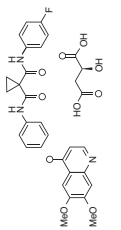
SPRYTIZ 20/50/70/100
Dasatinib Tablets 20 mg/ 50 mg/ 70 mg/ 100 mg

Rx only
COMPOSITION
SPRYTIZ 20
Dasatinib Tablets 20 mg
Each film-coated tablet contains:
Dasatinib 20 mg
Excipients q.s.
Colours: Titanium dioxide
SPRYTIZ 50
Dasatinib Tablets 50 mg
Each film-coated tablet contains:
Dasatinib 50 mg
Excipients q.s.
Colours: Titanium dioxide
SPRYTIZ 70
Dasatinib Tablets 70 mg
Each film-coated tablet contains:
Dasatinib 70 mg
Excipients q.s.
Colours: Titanium dioxide
SPRYTIZ 100
Dasatinib Tablets 100 mg
Each film-coated tablet contains:
Dasatinib 100 mg
Excipients q.s.
Colours: Titanium dioxide



DESCRIPTION
SPRYTIZ is a kinase inhibitor. The chemical name is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is $C_{22}H_{26}ClN_7O_2S \cdot H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol.

CLINICAL PHARMACOLOGY
Mechanism of Action: SPRYTIZ, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, SPRYTIZ is predicted to bind to multiple conformations of the ABL kinase.
In vitro, SPRYTIZ was active in leukemic cell lines representing variants of imatinib mesylate-sensitive and resistant disease. SPRYTIZ inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, SPRYTIZ 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.

Pharmacodynamics
Cardiac Electrophysiology: Of 2440 patients treated with SPRYTIZ at all doses tested in clinical trials, 16 patients (<1%) had QTc prolongation reported as an adverse reaction. Twenty-two patients (1%) experienced a QTcF > 500 ms. In 865 patients with leukemia treated with SPRYTIZ 70 mg BID in five Phase 2 studies, the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7 ms to 13.4 ms.
An analysis of the data from five Phase 2 studies in patients (70 mg BID) and a Phase 1 study in healthy subjects (100 mg single dose) suggests that there is a maximum increase of 3 to 6 milliseconds in Fridericia corrected QTc interval from baseline for subjects receiving therapeutic doses of SPRYTIZ, with associated upper 95% confidence intervals <10 msec.
Pharmacokinetics
The pharmacokinetics of SPRYTIZ exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg/day (0.15 times the lowest approved recommended dose) to 240 mg/day (1.7 times the highest approved recommended dose).
At 100 mg QD, the maximum concentration at steady state (Cmax) is 82.2 ng/mL (CV% 69%), area under the plasma drug concentration time curve (AUC) is 397 ng/mL*hr (CV% 55%). The clearance of SPRYTIZ is found to be time-invariant. When administered to adult healthy subjects as dispersed tablets in juice, the adjusted geometric mean ratio was 0.97 (90% CI: 0.85, 1.10) for Cmax and 0.84 (90% CI: 0.78, 0.91) for AUC as compared to intact tablets.

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

Distribution: The apparent volume of distribution is 2505 L (CV% 93%).
Binding of SPRYTIZ 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. SPRYTIZ is a P-gp substrate *in vitro.*

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

Metabolism: SPRYTIZ 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 SPRYTIZ metabolites.
The exposure of the active metabolite, which is equipotent to SPRYTIZ, represents approximately 5% of the AUC of SPRYTIZ. The active metabolite of SPRYTIZ 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 SPRYTIZ, 4% of the administered radioactivity was recovered in the urine and 85% in the feces within 10 days. Unchanged SPRYTIZ 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 AND USAGE
SPRYTIZ 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.

SPRYTIZ 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 SPRYTIZ in Adult Patients
The recommended starting dosage of SPRYTIZ for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of SPRYTIZ 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. SPRYTIZ can be taken with or without a meal, either in the morning or in the evening.

Dosage of SPRYTIZ in Pediatric Patients with CML or Ph+ ALL
The recommended starting dosage for pediatrics is based on body weight as shown in Table 1. The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary.
a For pediatric patients with Ph+ ALL, begin SPRYTIZ 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.

Dose Modification
Strong CYP3A4 Inducers: Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If patients must be coadministered a strong CYP3A4 inducer, consider a SPRYTIZ dose increase. If the dose of SPRYTIZ is increased, monitor the patient carefully for toxicity.
Strong CYP3A4 Inhibitors: Avoid the use of concomitant strong CYP3A4 inhibitors and grapefruit juice. Recommend selecting an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible. If SPRYTIZ must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:
- 40 mg daily for patients taking SPRYTIZ 140 mg daily.
- 20 mg daily for patients taking SPRYTIZ 100 mg daily.
- 20 mg daily for patients taking SPRYTIZ 70 mg daily.

For patients taking SPRYTIZ 60 mg or 40 mg daily, consider interrupting SPRYTIZ until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYTIZ.
These reduced doses of SPRYTIZ are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical

Size: 100 x 182 mm

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

data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYTIZ is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt SPRYTIZ until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the SPRYTIZ dose is increased

ADVERSE REACTIONS

The Following Clinically Significant Adverse Reactions Are Discussed In Greater Detail In Other Sections Of The Labeling:

- 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

None.

DRUG INTERACTIONS

Effect of Other Drugs on Dasatinib

Strong CYP3A4 Inhibitors

The coadministration with strong CYP3A inhibitors may increase SPRYTIZ concentrations. Increased SPRYTIZ concentrations may increase the risk of toxicity. Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, consider a SPRYTIZ dose reduction.

Strong CYP3A4 Inducers

The coadministration of SPRYTIZ with strong CYP3A inducers may decrease dasatinib concentrations. Decreased dasatinib concentrations may reduce efficacy. Consider alternative drugs with less enzyme induction potential. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, consider a SPRYTIZ dose increase.

Gastric Acid Reducing Agents

The coadministration of SPRYTIZ with a gastric acid reducing agent may decrease the concentrations of SPRYTIZ. Decreased SPRYTIZ concentrations may reduce efficacy.

Do not administer H2 antagonists or proton pump inhibitors with SPRYTIZ. Consider the use of antacids in place of H2 antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYTIZ. Avoid simultaneous administration of SPRYTIZ with antacids.

WARNINGS AND PRECAUTIONS

Myelosuppression: Treatment with SPRYTIZ is associated with severe (NCI 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.

Bleeding-Related Events: SPRYTIZ can cause serious and fatal bleeding. In all CML or Ph+ ALL clinical studies, Grade ≥3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYTIZ. The incidence of Grade 3/4 hemorrhage, occurred in 5.8% of adult patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of adult patients.

Cardiovascular Events: SPRYTIZ can cause cardiac dysfunction. After 5 years of follow-up in the randomized newly diagnosed chronic phase CML trial in adults (n=258), the following cardiac adverse reactions occurred: cardiac ischemic events (3.9% dasatinib vs 1.6% imatinib), cardiac-related fluid retention (8.5% dasatinib vs 3.9% imatinib), and conduction system abnormalities, most commonly arrhythmia and palpitations (7.0% dasatinib vs 5.0% imatinib).

Pulmonary Arterial Hypertension: SPRYTIZ 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 SPRYTIZ.

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 SPRYTIZ, and monitor electrolyte levels.

Embryo-Fetal Toxicity: SPRYTIZ can cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects of SPRYTIZ including hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to SPRYTIZ.

OVERDOSAGE

Experience with overdose of SPRYTIZ 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 SPRYTIZ is associated with severe myelosuppression, monitor patients who ingest more than the recommended dosage closely for myelosuppression and give appropriate supportive treatment.

HOW SUPPLIED

SPRYTIZ tablets 20mg, 50 mg, 70 mg & 100mg supplied in a bottle of 60 tablets packed in a HDPE container.

STORAGE

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15-30°C (59 to 86°F).

SHELF LIFE

24 months

MANUFACTURED & MARKETED BY:

Tizig Pharma Private Limited
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Regd. Office: Maligaun-5, Kathmandu, Nepal.