells and action potential prolongation in rabbit Purkinje fibres by dasatinib and a number of its metabolites suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT interval).

After 5 years of follow-up in the Phase III study in newly diagnosed chronic phase CML, 1 patient (< 1 %) in each of the dasatinib (n = 258) and imatinib (n = 258) treatment groups had QTc prolongation reported as an adverse reaction. The median changes in QTcF from baseline were 3.0 msec in dasatinib-treated patients compared to 8.2 msec in imatinib-treated patients. One patient (< 1 %) in each group experienced a QTcF > 500 msec. In 865 patients with leukaemia treated with dasatinib in Phase II, single-arm clinical studies, the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4–6 msec; the upper 95 % confidence intervals for all mean changes from baseline were < 7 msec. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy treated with dasatinib, 15 (1 %) had QT prolongation reported as an adverse reaction. Twenty-one (21) of these patients (1 %) experienced a QTcF > 500 msec.

Dasatinib should be administered with caution in patients who have or may develop prolongation of QTc. These include patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products which lead to QT prolongation and cumulative high dose anthracycline therapy. Hypokalaemia or hypomagnesaemia should be corrected prior to dasatinib administration.

Cardiac Adverse Reactions

Dasatinib was studied in a randomized trial of 519 patients with newly diagnosed CML in chronic phase which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction (1.9 %), pericardial effusion (4.3 %), arrhythmias (1.2 %), palpitations (1.9 %), QT prolongation (0.4 %) and myocardial infarction (0.4 %) (including fatal) were reported in patients taking dasatinib (n = 258). Adverse cardiac reactions were more frequent in patients with risk factors or a previous medical history of cardiac disease. Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately.

Patients with uncontrolled or significant cardiovascular disease were not included in the clinical studies.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), confirmed by right heart catheterization, has been reported in association with dasatinib treatment. In these cases, PAH was reported after initiation of dasatinib therapy, including after more than one year of treatment. Patients with PAH reported during dasatinib treatment were often taking concomitant medications or had co-morbidities in addition to the underlying malignancy.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib therapy. Patients who develop dyspnoea and fatigue after initiation of therapy should be evaluated for more common etiologies including pleural effusion, pulmonary oedema, anaemia, or lung infiltration. During this evaluation, guidelines for non-

hematologic adverse reactions should be followed (see section **4.2 Dose and method of administration, Dose adjustment for adverse reactions**): if the adverse reaction is severe, treatment must be withheld until the event has resolved or improved. If no alternative diagnosis is found, the diagnosis of PAH should be considered. If PAH is confirmed, dasatinib should be permanently discontinued. Follow up should be performed according to standard practice guidelines. Improvements in hemodynamic and clinical parameters have been observed in dasatinib treated patients with PAH following cessation of dasatinib therapy.

Thrombotic microangiopathy (TMA)

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

Hepatitis B Virus Reactivation

BCR-ABL TKIs have been associated with hepatitis B virus (HBV) reactivation including individual case reports for dasatinib. In some instances, HBV reactivation occurring in conjunction with other BCR-ABL TKIs resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Screening for HBV should be considered in accordance with published guidelines before starting therapy with dasatinib. Consultation with a physician with expertise in the treatment of HBV is recommended for patients who test positive for HBV serology.

Patients who are carriers of HBV and require treatment with BCR-ABL TKIs should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop reactivation of HBV while receiving dasatinib, prompt consultation with a physician with expertise in the treatment of HBV is recommended.

Severe Dermatological Reactions

Individual cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported with the use of dasatinib. Dasatinib should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified.

Lactose Content

This medicine contains 141 mg lactose in a 100 mg daily dose and 197 mg lactose in a 140 mg daily dose.

Hepatotoxicity

Dasatinib may cause hepatotoxicity as measured by elevations in bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (see **4.8 Adverse effects (Undesirable effects)**). Monitor transaminases at baseline and monthly or as clinically indicated during treatment. Reduce dose, withhold, or permanently discontinue dasatinib based on severity. When dasatinib is administered in combination with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Monitor hepatic function when dasatinib is used in combination with chemotherapy.

Paediatric use

The safety and efficacy of dasatinib in patients < 18 years of age have not been established.

Use in the elderly

Of the 2,712 patients in clinical studies of dasatinib, 617 (23 %) were 65 years of age and older and 123 (5 %) were 75 years of age and older.

Patients aged 65 years and older are more likely to experience the commonly reported adverse reactions appetite disturbance (14.5 % vs 8.0 %), fatigue (27.4 % vs 19.7 %), pleural effusion (46.2 vs 28.4), cough (13.6 % vs 8.4 %) and dyspnoea (34.5 % vs 17.7 %), and more likely to experience the less frequently reported adverse events abdominal distention (3.9 % vs 2.9 %), dizziness (7.1 % vs 4.6 %), lower gastrointestinal haemorrhage (2.4 % vs 0.7 %), pericardial effusion (7.6 % vs 4.9 %), congestive heart failure (3.1 % vs 0.7 %) and weight decrease (7.5 % vs 3.7 %), and should be monitored closely.

Comparisons based on efficacy are based on limited number of subjects in specific age groups in individual studies, however similar rates of cCCyR and MMR were observed between older and younger patients.

Effects on laboratory tests

Haematology and Biochemistry in Patients with Newly Diagnosed Chronic Phase CML

The comparative frequency of Grade 3 and 4 laboratory abnormalities in patients with newly diagnosed chronic phase CML is presented in Table 2. There were no discontinuations of dasatinib therapy due to the biochemical laboratory parameters.

Table 2: CTC Grade 3/4 Laboratory Abnormalities in a Phase III Study of Patients with Newly Diagnosed Chronic Phase

	Dasatinib (n = 258)	Imatinib (n = 258)
	Percent (%) of Patients	
Haematology Parameters		
Neutropenia	29	24
Thrombocytopenia	22	14
Anaemia	13	9
Biochemistry Parameters		
Hypophosphataemia	7	31
Hypokalaemia	0	3
Hypocalcaemia	4	3
Elevated SGPT (ALT)	< 1	2
Elevated SGOT (AST)	< 1	1
Elevated Bilirubin	1	0
Elevated Creatinine	1	1

CTC grades:

- neutropenia (Grade 3 ≥ 0.5 – < 1.0 × 10^9/L, Grade 4 < 0.5 × 10^9/L;
- thrombocytopenia (Grade 3 ≥ 25 – < 50 × 10^9/L, Grade 4 < 25 × 10^9/L);
- anaemia (haemoglobin Grade 3 ≥ 65 – < 80 g/L, Grade 4 < 65 g/L);
- elevated creatinine (Grade 3 > 3 – 6× upper limit of normal range (ULN), Grade 4 > 6× ULN);
- elevated bilirubin (Grade 3 > 3 – 10× ULN, Grade 4 > 10× ULN);
- elevated SGOT or SGPT (Grade 3 > 5 – 20× ULN, Grade 4 > 20× ULN);
- hypocalcaemia (Grade 3 < 7.0 – 6.0 mg/dL, Grade 4 < 6.0 mg/dl);
- hypophosphataemia (Grade 3 < 2.0 – 1.0 mg/dL, Grade 4 < 1.0 mg/dL);
- hypokalaemia (Grade 3 < 3.0 – 2.5 mmol/L, Grade 4 < 2.5 mmol/L).

Haematology and Biochemistry in Patients with Resistance or Intolerance to Prior Imatinib Therapy

Table 3 shows laboratory findings from clinical trials in CML patients with imatinib resistance or intolerance received at 24 months of follow up.

Table 3: CTC Grades 3/4 Laboratory Abnormalities in Studies of Patients with CML Resistant or Intolerant to Prior Imatinib Therapy[a]

	Chronic Phase[b] (n = 165)	Accelerated Phase[c] (n = 157)	Myeloid Blast Phase[c] (n = 74)	Lymphoid Blast Phase[c] (n = 33)	Ph+ ALL[c] (n = 40)
	Percent (%) of Patients				
Haematology Parameters					
Neutropenia	35	58	77	79	67
Thrombocytopenia	23	63	78	85	72
Anaemia	13	47	74	52	36
Biochemistry Parameters					
Hypophosphataemia	10	13	12	18	16
Hypokalaemia	2	7	11	15	8
Hypocalcaemia	< 1	4	9	12	5
Elevated SGPT (ALT)	0	2	5	3	8
Elevated SGOT (AST)	< 1	0	4	3	3
Elevated Bilirubin	< 1	1	3	6	3
Elevated Creatinine	0	2	8	0	0

a Phase III dose optimisation study results reported at 2 years study follow up.
b CA 180-034 study results in recommended starting dose of 100 mg once daily.
c CA 180-035 study results in recommended starting dose of 140 mg once daily.

CTC grades:
neutropenia (Grade 3 ≥ 0.5–< 1.0 × 10^9/L, Grade 4 < 0.5 × 10^9/L);
thrombocytopenia (Grade 3 ≥ 25–< 50 × 10^9/L, Grade 4 < 25 × 10^9/L);
anaemia (hemoglobin Grade 3 ≥ 65–< 80 g/L, Grade 4 < 65 g/L);
elevated creatinine (Grade 3 > 3–6× upper limit of normal range (ULN), Grade 4 > 6× ULN);
elevated bilirubin (Grade 3 > 3–10× ULN, Grade 4 > 10× ULN);
elevated SGOT or SGPT (Grade 3 > 5–20× ULN, Grade 4 > 20× ULN);
hypocalcaemia (Grade 3 < 7.0–6.0 mg/dL, Grade 4 < 6.0 mg/dL);
hypophosphataemia (Grade 3 < 2.0–1.0 mg/dL, Grade 4 < 1.0 mg/dL);
hypokalaemia (Grade 3 < 3.0–2.5 mmol/L, Grade 4 < 2.5 mmol/L).

Myelosuppression was commonly reported in all patient populations. In newly diagnosed chronic phase CML, myelosupression was less frequently reported than in chronic phase CML patients with resistance or intolerance to prior imatinib therapy. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia and anaemia was higher in patients with advanced CML or Ph+ ALL than in chronic phase CML.

In patients who experienced Grade 3 or 4 myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 2 % of newly diagnosed chronic phase CML patients in the Phase III study and in 5 % of patients with resistance or intolerance to prior imatinib therapy in the Phase III study.

Grade 3 or 4 elevations in transaminases or bilirubin and Grade 3 or 4 hypocalcaemia, hypokalaemia, and hypophosphataemia were reported in all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. In general, decreased calcium levels were not associated with clinical symptoms. Patients developing Grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation.

Use in hepatic impairment

Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose (see sections **4.2 Dose and method of administration** and **5.2 Pharmacokinetic properties, Special Populations**). Due to the limitations of this clinical study, caution is recommended when dasatinib is administered to patients with hepatic impairment.

Use in renal impairment

There are currently no clinical studies with dasatinib in patients with impaired renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine > 3 times the upper limit of the normal range, and clinical studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy have excluded patients with serum creatinine concentration > 1.5 times the upper limit of the normal range). Dasatinib and its metabolites are minimally excreted via the kidney. Since the renal excretion of unchanged dasatinib and its metabolites is < 4 %, a decrease in total body clearance is not expected in patients with renal insufficiency.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs that May Increase Dasatinib Plasma Concentrations

CYP3A4 Inhibitors

In vitro, dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, lopinavir, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving treatment with dasatinib, systemic administration of a potent CYP3A4 inhibitor is not recommended. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, the patient should be closely monitored for toxicity (see section **4.2 Dose and method of administration**).

Drugs that May Decrease Dasatinib Plasma Concentrations

CYP3A4 Inducers

Drugs that induce CYP3A4 activity may increase metabolism and decrease dasatinib plasma concentration. Therefore, concomitant use of potent CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) with dasatinib is not recommended. In healthy subjects, the concomitant use of dasatinib and rifampicin, a potent CYP3A4 inducer, resulted in a five-fold decrease in dasatinib exposure. In patients for whom rifampicin or other CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used. Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Antacids

Non-clinical data demonstrate that the solubility of dasatinib is pH dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with dasatinib reduced the AUC of a single dose of dasatinib by 55 % and the C_{max} by 58 %. However, when antacids were administered 2 hours prior to a single dose of dasatinib, no relevant changes in dasatinib, concentration or exposure were observed. Thus, antacids may

be administered up to 2 hours prior to or 2 hours following dasatinib. Simultaneous administration of dasatinib with antacids should be avoided.

Histamine-2 Antagonists/Proton Pump Inhibitors

Long-term suppression of gastric secretion by histamine-2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of histamine-2 antagonists or proton pump inhibitors with dasatinib is not recommended. In a single- dose study in healthy subjects, the administration of famotidine 10 hours prior to a single dose of dasatinib reduced dasatinib exposure by 61 %. The use of antacids should be considered in place of histamine-2 antagonists or proton pump inhibitors in patients receiving dasatinib therapy.

Drugs that May have their Plasma Concentration Altered by Dasatinib

CYP3A4 Substrates

In a study in healthy subjects, a single 100 mg dose of dasatinib increased exposure to simvastatin, a known CYP3A4 substrate, by 20 %. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving dasatinib (see section **5.1 Pharmacodynamic properties, Mechanism of action**).

Other interactions

In vitro data indicate a potential risk for interaction with CYP2C8 substrates, such as glitazones.

No specific drug interaction studies between dasatinib and chemotherapy regimens routinely used in newly diagnosed Ph+ ALL patients have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Dasatinib did not affect male or female fertility in a conventional rat fertility and early embryonic development study at approximately 1x human clinical exposure (100 or 140 mg dose). However, embryolethality was evident when dams were treated at these doses. Dasatinib caused atrophy/ degeneration of the testis in rats and monkeys and an increase in the number of corpora lutea in the ovaries in rats at doses producing plasma exposure levels below or close to that anticipated in patients receiving dasatinib therapy. Data evaluating reproductive toxicity in male patients taking dasatinib is limited (see section **4.6 Fertility, pregnancy and lactation, Use in pregnancy**).

Use in pregnancy

Category D

Dasatinib may cause fetal harm when administered to a pregnant woman (see section **4.6 Fertility, pregnancy and lactation, Embryofetal Toxicity**). In non-clinical studies, at exposure levels that are readily achievable in humans receiving therapeutic doses of 100 mg of dasatinib serious embryo fetal toxicity was observed in both pregnant rats and rabbits. Malformations (including skeletal alterations) and fetal death were observed in rats treated with dasatinib.

Dasatinib is therefore not recommended for use in women who are pregnant or contemplating pregnancy. Women must be advised to avoid becoming pregnant while on therapy. If dasatinib

is used during pregnancy, or if the patient becomes pregnant while taking dasatinib, the patient should be apprised of the potential hazard to the fetus.

The potential effects of dasatinib on sperm have been evaluated in an oral study of fertility and early embryonic development in rats. Dasatinib is not a reproductive toxicant in male rats at clinically relevant exposures (see section **4.6 Fertility, pregnancy and lactation, Effects on Fertility**). However, data evaluating reproductive toxicity in male patients taking dasatinib are limited.

Sexually active male or female patients of child bearing potential taking dasatinib should use adequate contraception.

Embryofetal Toxicity

Dasatinib can cause fetal harm when administered to a pregnant woman. There have been post-marketing reports of spontaneous abortion and fetal and infant anomalies from women who have taken dasatinib during pregnancy.

Use in lactation

It is unknown whether dasatinib is excreted in human milk. Women who are taking dasatinib should not breastfeed. In an exploratory peri- and post-natal development study in rats, dasatinib was detectable in the plasma of breast-fed pups with levels 30–40 % of the maternal levels. Pleural effusion and deaths were seen in maternally-exposed rat pups, indicating indirect exposure of dasatinib was incompatible with pup survival, even at sub-therapeutic maternal exposure.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The data described below reflect exposure to dasatinib at all doses studied in 324 patients with newly diagnosed chronic phase CML and in 2,388 patients with imatinib resistant or intolerant chronic or advanced phase CML or Ph+ ALL. The median duration of therapy in 2,712 dasatinib treated patients was 19.2 months (range 0–93.2 months).

In the Phase III study of patients with newly diagnosed chronic phase CML the median duration of therapy was approximately 60 months for both dasatinib (range 0.03–72.7 months) and imatinib (range 0.3–74.6 months). The median duration of therapy in 1,618 patients with chronic phase CML was 29 months (range 0–92.9 months). In 1,094 patients with advanced phase CML or Ph+ ALL, the median duration of treatment for patients was 6.2 months (range 0–93.2 months).

The majority of patients treated with dasatinib, regardless of dose or schedule, experienced adverse reactions at some time. In the overall population of 2,712 dasatinib-treated subjects, 520 (19 %) experience adverse drug reactions leading to treatment discontinuation.

In the Phase III study in patients with newly diagnosed chronic phase CML, treatment was discontinued for drug-related adverse reactions in 14 % of dasatinib-treated patients and 7 % of imatinib-treated patients with a minimum of 60 months follow-up. Among the pooled population of 1,618 dasatinib-treated subjects with chronic phase CML, adverse reactions leading to discontinuation were reported in 329 (20.3 %) subjects, and among the 1,094 dasatinib-treated subjects with advanced phase disease, adverse drug reactions leading to discontinuation were reported in 191 (17.5 %) subjects.

The majority of imatinib-intolerant patients in chronic phase CML were able to tolerate treatment with dasatinib. In clinical studies with 24 months minimum follow-up in chronic phase CML, 10 of the 215 imatinib-intolerant patients had the same Grade 3 or 4 non-haematological toxicity with dasatinib as they did with prior imatinib; 8 of the 10 patients were managed with dose reduction and were able to continue dasatinib treatment.

Adverse reactions reported in ≥ 10 % of patients, and other adverse reactions of interest, in a Phase III trial of newly diagnosed chronic phase CML at a median follow-up of approximately 60 months are presented in Table 5. In this study, drug-related pleural effusion was reported in 73 patients (28 %) receiving dasatinib. The median time to onset for Grade 1 or 2 pleural effusion events was 114 weeks (range 4–299 weeks). Fewer than 3 % of pleural effusion events were Grade 3 or 4. The cumulative incidence of drug-related pleural effusion (all grades) in dasatinib-treated subjects increased over time; the majority are low grade. With appropriate medical care, 58 patients (80 % of those with pleural effusion) were able to continue on dasatinib (see sections **4.4 Special warnings and precautions for use** and **4.2 Dose and method of administration**).

The most frequently reported adverse reactions in dasatinib-treated patients with resistance or intolerance to prior imatinib therapy were fluid retention (including pleural effusion), diarrhoea, nausea, headache, skin rash, dyspnoea, haemorrhage, fatigue, musculoskeletal pain, infection, vomiting, cough, abdominal pain and pyrexia. In the Phase III study in patients with resistance or intolerance to prior imatinib therapy, drug-related febrile neutropenia was reported in 2.1 % of dasatinib-treated patients.

Based on 2-year pooled data, the use of dasatinib is associated with fluid retention with Grade 3 and 4 cases in 11 % of patients with resistance or intolerance to prior imatinib therapy. Grade 3 or 4 pleural and pericardial effusion were reported in 7 % and 2 % of patients. Severe congestive heart failure/cardiac dysfunction was reported in 2% of patients. Grade 3 or 4 ascites and generalised oedema were each reported in < 1 %. One percent of patients experienced Grade 3 or 4 pulmonary oedema. Fluid retention reactions were typically managed by supportive care measures that include diuretics or short courses of steroids (see section **4.4 Special warnings and precautions for use**).

Bleeding drug-related events, ranging from petechiae and epistaxis to Grade 3 or 4 gastrointestinal haemorrhage and CNS bleeding, were reported in patients taking dasatinib. In the Phase III study in patients with newly diagnosed chronic phase CML, 2 patients (1 %) receiving dasatinib compared to 3 patients (1 %) receiving imatinib had Grade 3 or 4 haemorrhage. Based on 2-year pooled data for clinical studies in patients with resistance or intolerance to prior imatinib therapy, severe CNS haemorrhage occurred in < 1 % of patients. Eight cases were fatal and 6 of them were associated with CTC Grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 4 % of patients with resistance or intolerance to prior imatinib therapy and generally required treatment interruption and transfusions. Other Grade 3 or 4 haemorrhage occurred in 2 % of patients with resistance or intolerance to prior imatinib therapy. Most bleeding related events in these patients were typically associated with Grade 3 or 4 thrombocytopenia. Additionally, *in vitro* and *in vivo* platelet assays suggest that dasatinib treatment reversibly affects platelet activation.

Treatment with dasatinib is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML.

QT Prolongation: in the Phase III study in patients with newly diagnosed chronic phase CML, one patient (< 1 %) of the dasatinib-treated patients, and one patient (< 1 %) of the imatinib-treated patients had a QTcF > 500 msec (see section **4.4 Special warnings and precautions for use**).

Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (see section **4.4 Special warnings and precautions for use**).

In clinical trials with patients with resistance or intolerance to prior imatinib therapy, it was recommended that treatment with imatinib be discontinued at least 7 days before starting treatment with dasatinib.

The comparative frequency of adverse reactions (excluding laboratory abnormalities) that were reported in at least 10 % of the patients with newly diagnosed chronic phase CML are presented in Table 4.

Table 4: Adverse Reactions Reported in ≥ 10 % of Patients in a Phase III Study (Newly Diagnosed Chronic Phase CML, 60-month minimum follow-up)

	All Grades		Grade 3/4	
	Dasatinib (n = 258)	**Imatinib (n = 258)**	**Dasatinib (n = 258)**	**Imatinib (n = 258)**
Preferred Term	**Percent (%) of Patients**			
Fluid Retention[e]	39	45	5	1
Superficial localised oedema	14	38	0	< 1
Pleural effusion	28	1	3	0
Generalised oedema	4	7	0	0
Pericardial effusion	4	1	1	0
Congestive heart failure/cardiac dysfunction[a]	2	1	< 1	< 1
Pulmonary hypertension	5	1	< 1	0
Pulmonary oedema	1	0	0	0
Diarrhoea	22	23	1	1
Nausea	10	25	0	0
Abdominal pain	11	8	0	< 1
Vomiting	5	12	0	0
Headache	13	11	0	0
Rash[b]	14	18	0	2
Fatigue	11	12	< 1	0
Musculoskeletal pain	14	17	0	< 1
Myalgia	7	12	0	0
Arthralgia	7	10	0	< 1
Muscle spasm	5	21	0	< 1
Haemorrhage[c]	7	7	1	1
Gastrointestinal bleeding	2	1	1	0
Other bleeding[d]	6	6	0	1

a Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased and left ventricular dysfunction.

b Includes erythema, erythema multiforme, rash, rash generalised, rash macular, rash papular, rash pustular, skin exfoliation and rash vesicular.

c Important adverse reaction of special interest with < 10 % frequency.

d Includes conjunctival haemorrhage, ear haemorrhage, ecchymosis, epistaxis, eye haemorrhage, gingival bleeding, haematoma, haematuria, haemoptysis, intra-abdominal haematoma, petechiae, scleral haemorrhage, uterine haemorrhage and vaginal haemorrhage.

e Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as “fluid retention”.

A comparison of cumulative rates of selected adverse reactions in the Phase III study of newly diagnosed patients with chronic phase CML with minimum follow-up of one and five years are shown in Table 5.

Table 5: Selected Adverse Drug Reactions Reported in a Phase III Study [Newly Diagnosed Chronic Phase CML (n = 258)]

	Minimum of 1 Year Follow up		Minimum of 5 Years Follow up	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**
Preferred Term	**Percent (%) of Patients**			
Fluid Retention[f]	19	1	39	5
Pleural effusion	8	0	28	3
Superficial localised oedema	9	0	14	0
Face Oedema	6	0	10	0
Pulmonary hypertension	1	0	5	< 1
Generalised oedema	2	0	4	0
Pericardial effusion	1	< 1	4	1
Congestive heart failure/cardiac dysfunction[a]	2	< 1	2	1
Pulmonary oedema	< 1	0	1	0
Diarrhoea	17	< 1	22	1
Musculoskeletal pain	11	0	14	0
Rash[b]	11	0	14	0
Headache	12	0	14	0
Fatigue	8	< 1	11	< 1
Nausea	8	0	12	0
Myalgia	6	0	7	0
Arthralgia	5	0	7	0
Haemorrhage[c]	5	< 1	8	1
Gastrointestinal bleeding	1	< 1	2	1
Other bleeding[d]	4	0	6	0
Vomiting	5	0	5	0
Muscle spasm[e]	4	0	5	0

a Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased and left ventricular dysfunction.

b Includes erythema, erythema multiforme, rash, rash generalised, rash macular, rash papular, rash pustular, skin exfoliation and rash vesicular.

c Adverse reaction of special interest with < 10 % frequency.

d Includes conjunctival haemorrhage, ear haemorrhage, ecchymosis, epistaxis, eye haemorrhage, gingival bleeding, haematoma, haematuria, haemoptysis, intra-abdominal haematoma, petechiae, scleral haemorrhage, uterine haemorrhage and vaginal haemorrhage.

e In the 60-month analysis the term “muscle inflammation” was re-mapped to “muscle spasm”.

f Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as “fluid retention”.

In the Phase III dose-optimisation study in patients with chronic phase CML resistant or intolerant to imatinib, the overall median duration of therapy was approximately 30 months (range < 1–93 months), with a median duration in the 100 mg once daily group of 37 months (range 1–91 months). The study evaluated once daily and twice daily dosage regimens (100 mg and 140 mg once daily, and 50 mg and 70 mg twice daily). Following Year 2 analysis many patients switched to once daily dosing regimens during the subsequent extension of the study. Cumulative rates of selected adverse reactions that were reported in the 100 mg once daily recommended starting dose (n = 165) are shown in Table 6.

Table 6: Adverse Drug Reactions reported in Phase III Dose-Optimisation Study – Chronic Phase CML (Imatinib Intolerant or Resistant Chronic Phase CML)[a] (n = 165)

	Minimum of 2 Years Follow Up		Minimum of 5 Years Follow Up		Minimum of 7 Years Follow Up	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred Term	**Percent (%) of Patients**					
Diarrhoea	21	2	28	2	28	2
Fluid Retention[b]	34	4	42	6	48	7
Superficial oedema	18	0	21	0	22	0
Pleural effusion	18	2	24	4	28	5
Generalised oedema	3	0	4	0	4	0
Pericardial effusion	2	1	2	1	3	1
Pulmonary hypertension	0	0	0	0	2	1
Haemorrhage	11	1	11	1	12	1
Gastrointestinal bleeding	2	1	2	1	2	1

a Phase III dose optimisation study results reported in recommended starting dose of 100 mg once daily (n = 165) population.

b Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as “fluid retention”.

In the Phase III dose-optimisation study in patients with advanced phase CML and Ph+ ALL, the median duration of treatment was 14 months (range < 1–36 months) for accelerated phase CML; 3 months (range < 1–32 months) for myeloid blast CML; 4 months (< 1–22 months) for lymphoid blast CML; and 3 months (< 1–29 months) for Ph+ ALL. Selected adverse drug reactions that were reported at the recommended starting dose of 140 mg once daily are shown in Table 7. A 70 mg twice daily regimen was also studied. At Year 2 analysis, the 70 mg twice daily regimen showed a comparable efficacy profile to the 140 mg once daily regimen, but a less favourable safety profile; particularly the fluid retention (pleural effusion and pericardial effusion) was reported less frequently in patients treated with dasatinib 140 mg once daily than in those treated with 70 mg twice daily.

Table 7: Selected Adverse Drug Reactions Reported in a Phase III Dose Optimisation Study - Advanced Phase CML and Ph+ ALL

	140 mg once daily[a] (n = 304)	
	All Grades	**Grade 3/4**
Preferred Term	**Percent (%) of Patients**	
Diarrhoea	28	3
Fluid Retention[c]	33	7
Superficial oedema	15	< 1
Pleural Effusion	20	6
Generalised oedema	2	0
Congestive heart failure/cardiac dysfunction[b]	1	0
Pericardial effusion	2	1
Pulmonary oedema	1	1
Haemorrhage	23	8
Gastrointestinal bleeding	8	6

a Phase III dose optimisation study results reported at the recommended starting dose of 140 mg once daily (n = 304) population at 2 year final study follow up.

b Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

c Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as “fluid retention”.

The following adverse reactions, excluding laboratory abnormalities, were reported in patients in dasatinib clinical trials. These reactions are presented by system organ class and by frequency. Frequencies are defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<u>Investigations</u>

Common: weight decreased, weight increased

Uncommon: blood creatine phosphokinase increased, Gamma-glutamyltransferase increased

<u>Cardiac disorders</u>

Common: congestive heart failure/cardiac dysfunction[c], pericardial effusion, arrhythmia (including tachycardia), palpitations

Uncommon: myocardial infarction (including fatal outcomes), electrocardiogram QT prolonged, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased

Rare: cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis

Blood and lymphatic system disorders

Very common: myelosuppression (including anaemia, neutropenia, thrombocytopenia)

Common: febrile neutropenia

Uncommon: lymphadenopathy, lymphopenia

Rare: aplasia pure red cell

Nervous system disorders

Very common: headache

Common: neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence

Uncommon: CNS bleeding[b], syncope, tremor, amnesia, balance disorder

Rare: cerebrovascular accident, transient ischemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia

Eye disorders

Common: visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye

Uncommon: conjunctivitis, visual impairment, photophobia, lacrimation increased

Ear and labyrinth disorders

Common: tinnitus

Uncommon: hearing loss, vertigo

Respiratory, thoracic and mediastinal disorders

Very common: pleural effusion, dyspnoea

Common: pulmonary oedema, pulmonary hypertension, lung infiltration, pneumonitis, cough

Uncommon: bronchospasm, asthma, dysphonia, pulmonary arterial hypertension

Rare: acute respiratory distress syndrome, pulmonary embolism

Gastrointestinal disorders

Very common: diarrhoea, vomiting, nausea, abdominal pain

Common: gastrointestinal bleeding (including fatal), colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder

Uncommon: pancreatitis, upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia, gastro-oesophageal reflux disease

Rare: protein-losing gastroenteropathy, ileus, pancreatitis acute, anal fistula

Renal and urinary disorders

Uncommon: renal failure, urinary frequency, proteinuria

Rare: renal impairment

Skin and subcutaneous tissue disorders

Very common: skin rash[e]

Common: alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis

Uncommon: neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder

Rare: leukocytoclastic vasculitis, skin fibrosis

Musculoskeletal and connective tissue disorders

Very common: musculoskeletal pain

Common: arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm

Uncommon: rhabdomyolysis, tendonitis, muscle inflammation, osteonecrosis, arthritis

Rare: epiphyses delayed fusion[g], growth retardation[g]

Metabolism and nutrition disorders

Common: appetite disturbances[a], hyperuricaemia

Uncommon: dehydration, hypoalbuminaemia, hypercholesterolemia, tumour lysis syndrome

Rare: diabetes mellitus

Infections and infestations

Very common: infection (including bacterial, viral, fungal, non-specified)

Common: pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including uncommon reports of fatal outcome)

Injury, poisoning, and procedural complications

Common: contusion

Vascular disorders

Very common: haemorrhage[d]

Common: hypertension, flushing

Uncommon: hypotension, thrombophlebitis, thrombosis

Rare: deep vein thrombosis, embolism, livedo reticularis

Not known: thrombotic microangiopathy

General disorders and administration site conditions

Very common: peripheral oedema[g] fatigue, face oedema[h], pyrexia

Common: asthenia, pain, chest pain, generalised oedema[i], chills

Uncommon: malaise, other superficial oedema[j]

Rare: gait disturbance

Immune system disorders

Uncommon: hypersensitivity (including erythema nodosum)

Rare: anaphylactic shock[k]

Endocrine disorders

Uncommon: hypothyroidism

Rare: hyperthyroidism, thyroiditis

Hepatobiliary disorders

Uncommon: hepatitis, cholecystitis, cholestasis

Reproductive system and breast disorders

Uncommon: gynecomastia, menstrual disorder

Pregnancy, puerperium and perinatal conditions

Rare: abortion

Psychiatric disorders

Common: depression, insomnia

Uncommon: anxiety, confusional state, affect lability, libido decreased

a Includes decreased appetite, early satiety, increased appetite

b Includes central nervous system haemorrhage, cerebral haematoma, cerebral haemorrhage, extradural haematoma, haemorrhage intracranial, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.

c Includes brain natriuretic peptide increased, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, ventricular failure, left ventricular failure, right ventricular failure, and ventricular hypokinesis.

d Excludes gastrointestinal bleeding and CNS bleeding; these ADRs are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.

e Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriasis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, toxic skin eruption, urticaria vesiculosa, and vasculitic rash.

f Reported only in paediatric studies. Frequency reported as common in paediatric studies vs rare in overall monotherapy population.

g Includes gravitational oedema, localised oedema, oedema peripheral.

h Includes conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbital oedema, swelling face.

i Includes fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, peripheral swelling (reported only in paediatric studies), oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.

j Includes genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling.

k Reported only in paediatric studies.

Postmarketing Experience

The following additional adverse events have been identified during post approval use of dasatinib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations:	hepatitis B reactivation
Cardiac disorders:	atrial fibrillation/atrial flutter[a]
Respiratory, thoracic and mediastinal disorders:	interstitial lung disease, pleural effusion, chylothorax.
Skin and subcutaneous tissue disorders:	Stevens-Johnson syndrome[b]
Renal and urinary disorders:	nephrotic syndrome
Hepatobiliary disorders:	hepatotoxicity

a Typically reported in elderly patients or in patients with confounding factors including significant underlying or concurrent cardiac or cardiovascular disorders, or other significant comorbidities (e.g. severe infection/sepsis, electrolyte abnormalities).

b In the post-marketing setting, individual cases of Stevens-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to dasatinib or to concomitant medications.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

Experience with overdose of dasatinib in clinical studies is limited to isolated cases. The highest overdosage of 280 mg per day for one week was reported in two patients and both developed a significant decrease in platelet counts. Since dasatinib is associated with severe myelosuppression, patients who ingest more than the recommended dosage should be closely monitored for myelosuppression and given appropriate supportive treatment.

Treatment

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dasatinib is a potent inhibitor of multiple oncogenic kinases, cellular enzymes involved in the transmission of growth signals from the cell membrane to the nucleus. Dasatinib inhibits the activity of the BCR-ABL kinase and SRC-family kinases at low nanomolar or subnanomolar concentrations. Dasatinib also inhibits a number of other kinases including c-KIT, the EPHA2 receptor and the PDGFβ receptor. Unlike imatinib, it binds not only to the inactive but also to the active conformation of the BCR-ABL kinase. This suggests a reduced propensity for acquired drug resistance due to the emergence of mutations that promote the adoption of kinase's active conformation.

Dasatinib has been demonstrated to inhibit the survival/proliferation of human leukaemic cell lines *in vitro* and to inhibit the growth of human chronic myeloid leukaemia (CML) xenografts in SCID mice, in both imatinib-sensitive and resistant models of the disease. Antileukaemic activity was seen in dasatinib-treated mice in a model of CML with CNS involvement. Non-clinical studies show that dasatinib can overcome imatinib resistance resulting from BCR-ABL independence, most BCR-ABL kinase domain mutations, activation of alternate signalling pathways involving SRC-family kinases (LYN and FYN) and P-glycoprotein (multi-drug resistance protein 1) overexpression.

Clinical trials

In the Phase I study, haematological and cytogenetic responses were observed in all phases of CML and in Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) (Ph+ ALL) in the first 84 patients treated and followed for up to 27 months. Responses were durable across all phases of CML and Ph+ ALL.

Four single-arm, uncontrolled, open-label Phase II clinical trials were conducted to determine the safety and efficacy of dasatinib in patients with CML in chronic, accelerated or myeloid blast phase, who were either resistant or intolerant to imatinib.

One randomized, comparative trial was conducted in chronic phase patients who failed initial treatment with 400 or 600 mg imatinib. The starting dose of dasatinib was 70 mg twice daily. Dose modifications were allowed for improving activity or management of toxicity.

Two randomized, open-label Phase III trials were conducted to evaluate the efficacy of dasatinib administered once daily compared with dasatinib administered twice daily. In addition, one open-label, randomized, comparative Phase III study was conducted in adult patients with newly diagnosed chronic phase CML.

The efficacy of dasatinib is based on haematological and cytogenetic response rates. Durability of response and estimated survival rates provide additional evidence of dasatinib clinical benefit.

A total of 2,712 patients were evaluated in clinical trials of CML; of these 23 % were ≥ 65 years of age and 5 % were ≥ 75 years of age.

Chronic Phase CML – Newly Diagnosed

An international open-label, multi-centre, randomized, comparative Phase III study was conducted in adult patients with newly diagnosed chronic phase CML. Patients were randomized to receive either dasatinib 100 mg once daily or imatinib 400 mg once daily. The primary end-point was the rate of confirmed complete cytogenetic response (cCCyR) within 12 months. Secondary endpoints included time in cCCyR (measure of durability of response), time to cCCyR, major molecular response (MMR) rate, time to MMR, progression free survival (PFS) and overall survival (OS). Other relevant efficacy results included CCyR and complete molecular response (CMR) rates.

A total of 519 patients were randomized to a treatment group: 259 to dasatinib and 260 to imatinib. Baseline characteristics were well balanced between the two treatment groups with respect to age (median age was 46 years for the dasatinib group and 49 years for the imatinib group with 10 % and 11 % of patients 65 years of age or older, respectively), gender (women 44 % and 37 %, respectively), and race (Caucasian 51 % and 55 %; Asian 42 % and 37 %, respectively). At baseline, the distribution of Hasford Scores was similar in the dasatinib and imatinib treatment groups (low risk, 33 % and 34 %; intermediate risk, 48 % and 47 %; high risk, 19 % and 19 %; respectively).

With a minimum of 12 months follow-up, 85 % of patients randomized to the dasatinib group and 81 % of patients randomized to the imatinib group were still receiving first-line treatment. Discontinuation due to disease progression occurred in 3 % of dasatinib-treated patients and 5 % of imatinib-treated patients. With a minimum of 60 months follow-up, 61% of patients randomized to the dasatinib group and 63 % of patients randomized to the imatinib group were still receiving first-line treatment. Discontinuation due to disease progression occurred in 7 % of dasatinib -treated patients and 9 % of imatinib-treated patients.

Efficacy results are presented in Table 8. A statistically significantly greater proportion of patients in the dasatinib group achieved a cCCyR compared with patients in the imatinib group within the first 12 months of treatment. Efficacy of dasatinib was consistently demonstrated across different subgroups, including age, gender and baseline Hasford score.

For time-to cCCyR, a hazard ratio of 1.55 indicates that a patient treated with dasatinib is 55 % more likely to achieve a cCCyR at any time compared to a patient treated with imatinib. Similarly, for time-to MMR, a hazard ratio of 2.01 indicates a patient treated with dasatinib is more than two times more likely to achieve a MMR at any time compared to a patient treated with imatinib. For durability of cCCyR (time-in response), a hazard ratio of 0.7 indicates a patient treated with dasatinib is 30 % less likely to have disease progression after achieving a cCCyR (or never achieving a cCCyR) compared to a patient treated with imatinib.

Table 8: Efficacy Results in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

	Dasatinib (n = 259)	**Imatinib (n = 260)**	**p-value[d]**
	Response Rate (95 % CI)		
Cytogenetic Response within 12 months			
cCCyR[a]	76.8 % (71.2–81.8)	66.2 % (60.1–71.9)	p < 0.007*
CCyR[b]	85.3 % (80.4–89.4)	73.5 % (67.7–78.7)	-
Cytogenetic Response within 24 months			
cCCyR[a]	80.3 %	74.2 %	-
CCyR[b]	87.3 %	82.3 %	-
Cytogenetic Response within 36 months			
cCCyR[a]	82.6 %	77.3 %	-
CCyR[b]	88.0 %	83.5 %	-
Cytogenetic Response within 48 months			
cCCyR[a]	82.6 %	78.5 %	-
CCyR[b]	87.6 %	83.8 %	-
Cytogenetic Response within 60 months			
cCCyR[a]	83.0 %	78.5 %	-
CCyR[b]	88.0 %	83.8 %	-
Major Molecular Response[c]			
12 months	52.1 % (45.9–58.3)	33.8 % (28.1–39.9)	p < 0.00003*
24 months	64.5 % (58.3–70.3)	50 % (43.8–56.2)	-
36 months	69.1 % (63.1–74.7)	56.2 % (49.9–62.3)	-
48 months	75.7 % (70.0–80.8)	62.7 % (56.5–68.6)	_
60 months	76.4 % (70.8–81.5)	64.2 % (58.1–70.1)	p = 0.0021[e]
	Hazard Ratio		
	within 12 months (99.99 % CI)		
Time-to cCCyR	1.55 (1.0–2.3)		p < 0.0001*
Time-to MMR	2.01 (1.2–3.4)		p < 0.0001*
Durability of cCCyR	0.7 (0.4–1.4)		p < 0.035**
	within 24 months (95 % CI)		
Time-to cCCyR	1.49 (1.22–1.82)		–
Time-to MMR	1.69 (1.34–2.12)		–
Durability of cCCyR	0.77 (0.55–1.10)		–
	within 36 months (95 % CI)		
Time-to cCCyR	1.48 (1.22–1.80)		–
Time-to MMR	1.59 (1.28–1.99)		–
Durability of cCCyR	0.77 (0.53–1.11)		–
	within 48 months (95 % CI)		
Time-to cCCyR	1.45 (1.20–1.77)		–
Time-to MMR	1.55 (1.26–1.91)		–
Durability of cCCyR	0.81 (0.56–1.17)		–

	Dasatinib (n = 259)	Imatinib (n = 260)	p-value[d]
	within 60 months (95 % CI)		
Time-to cCCyR	1.46 (1.20–1.77)		p = 0.0001[e]
Time-to MMR	1.54 (1.25–1.89)		p < 0.0001[e]
Durability (Time-in) cCCyR	0.79 (0.55–1.13)		p = 0.1983[e]

a Confirmed complete cytogenetic response (cCCyR) is defined as a response noted on two consecutive occasions (at least 28 days apart).
b Cytogenetic response (CCyR) is based on a single bone marrow cytogenetic evaluation. The CCyR results refer to best unconfirmed cytogenic response within 12 months for any number of metaphases.
c Major molecular response (at any time) was defined as BCR-ABL ratios ≤ 0.1 % by RQ-PCR in peripheral blood samples standardized on the International scale. These are cumulative rates representing minimum follow-up for the timeframe specified.
d Formal statistical comparison of cCCyR and MMR rates was only performed at the time of the primary endpoint (cCCyR within 12 months).
e P-values of secondary endpoints are nominal, that is, for descriptive purposes, and therefore not statistically significant.
* Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.
** Not significant.
CI = Confidence Interval

After 60 months follow-up, median time to cCCyR was 3.1 months in the 214 dasatinib group responders and 5.8 months in the 204 imatinib group responders. Median time to MMR after 60 months follow-up was 9.3 months in the 196 dasatinib group responders and 15.0 months in the 163 imatinib group responders. The rates of cCCyR in the dasatinib and imatinib treatment groups, respectively, within 3 months (54 % and 30 %), 6 months (70 % and 56 %), 9 months (75 % and 63 %), 24 months (80 % and 74 %), 36 months (83 % and 77 %), 48 months (83 % and 79 %) and 60 months (83 % and 79 %) were consistent with the primary endpoint. The rates of MMR in the dasatinib and imatinib treatment groups, respectively, within 3 months (8 % and 0.4 %), 6 months (27 % and 8 %), 9 months (39 % and 18 %), 12 months (46 % and 28 %), 24 months (64 % and 46 %), 36 months (67 % and 55 %), 48 months (73 % and 60 %) and 60 months (76 % and 64 %) were also consistent with the primary endpoint. With a minimum of 60 months follow up, the rate of CMR (*i.e*. at least 4.5-log reduction from a standardised baseline value BCR-ABL ratio ≤ 0.0032 %) at any time was 44 % versus 34 % in the dasatinib and imatinib treatment groups, respectively.

In an exploratory subgroup analysis the rate of MMR at any time in each risk group determined by Hasford score was higher in the dasatinib group compared with the imatinib group (low risk, 90 % and 69 %; intermediate risk, 71 % and 65 %; high risk, 67 % and 54 %; respectively).

In an exploratory analysis, more dasatinib-treated subjects (84 %) achieved early molecular response (defined as BCR-ABL levels ≤ 10 % at 3 months) compared with imatinib-treated subjects (64 %). Subjects achieving early molecular response had a lower risk of transformation, higher rate of progression-free survival (PFS) and higher rate of overall survival (OS), as shown in Table 9 and Table 10.

Table 9: Dasatinib-treated Subjects with BCR-ABL ≤ 10 % and > 10 % at 3 Months

Dasatinib (n = 235)	Subjects with BCR-ABL ≤ 10 % at 3 Months	Subjects with BCR-ABL > 10 % at 3 Months
Number of Subjects (%)	198 (84.3)	37 (15.7)
Transformation at 60-months, n/N (%)	6/198 (3.0)	5/37 (13.5)
Rate of PFS at 60 Months (95 % CI)	92.0 % (89.6, 95.2)	73.8 % (52.0, 86.8)
Rate of OS at 60 Months (95 % CI)	93.8 % (89.3, 96.4)	80.6 % (63.5, 90.2)

Table 10: Imatinib-treated Subjects with BCR-ABL ≤ 10 % and > 10 % at 3 Months

Imatinib (n = 239)	Subjects with BCR-ABL ≤ 10 % at 3 Months	Subjects with BCR-ABL > 10 % at 3 Months
Number of Subjects (%)	154 (64.4)	85 (35.6)
Transformation at 60-months, n/N (%)	5/154 (3.2)	13/85 (15.3)
Rate of PFS at 60 Months (95 % CI)	93.5 % (87.8, 96.6)	79.3 % (67.3, 87.3)
Rate of OS at 60 Months (95 % CI)	95.4 % (90.5, 97.8)	80.5 % (70.1, 87.6)

The progression-free survival rate by specific timepoint is displayed graphically in Figure 1. Rate of PFS was consistently higher in dasatinib-treated patients who achieved BCR-ABL level ≤ 10 % at 3 months than those who did not.

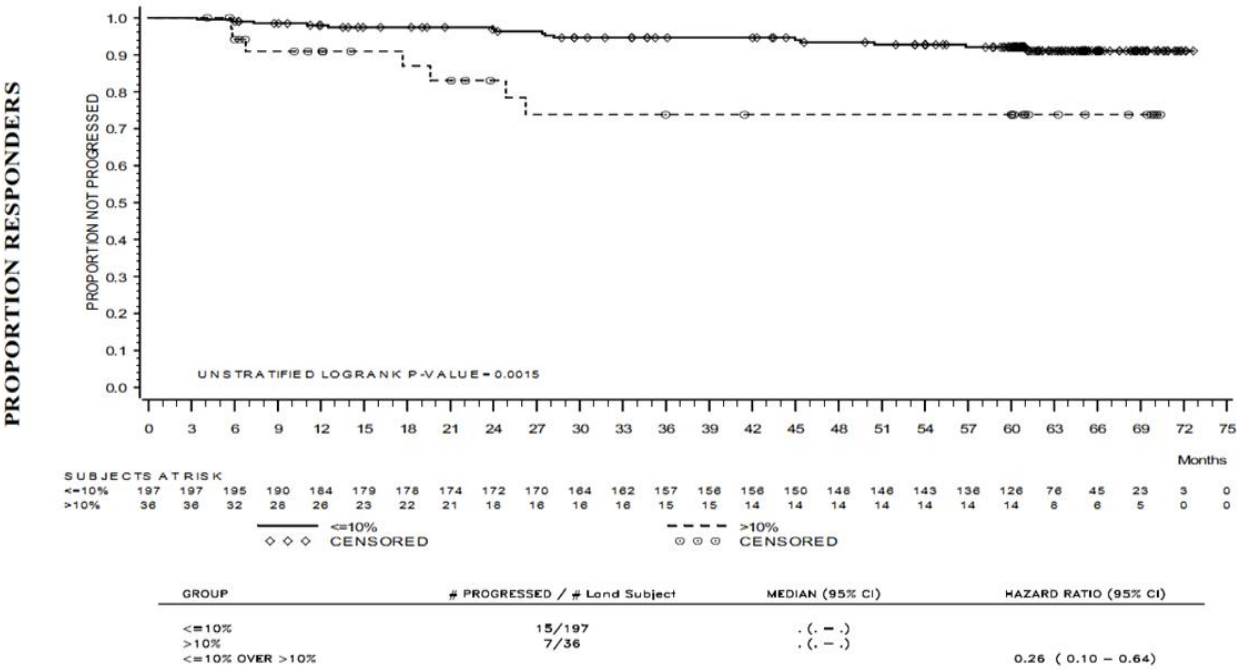


Figure 1: Landmark Plot for Progression-free Survival for Dasatinib by BCR-ABL Level (≤ 10 % or ≥ 10 % at 3 Months in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

The overall survival rate by specific timepoint is displayed graphically in Figure 2. Rate of OS was consistently higher in dasatinb-treated patients who achieved BCR-ABL level ≤ 10 % at 3 months than those who did not.

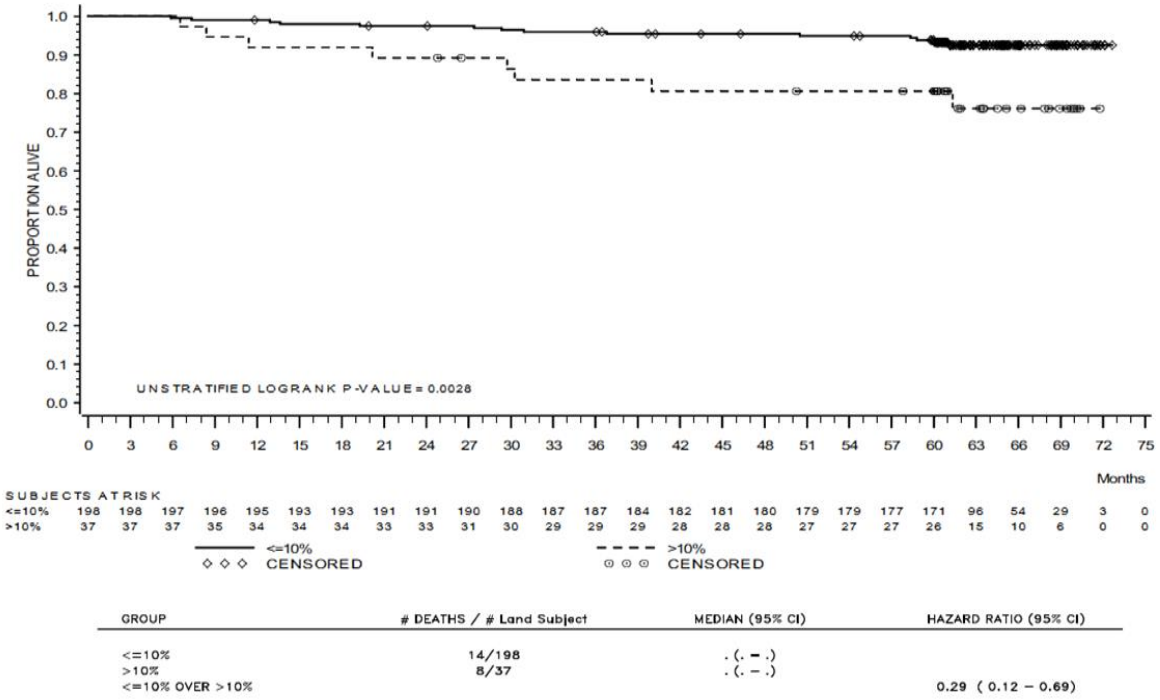


Figure 2: Landmark Plot for Overall Survival for Dasatinib by BCR-ABL Level (≤ 10 % or > 10 %) at 3 Months in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

The time to MMR is displayed graphically in Figure 3. The time to MMR was consistently shorter in dasatinib-treated subjects compared with imatinib-treated subjects.

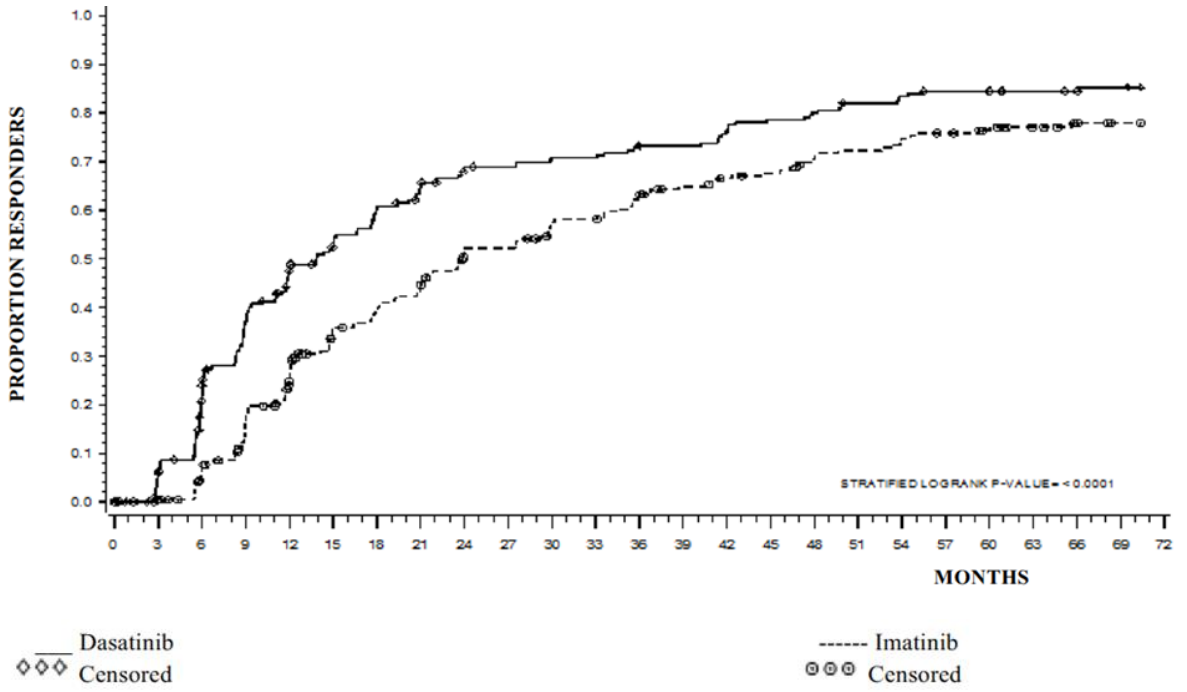


Figure 3: Kaplan-Meier Estimate of Time to Major Molecular Response (MMR) in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

MMR rates by specific timepoint are displayed graphically in Figure 4. Rates of MMR were consistently higher in dasatinib-treated subjects compared with imatinib-treated subjects.

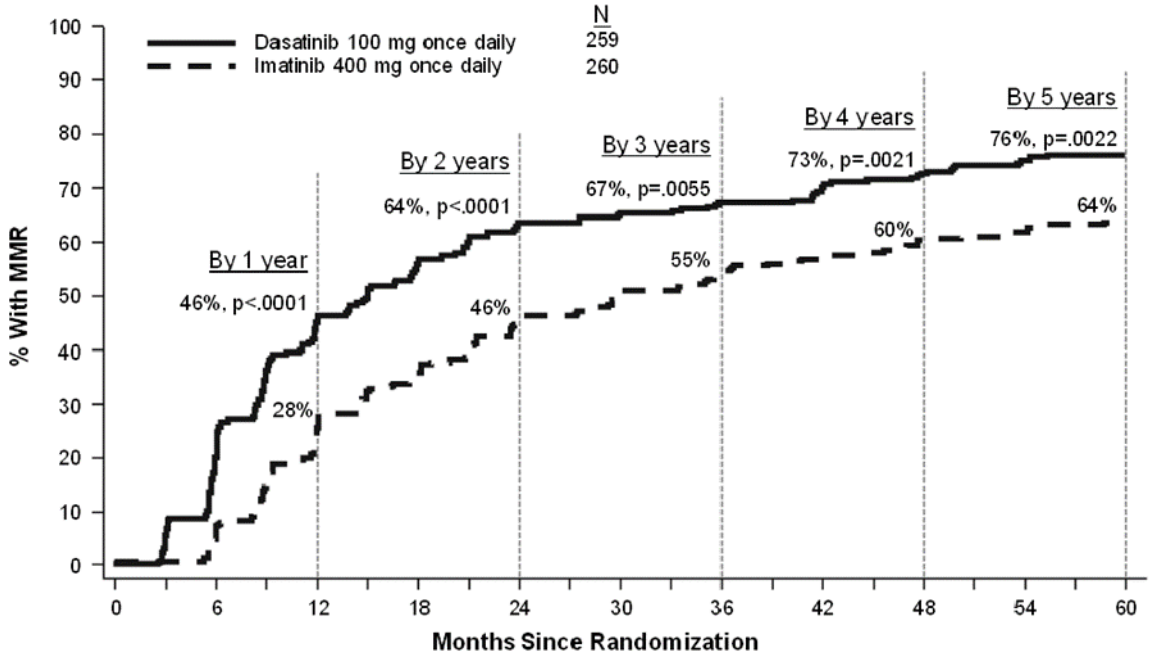


Figure 4: MMR Rates Over Time – All Randomized Subjects in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

MR4.5 rates over time are displayed graphically in Figure 5. Rate of MR4.5 over time was consistently higher in dasatinib -treated subjects compared with imatinib-treated subjects.

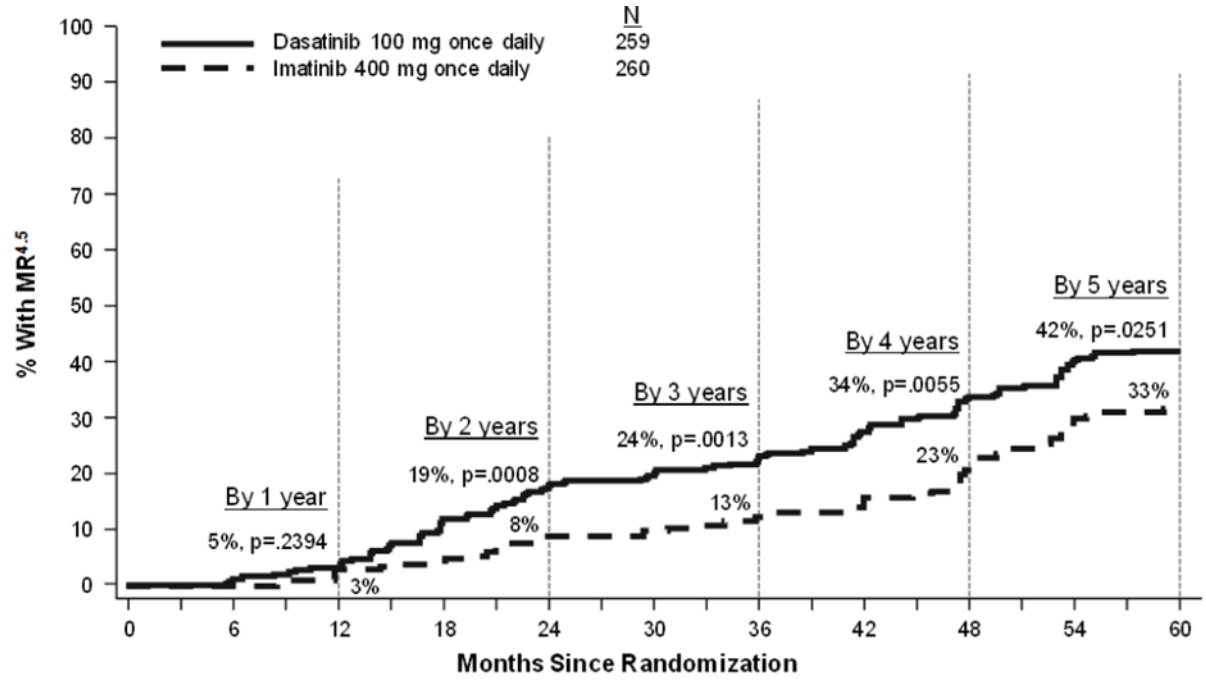


Figure 5: MR4.5 Rates Over Time – All Randomized Subjects in a Phase III Study of Newly Diagnosed Patients with Chronic Phase CML

Disease progression was defined as increasing white blood cells despite appropriate therapeutic management, loss of CHR (complete haematological response), partial CyR or CCyR, progression to accelerated phase or blast phase, or death. The estimated 60-month PFS rate was 88.9 % (CI: 84.0 %–92.4 %) and 89.2 % (CI: 84.3 %–92.7 %) for the dasatinib and imatinib treatment groups, respectively. Transformation to accelerated or blast phase occurred less frequently with dasatinib (n = 8; 3.1 %) than with imatinib-treated patients (n = 15; 5.8 %). The estimated 60-month survival rates for dasatinib and imatinib-treated patients were 90.9% (CI: 86.6 %–93.8 %) and 89.6 % (CI: 85.2 %–92.8 %), respectively.

In a phase III trial of newly diagnosed chronic phase CML, BCR-ABL sequencing was performed on blood samples from patients who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317I/L and V299L. Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

Phase III Clinical Trials in Patients with CML in Chronic, Accelerated or Myeloid Blast Phase, and Ph+ ALL who were Resistant or Intolerant to Imatinib

Two randomized, open-label studies were conducted to evaluate the efficacy of dasatinib administered once daily compared with dasatinib administered twice daily. The results described in Tables 11 and 12 are based on a minimum of 24 months and 60 months follow-up after the start of dasatinib therapy.

In the non-inferiority study in chronic phase CML, the primary endpoint was MCyR (once daily vs. twice daily) in imatinib-resistant patients. The main secondary endpoint was MCyR by total daily dose level in the imatinib-resistant patients. Other secondary endpoints included duration of MCyR, progression-free survival and overall survival. A total of 670 patients, of whom 497 were imatinib-resistant, were randomized to the dasatinib 100 mg once daily, 140 mg once daily, 50 mg twice daily or 70 mg twice daily group. The non-inferiority criteria were met for the primary efficacy endpoint at 6 months analysis. Results for each of the 4 individual regimens demonstrated comparable efficacy for MCyR and for a variety of secondary endpoints. At 2-Year analysis, the median duration of treatment was approximately 22 months (range: < 1–31 months). In patients with resistant or intolerant chronic phase CML, the median duration of treatment for patients still on therapy (n = 205) was 59 months (range: 28–66 months).

Efficacy results at 2-year analysis are presented in Tables 11 and 12. Efficacy was achieved across all dasatinib treatment groups, with the once daily schedule demonstrating comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MCyR 1.9 %; 95 % confidence interval [-6.8 %–10.6 %]). However, the 100 mg once daily regimen had improved tolerability.

Table 11: Efficacy of Dasatinib in Phase III Dose-Optimisation Study – Chronic Phase CML (2-year results)

100 mg once daily[a]	
All Patients	**n = 167**
Imatinib-Resistant Patients	**n = 124**
Haematological Response Rate[b] (%) (95 % CI)	
CHR	92 % (86–95)
Cytogenetic Response[c] (%) (95 % CI)	
MCyR	
All Patients	63 % (56–71)
Imatinib-Resistant Patients	59 % (50–68)
CCyR	
All Patients	50 % (42–58)
Imatinib-Resistant Patients	44 % (35–53)
Major Molecular Response[d] (%) (95 % CI)	
All Patients	69 % (58–79)
Imatinib-Resistant Patients	72 % (58–83)

a Not a recommended starting dosage of dasatinib for chronic phase CML.

b **Haematological response criteria** (all responses confirmed after 4 weeks):
Complete haematological response (CHR) (chronic CML): WBC ≤ institutional ULN, platelets < 450 x 10^9/L, no blasts or promyelocytes in peripheral blood, < 5 % myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20 %, and no extramedullary involvement. ULN = upper limit of normal range.

c **Cytogenetic response criteria:**
Complete (0 % Ph+ metaphases) or partial (> 0 %–35 %).
MCyR (0 %–35 %) combines both complete and partial responses.

d **Major molecular response criteria:**
Defined as BCR-ABL/control transcripts ≤ 0.1 % by RQ-PCR in peripheral blood samples. Molecular response was evaluated in a subset of assessed patients who had a CCyR

CI = Confidence Interval.

Efficacy was also assessed in patients who were intolerant to imatinib. In this population of patients who received 100 mg once daily, MCyR was achieved in 77 % and CCyR in 67 % with a minimum of 2 years follow-up.

Approximately 20% of subjects remained on study therapy through study completion (*i.e*. a minimum of 7 years), discontinuing study treatment due to study closure. Table 12 represents the comparative data (1–7 years), for the recommended starting dose 100 mg once daily in CML chronic phase.

Table 12: Long-Term Efficacy of Dasatinib in Phase III Dose Optimization Study – Imatinib Resistant or Intolerant Chronic Phase CML[a]

	Minimum Follow-up Period			
	1 year	**2 years**	**5 years**	**7 years**
Major Molecular Response				
All subjects	NA	37% (57/154)	44% (71/160)	46% (73/160)
Imatinib-resistant patients	NA	35% (41/117)	42% (50/120)	43% (51/120)
Imatinib-intolerant patients	NA	43% (16/37)	53% (21/40)	55% (22/40)
Progression-Free Survival[b]				
All subjects	90% (86, 95)	80% (73, 87)	51% (41, 60)	42% (33, 51)
Imatinib-resistant patients	88% (82, 94)	77% (68, 85)	49% (39, 59)	39% (29, 49)
Imatinib-intolerant patients	97% (92, 100)	87% (76, 99)	56% (37, 76)	51% (32, 67)
Overall Survival				
All subjects	96% (93, 99)	91% (86, 96)	78% (72, 85)	65% (56, 72)
Imatinib-resistant patients	94% (90, 98)	89% (84, 95)	77% (69, 85)	63% (53, 71)
Imatinib-intolerant patients	100% (100, 100)	95% (88, 100)	82% (70, 94)	70% (52, 82)

a Results reported in recommended starting dose of 100 mg once daily.
b Progression was defined as increasing WBC count, loss of CHR or MCyR, ≥ 30 % increase in Ph+ metaphases, confirmed AP/BP disease or death. PFS was analyzed on an intent-to-treat principle and patients were followed to events including subsequent therapy.

In the Phase III, randomized, open-label study in patients with advanced phase CML and Ph+ ALL, whose disease was resistant to or who were intolerant to imatinib, the primary endpoint was MaHR. A total of 611 patients were randomized to either the dasatinib 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months (range < 1–31 months).

The once daily schedule demonstrated comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MaHR 0.8 %; 95 % confidence interval [-7.1%–8.7%]); the response rates are presented in Table 13.

Table 13: Efficacy of Dasatinib in Phase III Dose-Optimisation Study – Advanced Phase CML and Ph+ ALL (2-year Results)

	140 mg Once Daily			
	Accelerated (n = 158)	**Myeloid Blast (n = 75)**	**Lymphoid Blast (n = 33)**	**Ph+ ALL (n = 40)**
MaHR[b] (95% CI)	66% (59–74)	28% (18–40)	42% (26–61)	38% (23–54)
CHR[b] (95% CI)	47% (40–56)	17% (10–28)	21% (9–39)	33% (19–49)
NEL[b] (95% CI)	19% (13–26)	11% (5–20)	21% (9–39)	5% (1–17)
MCyR[c] (95% CI)	39% (31–47)	28% (18–40)	52% (34–69)	70% (54–83)
CCyR (95% CI)	32% (25–40)	17% (10–28)	39% (23–58)	50% (34–66)

a Results reported in recommended starting dose of 140 mg once daily.
b Haematological response criteria (all responses confirmed after 4 weeks):
Major haematological response (MaHR) = complete haematological response (CHR) + no evidence of leukaemia (NEL).
CHR: WBC ≤ institutional ULN, ANC ≥ 1.0 x 10^9/L, platelets ≥ 100 x 10^9/L, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤ 5 %, < 5 % myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20 %, and no extramedullary involvement. ULN = upper limit of normal range.
NEL: same criteria as for CHR but ANC ≥ 0.5 x 10^9/Land < 1.0 x 10^9/L, or platelets ≥ 20 x 10^9/L and ≤ 100 x 10^9/L.
c MCyR combines both complete (0% Ph+ metaphases) and partial (> 0%–35%) responses.
CI = Confidence Interval.

In patients with accelerated phase CML treated with the 140 mg once daily regimen, the median duration of MaHR and the median overall survival in patients with accelerated phase CML was not reached for either group; the median PFS was 25 months and 26 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; and the median overall survival was not reached for the 140 mg once daily group and 31 months for the 70 mg twice daily group.

In patients with myeloid blast phase CML treated with the 140 mg once daily regimen, the median duration of MaHR was 8 months, and 9 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 4 months for both groups; and the median overall survival was 8 months for both groups. In patients with lymphoid blast phase CML, the median duration of MaHR was 5 months and 8 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 5 months for both groups, and the median overall survival was 11 months and 9 months, respectively.

In patients with Ph+ ALL treated with the 140 mg once daily regimen, the median duration of MaHR was 5 months and 12 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 4 months and 3 months respectively, and the median overall survival was 7 months and 9 months, respectively.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of dasatinib were evaluated in 235 healthy subjects and in 84 patients with leukaemia.

Absorption

Dasatinib is rapidly absorbed in patients following oral administration. The absolute bioavailability of dasatinib has not been determined. Peak concentrations were observed between 0.5–6 hours. Following oral administration, the increase in the mean exposure (AUC_T) is approximately proportional to the dose increment across doses ranging from 15 mg to 240 mg daily.

Data from a study of healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following consumption of a high-fat meal indicated a 14 % increase in the mean AUC of dasatinib. Consumption of a low-fat meal 30 minutes prior to dasatinib resulted in a 21 % increase in the mean AUC of dasatinib. The observed food effects are unlikely to be clinically significant. Dasatinib exposure variability is higher under fasted conditions (47% CV) compared to light-fat meal (39% CV) and high-fat meal (32% CV) conditions.

Based on the patient population PK analysis, variability in dasatinib exposure was estimated to be mainly due to inter-occasion variability in bioavailability (44% CV) and, to a lesser extent, due to inter-individual variability in bioavailability and inter-individual variability in clearance (30% and 32% CV, respectively). The random inter-occasion variability in exposure is not expected to affect the cumulative exposure and efficacy.

Distribution

In patients, dasatinib has a large apparent volume of distribution (2,505 L) suggesting that the drug is extensively distributed in the extravascular space.

Metabolism

Dasatinib is extensively metabolized in humans. In a study of 8 healthy subjects administered 100mg [^{14}C]-labelled dasatinib, unchanged dasatinib represented 29% of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the

drug. The overall mean terminal half-life of dasatinib is approximately 5–6 hours. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib.

Excretion

Elimination is predominantly in the faeces, mostly as metabolites. Following a single oral dose of [^{14}C]-labelled dasatinib, approximately 89% of the dose was eliminated within 10 days, with 4% and 85% of the administered radioactivity recovered in the urine and faeces, respectively. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and faeces, respectively, with the remainder of the dose being metabolites.

Special Populations

Age and gender

Pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age and gender on the pharmacokinetics of dasatinib.

The pharmacokinetics of dasatinib has not been evaluated in paediatric patients.

Hepatic impairment

The effect of hepatic impairment on the single-dose pharmacokinetics of dasatinib was assessed in 8 moderately hepatic-impaired subjects who received a 50mg dose and 5 severely hepatic-impaired subjects who received a 20 mg dose compared to matched healthy subjects who received a 70mg dose of dasatinib. The mean C_{max} and AUC of dasatinib adjusted for the 70mg dose was decreased by 47% and 8%, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In severely hepatic- impaired subjects, the mean C_{max} and AUC adjusted for the 70mg dose was decreased by 43% and 28% respectively, compared to subjects with normal hepatic function (see sections **4.4 Special warnings and precautions for use** and **4.2 Dose and method of administration**).

Renal impairment

There are no clinical studies of dasatinib in patients with impaired renal function. Less than 4% of dasatinib and its metabolites are excreted via the kidney (see sections **4.4 Special warnings and precautions for use** and **4.2 Dose and method of administration**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Dasatinib was not mutagenic when tested in *in vitro* bacterial cell assays (Ames test) and was not clastogenic in an *in vivo* rat micronucleus study. Clastogenicity was observed with dasatinib *in vitro* in assays with Chinese hamster ovary cells in the absence and presence of metabolic activation.

Carcinogenicity

In a two-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1 and 3 mg/kg/day. The highest dose resulted in a plasma drug exposure (AUC) level generally equivalent to or slightly lower than calculated human exposure at the recommended range of starting doses 100 mg or 140 mg daily. A statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose female rats and of prostate adenoma in low-dose male rats was noted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Microcrystalline cellulose
- ethylcellulose
- lactose monohydrate
- croscarmellose sodium
- magnesium stearate
- colloidal anhydrous silica
- hypromellose
- hyprolose
- triethyl citrate
- titanium dioxide

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

20 mg Tablet:

Blister pack (clear PVC/Aclar/Al) of 60 tablets (AUST R 290135).

Bottle (white, round HDPE bottle with child-resistant cap and desiccant) of 60 tablets (AUST R 290130).

50 mg Tablet:

Blister pack (clear PVC/Aclar/Al) of 60 tablets (AUST R 290142).

Bottle (white, round HDPE bottle with child-resistant cap and desiccant) of 60 tablets (AUST R 290133).

70 mg Tablet:

Blister pack (clear PVC/Aclar/Al) of 60 tablets (AUST 290138).

Bottle (white, round HDPE bottle with child-resistant cap and desiccant) of 60 tablets (AUST R 290141).

100 mg Tablet:

Blister pack (clear PVC/Aclar/Al) of 30 tablets (AUST R 290139).

Bottle (white, round HDPE bottle with child-resistant cap and desiccant) of 30 tablets (AUST R 290132).

Note: Not all packs sizes and/or pack types may be available.

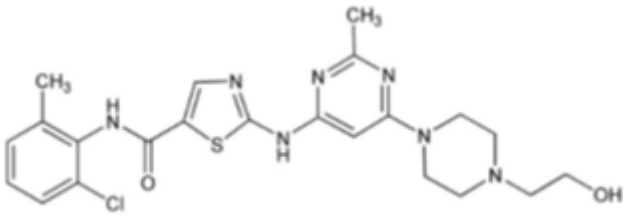
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Dasatinib is a white to off-white powder. The drug substance is insoluble in water (0.008 mg/mL) at 24 ± 4ºC. The pH of a saturated solution of dasatinib in water is about 6.0. Two basic ionization constants (pKa) were determined to be 6.8 and 3.1, and one weakly acidic pKa was determined to be 10.8. The solubilities of dasatinib in various solvents at 24 ± 4 ºC are as follows: slightly soluble in ethanol (USP), methanol, polyethylene glycol 400, and propylene glycol; very slightly soluble in acetone and acetonitrile; and practically insoluble in corn oil.

Chemical structure



Chemical Name: *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide

Molecular Formula: $C_{22}H_{26}ClN_7O_2S$

Molecular Weight: 488.01

CAS number 302962-49-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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Contact: info@helixpharmaceuticals.com.au

9 DATE OF FIRST APPROVAL

31 July 2018

10 DATE OF REVISION

20 March 2024

Summary table of changes

Section Changed	Summary of new information
4.4	Addition of warnings and precautions on hepatotoxicity.
4.8	Addition of hepatotoxicity as adverse effect.
5.2	Addition of subheadings for Special Populations