TAZATRED (Dasatinib Film-Coated Tablets 50 mg)
TAZATRED (Dasatinib Film-Coated Tablets 70 mg)

Prescribing Information

COMPOSITION

TAZATRED (Dasatinib tablet 50 mg):
Each Film-Coated Tablet Contains 50 mg of Dasatinib

TAZATRED (Dasatinib Tablets 70mg):
Each Film-Coated Tablet Contains 70 mg of Dasatinib

Excipients: Hydrogenated Castrol oil, Microcrystalline cellulose, Colloidal Silicon Dioxide, Anhydrous Lactose, Croscarmellose Sodium & Magnesium Stearate

CLINICAL INFORMATION

Therapeutic indication

TAZATRED (dasatinib) is indicated for the treatment of adults aged 18 years and over with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib. The effectiveness of TAZATRED is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

TAZATRED is also indicated for the treatment of adults aged 18 years and over with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

Posology and method of administration

The recommended starting dosage of TAZATRED (dasatinib) for chronic phase CML is 100 mg administered orally once daily (QD), either in the morning or in the evening. The recommended starting dosage of TAZATRED for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg/day administered orally in two divided doses (70 mg twice daily [BID]), one in the morning and one in the evening. Tablets should not be crushed or cut; they should be swallowed whole. TAZATRED can be taken with or without a meal.

In clinical studies, treatment with TAZATRED was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment after the achievement of a complete cytogenetic response (CCyR) has not been investigated.

Dose Modification

Concomitant Strong CYP3A4 inducers: The use of concomitant strong CYP3A4 inducers may decrease dasatinib plasma concentrations and should be avoided (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). St. John"s Wort may decrease dasatinib plasma concentrations unpredictably and should be avoided. If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, a TAZATRED dose increase should be considered.
If the dose of TAZATRED is increased, the patient should be monitored carefully for toxicity [see Interaction with other medicinal products and other forms of interaction].

Concomitant Strong CYP3A4 inhibitors: CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) may increase dasatinib plasma concentrations. Grapefruit juice may also increase plasma concentrations of dasatinib and should be avoided.

Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. If TAZATRED must be administered with a strong CYP3A4 inhibitor, a dose decrease to 20 mg daily should be considered. If 20 mg/day is not tolerated, either the strong CYP3A4 inhibitor must be discontinued, or TAZATRED should be stopped until treatment with the inhibitor has ceased. When the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TAZATRED dose is increased. [See Interaction with other medicinal products and other forms of interaction].

Dose Escalation

In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 100 mg twice daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended starting dosage.

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Dose Adjustment for Adverse Reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic 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 x 10^9/L or Platelets <50 x 10^9/L	1. Stop TAZATRED until ANC ≥1.0 x 10^9/L and platelets ≥50 x 10^9/L. 2. Resume treatment with TAZATRED at the original starting dose if recovery occurs in ≤7 days. 3. If platelets <25 x 10^9/L or recurrence of ANC <0.5 x 10^9/L for >7 days, repeat Step 1 and resume TAZATRED at a reduced dose of 80 mg once daily (second episode) or discontinue (third episode).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 70 mg twice daily)	ANC <0.5 x 10^9/L or Platelets <10 x 10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop TAZATRED until ANC ≥1.0 x 10^9/L and platelets ≥ 20 x 10^9/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume TAZATRED at a reduced dose of 50 mg twice daily (second episode) or 40 mg twice daily (third episode). 4. If cytopenia is related to leukemia, consider dose escalation to 100 mg twice daily.

*ANC: absolute neutrophil count

Non-hematological adverse reactions

If a severe non-hematological adverse reaction develops with TAZATRED 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 initial severity of the event.

Contraindications

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

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 adult 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.

In adult 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.

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

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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 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

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.

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Cardiac adverse reactions

Dasatinib was studied in a randomised 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 Posology 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 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 dermatologic 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

TAZATRED contains 20 mg of lactose in a 100 mg daily dose and 28 mg of lactose in a 140 mg daily dose.

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 Section Posology and method of administration – Special populations). Due to the limitations of this clinical study, caution is recommended when dasatinib is administered to patients with hepatic impairment.

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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.

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
Biochemist 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 $\geq 0.5 - < 1.0 \times 10^9$/l, Grade 4 $< 0.5 \times 10^9$/l); thrombocytopenia (Grade 3 $\geq 25 - < 50 \times 10^9$/l, Grade 4 $< 25 \times 10^9$/l); anaemia (haemoglobin Grade 3 $\geq 65 - < 80$ 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 adult 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 CMLResistant 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.

Interaction with other medicinal products and other forms of interaction
Drugs That May Increase Dasatinib Plasma Concentrations
CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. In a study of 18 patients with solid tumors, 20-mg DASATINIB once daily coadministered with 200 mg of ketoconazole twice daily increased the dasatinib Cmax and AUC by four- and five-fold, respectively. Concomitant use of DASATINIB and drugs that inhibit CYP3A4 may increase exposure to dasatinib and should be avoided. In patients receiving treatment with DASATINIB, close monitoring for toxicity and a DASATINIB dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided. [see Posology and method of administration].

Drugs That May Decrease Dasatinib Plasma Concentrations
CYP3A4 Inducers: When a single morning dose of DASATINIB was administered following 8 days of continuous evening administration of 600 mg of rifampin, a potent CYP3A4 inducer, the mean Cmax and AUC of dasatinib were decreased by 81% and 82%, respectively. Alternative agents with less enzyme induction potential should be considered. If DASATINIB must be administered with a CYP3A4 inducer, a dose increase in DASATINIB should be considered [see Posology and method of administration].

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Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. In a study of 24 healthy subjects, administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single 50-mg dose of DASATINIB was associated with no relevant change in dasatinib AUC; however, the dasatinib Cmax increased 26%. When 30 mL of aluminum hydroxide/magnesium hydroxide was administered to the same subjects concomitantly with a 50- mg dose of DASATINIB, a 55% reduction in dasatinib AUC and a 58% reduction in Cmax were observed. Simultaneous administration of DASATINIB with antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of DASATINIB.

H2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H2 antagonists or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. In a study of 24 healthy subjects, administration of a single 50-mg dose of
DASATINIB 10 hours following famotidine reduced the AUC and Cmax of dasatinib by 61% and 63%, respectively. The concomitant use of H2 blockers or proton pump inhibitors with DASATINIB is not recommended. The use of antacids should be considered in place of H2 blockers or proton pump inhibitors in patients receiving DASATINIB therapy.

Drugs That May Have Their Plasma Concentration Altered By Dasatinib
CYP3A4 Substrates: Single-dose data from a study of 54 healthy subjects indicate that the mean Cmax and AUC of simvastatin, a CYP3A4 substrate, were increased by 37% and 20%, respectively, when simvastatin was administered in combination with a single 100-mg dose of DASATINIB. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving DASATINIB.

Fertility, pregnancy and lactation
Pregnancy
Pregnancy Category D [see Special warnings and precautions for use].

Nursing Mothers
It is unknown whether DASATINIB is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DASATINIB, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Effects on ability to drive and use machines
Dasatinib has minor influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as dizziness or blurred vision during treatment with dasatinib. Therefore, caution should be recommended when driving a car or operating machines.

Undesirable effects
Dasatinib as a single-agent therapy
In total, the clinical trial experience for dasatinib administered as single-agent therapy represents 2809 patients, of which 2712 were adult and 97 paediatric. In the 2712 adult patients with either chronic phase CML, advance phase CML or Ph+ ALL, the median duration of therapy was 19.2 months (range 0 to 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 2712 dasatinib-treated adult subjects, 520 (19%) experience adverse drug reactions leading to treatment discontinuation.

No dedicated clinical trials have been conducted investigating the safety of dasatinib in newly diagnosed Ph+ ALL as a primary outcome. The safety profile of dasatinib in 4 Phase II clinical trials in newly diagnosed patients with Ph+ALL, was generally consistent with the safety profile in patients who were resistant or intolerant to prior therapy.

The following adverse reactions, excluding laboratory abnormalities, were reported in patients in dasatinib clinical trials where dasatinib was administered as single-agent therapy. 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.

Investigations

Common: weight decreased, weight increased

Uncommon: blood creatine phosphokinase increased, gamma-glutamyl transferase increased

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Cardiac disorders

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 erythemanodosum)

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, hemorrhagic 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

Post marketing 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

[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 (eg, 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.

Overdose

Experience with overdose of DASATINIB in clinical studies is limited to isolated cases. The highest reported dosage ingested was 280 mg per day for 1 week in two patients and both developed severe myelosuppression and bleeding. Since DASATINIB is associated with severe myelosuppression [see Special warnings and precautions for use and Undesirable effects], patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and appropriate supportive treatment given.

Acute overdose in animals was associated with cardiotoxicity. Evidence of cardiotoxicity included ventricular necrosis and valvular/ventricular/atrial hemorrhage at single doses ≥ 100 mg/kg (600 mg/m^2) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥10 mg/kg (120 mg/m^2).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCR- ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

Pharmacokinetic properties

Absorption

Maximum plasma concentrations (Cmax) of dasatinib are observed between 0.5 and 6 hours (Tmax) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The overall mean terminal half-life of dasatinib is 3–5 hours.

Data from a study of 54 healthy subjects administered a single, 100-mg dose of dasatinib 30 minutes following consumption of a high-fat meal resulted in a 14% increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant.

Distribution

In patients, dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. Binding of dasatinib and its active metabolite to human plasma proteins in vitro was approximately 96% and 93%, respectively, with no concentration dependence over the range of 100–500 ng/mL.

Prescribing Information

Metabolism

Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. Flavin- containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of dasatinib metabolites. In human liver microsomes, dasatinib was a weak time-dependent inhibitor of CYP3A4.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the dasatinib AUC. This indicates that the active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also had several other inactive oxidative metabolites.
Dasatinib is a time-dependent inhibitor of CYP3A4. At clinically relevant concentrations, dasatinib does not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib is not an inducer of human CYP enzymes.

Elimination

Elimination is primarily via the feces. Following a single oral dose of [14C]-labeled dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces, respectively, within 10 days. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites.

Effects of 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.

Preclinical Safety Data

Carcinogenicity studies were not performed with dasatinib.

Dasatinib was clastogenic when tested in vitro in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an in vitro bacterial cell assay (Ames test) and was not genotoxic in an in vivo rat micronucleus study.

The effects of dasatinib on male and female fertility have not been studied. However, results of repeat-dose toxicity studies in multiple species indicate the potential for dasatinib to impair reproductive function and fertility. Effects evident in male animals included reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

Shelf Life

18 months - TAZATRED (Dasatinib Film-Coated Tablets 50 mg)
24 months - TAZATRED (Dasatinib Film-Coated Tablets 70 mg)

Storage conditions

Store below 30°C

Precautions for Storage

Keep out of reach of children

Nature and contents of container

10’s Blister and such 6 blisters are placed in a carton with a pack insert

MANUFACTURED IN INDIA BY:

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MANUFACTURED FOR:

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Prescribing Information

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Date of revision
September 2024