Dasinib

Dasatinib Monohydrate INN Tablet

DRUG INTERNATIONAL LTD.

COMPOSITION

Each film coated tablet contains Dasatinib 100mg as Dasatinib Monohydrate INN.

CLINICAL PHARMACOLOGY

Mechanism of Action: 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 could 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.

Pharmacokinetics:

Absorption: The maximum plasma concentrations (Cmax) of Dasatinib are observed between 0.5 hours and 6 hours (Tmax) following oral administration.

Food Effect : A high-fat meal increased the mean AUC of Dasatinib following a single dose of 100 mg by 14%. The total calorie content of the high-fat meal was 985 kcal. The calories derived from fat, carbohydrates, and protein were 52%, 34%, and 14% for the high-fat meal.

Distribution: The apparent volume of distribution is 2505 l (CV% 93%).

Binding of Dasatinib to human plasma proteins in vitro was approximately 96% and of its active metabolite was 93%, with no concentration dependence over the range of 100 ng/ml to 500 ng/ml.

Dasatinib is a P-gp substrate in vitro.

Elemination: The mean terminal half-life of Dasatinib is 3 hours to 5 hours. The mean apparent oral clearance is 363.8 l/hr (CV% 81.3%).

Metabolism: Dasatinib is metabolized in humans, primarily by CYP3A4. CYP3A4 is 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.

The exposure of the active metabolite, which is equipotent to Dasatinib, represents approximately 5% of the AUC of Dasatinib. The active metabolite of Dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also has several other inactive oxidative metabolites.

Excretion: Elimination is primarily via the feces. Following a single radiolabeled dose of oral Dasatinib, 4% of the administered radioactivity was recovered in the urine and 85% in the feces within 10 days. Unchanged Dasatinib accounted for 0.1% of the administered dose in the urine and 19% of the administered dose in the feces with the remainder of the dose being metabolites.

INDICATIONS

Dasatinib is indicated for the treatment of adult patients with

• Newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.

• Chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including Imatinib.

• Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

Dasatinib is indicated for the treatment of pediatric patients 1 year of age and older with

• Ph+ CML in chronic phase.

• Newly diagnosed Ph+ ALL in combination with chemotherapy.

DOSAGE AND ADMINISTRATION

Dosage of Dasatinib In Adult Patients: The recommended starting dosage of Dasatinib for chronic phase CML in adults 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 in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed; they should be swallowed whole. The exposure in patients receiving a crushed tablet is lower than in those swallowing an intact tablet. Dasatinib can be taken with or without a meal, either in the morning or in the evening.

Dosage of Dasatinib In Pediatric Patients: With CML, or Ph+ ALL : The recommended starting dosage for pediatrics is based on body weight as shown in Table. The recommended dose should be administered orally once daily with or without food. The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary.

Table: Dosage of Dasatinib for Pediatric Patients[a]

Body Weight (kg)[b]	Daily Dose (mg)
10 to less than 20	40 mg
20 to less than 30	60 mg
30 to less than 45	70 mg
at least 45	100 mg

[a]For pediatric patients with Ph+ALL, begin Dasatinib therapy on or before day 15 of induction chemotherapy, when diagnosis is confirmed and continue for 2 years.

[b]Tablet dosing is not recommended for patients weighing less than 10 kg.

Or, as directed by the registered physician.

SIDE EFFECTS

Myelosuppression, bleeding-related events, fluid retention, cardiovascular events, pulmonary arterial hypertension, QT prolongation, severe dermatologic reactions, tumor lysis syndrome, effects on growth and development in pediatric patients.

CONTRAINDICATIONS

It is contraindicated in patients with known hypersensitivity to Dasatinib or to any component of the formulation.

DRUG INTERACTIONS

Effect of Other Drugs On Dasatinib:

Strong CYP3A4 Inhibitors: The coadministration with strong CYP3A inhibitors may increase Dasatinib concentrations. Increased Dasatinib concentrations may increase the risk of toxicity. Concomitant use of strong CYP3A4 inhibitors should be avoided. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, Dasatinib dose reduction should be considered.

Strong CYP3A4 Inducers: The coadministration of Dasatinib with strong CYP3A inducers may decrease Dasatinib concentrations. Decreased Dasatinib concentrations may reduce efficacy. Alternative drugs with less enzyme induction potential should be considered. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, Dasatinib dose increase should be considered.

Gastric Acid Reducing Agents: The coadministration of Dasatinib with a gastric acid reducing agent may decrease the concentrations of Dasatinib. Decreased Dasatinib concentrations may reduce efficacy. H2 antagonists or proton pump inhibitors should not be administered with Dasatinib. The use of antacids in place of H2 antagonists or proton pump inhibitors should be considered. The antacid at least 2 hours prior to or 2 hours after the dose of Dasatinib should be administered. Simultaneous administration of Dasatinib with antacids should be avoided.

PRECAUTIONS

Myelosuppression: Treatment with Dasatinib is associated with severe (NCT CTCAE Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, 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, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs 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 and/or dose reduction.

Bleeding-Related Events: Dasatinib can cause serious and fatal bleeding. Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

Fluid Retention: Dasatinib may cause fluid retention. Fluid retention events were typically managed by supportive care measures that may include diuretics or short courses of steroids. Severe pleural effusion may require thoracentesis and oxygen therapy. Dose reduction or treatment interruption should be corsidered.

Cardiovascular Events: Dasatinib can cause cardiac dysfunction. Patients should be monitored for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

Pulmonary Arterial Hypertension: Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) in adult and pediatric patients which may occur any time after initiation, including after more than 1 year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. PAH may be reversible on discontinuation of Dasatinib. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating Dasatinib and during treatment. If PAH is confirmed, Dasatinib should be permanently discontinued.

QT Prolongation: Dasatinib may increase the risk of prolongation of QTc in patients including those with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to and during Dasatinib administration.

Severe Dermatologic Reactions: Cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported in patients treated with Dasatinib. In patients who experience a severe mucocutaneous reaction should be discontinued permanently during treatment if no other etiology can be identified.

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported in patients with resistance to prior Imatinib therapy, primarily in advanced phase disease. Due to potential for tumor lysis syndrome, maintain adequate hydration, correct uric acid levels prior to initiating therapy with Dasatinib, and monitor electrolyte levels. Patients with advanced stage disease and/or high tumor burden may be at increased risk and should be monitored more frequently.

Pediatric Use: The safety profile of Dasatinib in pediatric subjects was comparable to that reported in studies in adult subjects with chronic phase CML. Bone growth and development in pediatric patients should be monitored.

Use in Pregnancy: Dasatinib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to avoid pregnancy, which may include the use of effective contraceptive methods, during treatment with Dasatinib and for 30 days after the final dose.

Use in Lactation: Women should be advised that breastfeeding is not recommended during treatment with Dasatinib and for 2 weeks after the final dose.

OVERDOSE

Experience with overdose of Dasatinib in clinical studies is limited to isolated cases. The highest overdosage of 280 mg per day for 1 week was reported in two patients and both developed severe myelosuppression and bleeding. Since Dasatinib is associated with severe myelosuppression, patients should be monitored who ingest more than the recommended dosage closely for myelosuppression and give appropriate supportive treatment.

PHARMACEUTICAL INFORMATION

Storage: Store below 30^{O} C in a dry place. Protect from light. Keep out of the reach of children.

Packing: Dasinib: Each box contains 20 tablets in Alu-Alu blister pack.