PRESCRIBING INFORMATION
Not be sold by retail without the prescription of a "Registered Medical Practitioner only

Dasatinib Tablets 50/70 mg

Dasakast™

1. GENERIC NAME:
Dasatinib Tablets 50/70 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

50 mg	70 mg
Each film-coated tablet contains:	Each film-coated tablet contains:
Dasatinib .....50 mg	Dasatinib .....70 mg
Excipients ……. q.s.	Excipients ……. q.s.
Colours: Titanium Dioxide IP.	Colours: Titanium Dioxide IP.

The excipients used are Microcrystalline Cellulose, Lactose Monohydrate, Hydroxypropyl cellulose, Isopropyl alcohol, Croscarmellose Sodium, Magnesium stearate, Opadry white.

3. DOSAGE FORM AND STRENGTH:-
Oral (Film-coated tablets) and 50/70 mg

4. CLINICAL PARTICULARS:
4.1 Therapeutic Indication
Dasatinib is indicated
- For the treatment of adults with chronic accelerated or myeloid or lymphoid blast phase chronic myeloid leukemai (CML).
- Treatment of newly Diagnosed Adults with Chronic Myeloid Leukaemia (CML) in Chronic Phase.
- Treatment of Paediatric patients with Philadelphia Chromosome Positive Chronic myeloid leukemia (Ph+ CML) in chronic phase.

4.2 Posology and method of administration
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 administered orally once daily. Tablets should not be crushed or cut; they should be swallowed whole. DASATINIB can be taken with or without a meal, either in the morning or in the evening.
Paediatric population (Ph+ CML-CP)
Dosing for children and adolescents is on the basis of body weight (see Table 1). Dasatinib is administered orally once daily in the form of either DASATINIB film-coated tablets or DASATINIB powder for oral suspension (see Summary of Product Characteristics for DASATINIB powder for oral suspension). The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary. The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients. Dose increase or reduction is recommended based on individual patient response and tolerability. There is no experience with DASATINIB treatment in children under 1 year of age.
DASATINIB film-coated tablets and DASATINIB powder for oral suspension are not bioequivalent. Patients who are able to swallow tablets and who desire to switch from DASATINIB powder for oral suspension to DASATINIB tablets or patients who are not able to swallow tablets and who desire to switch from tablets to oral suspension, may do so, provided that the correct dosing recommendations for the dosage form are followed. The recommended starting daily dosage of DASATINIB tablets in paediatric patients is shown in Table 1.

Table 1: Dosage of DASATINIB tablets for paediatric patients with Ph+ CML-CP

Body weight (kg)[a]	Daily dose (mg)
10 to less than 20 kg	40 mg
20 to less than 30 kg	60 mg
30 to less than 45 kg	70 mg
at least 45 kg	100 mg

[a] The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients.

Treatment duration
In clinical studies, treatment with DASATINIB in adults with Ph+ CML-CP, accelerated, myeloid or lymphoid blast phase (advanced phase) CML, or Ph+ ALL and paediatric patients with Ph+ CML-CP 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 or molecular response [including complete cytogenetic response (CCyR), major molecular response (MMR) and MR4.5] has not been investigated.
Dose escalation
In clinical studies in adult CML patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dose.
The following dose escalations shown in Table 2 are recommended in paediatric patients with Ph+ CML-CP who do not achieve a haematologic, cytogenetic and molecular response at the recommended time points, per current treatment guidelines, and who tolerate the treatment.

Table 2: Dose escalation for paediatric patients with Ph+ CML-CP

	Dose (maximum dose per day)	
	Starting dose	**Escalation**
Tablets	40 mg	50 mg
	60 mg	70 mg
	70 mg	90 mg
	100 mg	120 mg

Dose adjustment for adverse reactions
Myelosuppression
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 in adults are summarised in Table 3 and in paediatric patients with Ph+ CML-CP in Table 4. Guidelines for paediatric patients with Ph+ ALL treated in combination with chemotherapy are in a separate paragraph following the tables.

Table 3: Dose adjustments for neutropaenia and thrombocytopaenia in adults

Adults with chronic phase CML (starting dose 100 mg once daily)	ANC < 0.5 x 10^9/L and/or platelets < 50 x 10^9/L	1 Stop treatment until ANC ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L. 2 Resume treatment at the original starting dose. 3 If platelets < 25 x 10^9/L and/or recurrence of ANC < 0.5 x 10^9/L for > 7 days, repeat step 1 and resume treatment 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).
Adults with accelerated and blast phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC < 0.5 x 10^9/L and/or platelets < 10 x 10^9/L	1 Check if cytopaenia is related to leukaemia (marrow aspirate or biopsy). 2 If cytopaenia is unrelated to leukaemia, stop treatment 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 cytopaenia, repeat step 1 and resume treatment at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode). 4 If cytopaenia is related to leukaemia, consider dose escalation to 180 mg once daily.

ANC: absolute neutrophil count

Table 4: Dose adjustments for neutropaenia and thrombocytopaenia in paediatric patients with Ph+ CML-CP

		Dose (maximum dose per day)		
1. If cytopaenia persists for more than 3 weeks, check if cytopaenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopaenia is unrelated to leukaemia, stop treatment until ANC ≥1.0 × 10^9/L and platelets ≥75 × 10^9/L and resume at the original starting dose or at a reduced dose. 3. If cytopaenia recurs, repeat marrow aspirate/ biopsy and resume treatment at a reduced dose.		**Original starting dose**	**One-level dose reduction**	**Two-level dose reduction**
	Tablets	40 mg	20 mg	*
		60 mg	40 mg	20 mg
		70 mg	60 mg	50 mg
		100 mg	80 mg	70 mg

ANC: absolute neutrophil count
*lower tablet dose not available
For paediatric patients with Ph+ CML-CP, if Grade ≥3 neutropaenia or thrombocytopaenia recurs during complete haematologic response (CHR), DASATINIB should be interrupted, and may be subsequently resumed at a reduced dose. Temporary dose reductions for intermediate degrees of cytopaenia and disease response should be implemented as needed.

Non-haematologic 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, treatment must be withheld until the adverse reaction has resolved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the adverse reaction. For 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 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. In CML-CP paediatric patients with non-haematologic adverse reactions, the dose reduction recommendations for haematologic adverse reactions that are described above should be followed. In Ph+ ALL paediatric patients with non-haematologic adverse reactions, if needed, one level of dose reduction should be followed, according to the dose reduction recommendations for haematologic adverse reactions that are described above.

4.3 Contraindications
None

4.4 Special warnings and precautions for use
Myelosuppression
Treatment with DASATINIB is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. In a dose-optimization study in patients with resistance or intolerance to prior imatinib therapy and chronic phase CML, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with 100 mg once daily than in patients treated with other dosing regimens. Perform complete blood counts weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding DASATINIB temporarily or dose reduction.

Bleeding Related Events
Dasatinib Tablets 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 Dasatinib Tablets. 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. The most frequent site of hemorrhage was gastrointestinal. Most bleeding events in clinical studies were associated with severe thrombocytopenia. In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction in vitro.
Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

Cardiovascular
Events DASATINIB 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). Two cases (0.8%) of peripheral arterial occlusive disease occurred with imatinib and 2 (0.8%) transient ischemic attacks occurred with dasatinib. Monitor patients 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. Evaluate patients 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. Correct hypokalemia or hypomagnesemia 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. Discontinue permanently in patients who experience a severe mucocutaneous reaction 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.
Embryo-Fetal Toxicity
Based on limited human data, DASATINIB can cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects of DASATINIB including hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to DASATINIB. Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraception, during treatment with DASATINIB and for 30 days after the final dose.
Effects on Growth and Development in Pediatric Patients
In pediatric trials of DASATINIB in chronic phase CML after at least 2 years of treatment, adverse reactions associated with bone growth and development were reported in 5 (5.2%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 5 cases included cases of epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia.

4.5 Drugs Interactions
Active substances that may increase dasatinib plasma concentrations
In vitro studies indicate that dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and medicinal products or substances which potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin, grapefruit juice) may increase exposure to dasatinib. Therefore, in

patients receiving dasatinib, systemic administration of a potent CYP3A4 inhibitor is not recommended.
At clinically relevant concentrations, binding of dasatinib to plasma proteins is approximately 96% on the basis of *in vitro* experiments. No studies have been performed to evaluate dasatinib interaction with other protein-bound medicinal products. The potential for displacement and its clinical relevance are unknown.
Active substances that may decrease dasatinib plasma concentrations
When dasatinib was administered following 8 daily evening administrations of 600 mg rifampicin, a potent CYP3A4 inducer, the AUC of dasatinib was decreased by 82%. Other medicinal products that induce CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, phenobarbital or herbal preparations containing *Hypericum perforatum*, also known as St. John´s Wort) may also increase metabolism and decrease dasatinib plasma concentrations. Therefore, concomitant use of potent CYP3A4 inducers with dasatinib is not recommended. In patients in whom rifampicin or other CYP3A4 inducers are indicated, alternative medicinal products 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.
Histamine-2 antagonists and proton pump inhibitors
Long-term suppression of gastric acid secretion by H_2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. 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%. In a study of 14 healthy subjects, administration of a single 100-mg dose of DASATINIB 22 hours following a 4-day, 40-mg omeprazole dose at steady state reduced the AUC of dasatinib by 43% and the C_{max} of dasatinib by 42%. The use of antacids should be considered in place of H_2 antagonists or proton pump inhibitors in patients receiving DASATINIB therapy.
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 .
Active substances that may have their plasma concentrations altered by dasatinib
Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. In a study in healthy subjects, a single 100 mg dose of dasatinib increased AUC and C_{max} exposure to simvastatin, a known CYP3A4 substrate, by 20 and 37% respectively. It cannot be excluded that the effect is larger after multiple doses of dasatinib. Therefore, CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving dasatinib

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
In a 2-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 approximately 60% of the human exposure at 100 mg once daily. Dasatinib induced a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and prostate adenoma in low-dose males. 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. Dasatinib did not affect mating or fertility in male and female rats at plasma drug exposure (AUC) similar to the human exposure at 100 mg daily. In repeat dose studies, administration of dasatinib resulted in 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.

4.7 Effects on ability to drive and use machines
Dasatinib Tablet 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.

4.8 Undesirable effects:
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

4.9 Overdose:-
Experience with overdose of DASATINIB in clinical studies is limited to isolated cases. 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 myelo-suppression, patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and given appropriate supportive treatment. 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).

5. PHARMACOLOGICAL PROPERTIES:
5.1 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 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.

5.2 Pharmacodynamic properties
Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01XE06
Dasatinib inhibits the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. Dasatinib is a potent, subnanomolar inhibitor of the BCR-ABL kinase with potency at concentration of 0.6-0.8 nM. It binds to both the inactive and active conformations of the BCR-ABL enzyme.

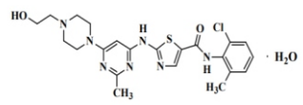
5.3 Pharmacokinetic properties
Absorption
Maximum plasma concentrations (Cmax) of dasatinib are observed between 0.5 and 6 hours (Tmax) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. 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.
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. 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 weak time-dependent inhibitor of CYP3A4. At clinically relevant concentrations, dasatinib does not inhibit CYP1A2, 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.

Hepatic Impairment
Dasatinib doses of 50 mg and 20 mg were evaluated in eight patients with moderate (Child-Pugh class B) and seven patients with severe (Child-Pugh class C) hepatic impairment, respectively. Matched controls with normal hepatic function (n=15) were also evaluated and received a dasatinib dose of 70 mg. Compared to subjects with normal liver function, patients with moderate hepatic impairment had decreases in dose normalized Cmax and AUC by 47% and 8%, respectively. Patients with severe hepatic impairment had dose normalized Cmax decreased by 43% and AUC decreased by 28% compared to the normal controls. These differences in Cmax and AUC are not clinically relevant. Dose adjustment is not necessary in patients with hepatic impairment.

6. NONCLINICAL PROPERTIES:
6.1 Animal Toxicology or Pharmacology
Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2-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 approximately 60% of the human exposure at 100 mg once daily. Dasatinib induced a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and prostate adenoma in low-dose males. 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.
Dasatinib did not affect mating or fertility in male and female rats at plasma drug exposure (AUC) similar to the human exposure at 100 mg daily. In repeat dose studies, administration of dasatinib resulted in 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.

7. DESCRIPTION:
DASATINIB (dasatinib) is a kinase inhibitor. The chemical name for dasatinib 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 $C_{22}H_{26}ClN_7O_2S$ • H2O, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol. Dasatinib tablets are white to off-white, biconvex, film-coated tablets containing Dasatinib.

8. PHARMACEUTICAL PARTICULARS
8.1 Incompatibilities
Not Applicable

8.2 Shelf-life
Please see manufacturing date and expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

8.3 Packaging information
Dasatinib Tablets 50/70 mg: HDPE bottle containing 60 tablets are packed in a mono carton along with pack insert.

8.4 Storage and handing instructions:
Do not store above 30°C.
Keep all medicine out of reach & sight of children.

9. PATIENT COUNSELLING INFORMATION
Advise the patient to read the patient labeling (Patient Information).
Bleeding
Inform patients of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising).
Myelosuppression
Inform patients of the possibility of developing low blood cell counts. Advise patients to immediately report fever particularly in association with any suggestion of infection.
Fluid Retention
Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, dry cough, chest pain on respiration, or shortness of breath) and advised to seek medical attention promptly if those symptoms arise
Pulmonary Arterial Hypertension
Inform patients of the possibility of developing pulmonary arterial hypertension (dyspnea, fatigue, hypoxia, and fluid retention) and advise them to seek medical attention promptly if those symptoms arise
Tumor Lysis Syndrome
Inform patients to immediately report and seek medical attention for any symptoms such as nausea, vomiting, weakness, edema, shortness of breath, muscle cramps, and seizures, which may indicate tumor lysis syndrome.
Growth and Development in Pediatric Patients
Inform pediatric patients and their caregivers of the possibility of developing bone growth abnormalities, bone pain, or gynecomastia and advise them to seek medical attention promptly if those symptoms arise.
Embryo-Fetal Toxicity
• Advise pregnant women of the potential risk to a fetus
• Advise females of reproductive potential to avoid pregnancy, which may include use of effective contraception during treatment with Dasatinib and for 30 days after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking dasatinib.
Lactation
Advise women that breastfeeding is not recommended during treatment with Dasatinib and for 2 weeks after the final dose.
Gastrointestinal
Complaints Inform patients that they may experience nausea, vomiting, or diarrhea with DASATINIB. Advise patients to seek medical attention if these symptoms are bothersome or persistent. Advise patients using antacids to avoid taking DASATINIB and antacids less than 2 hours apart.
Pain
Inform patients that they may experience headache or musculoskeletal pain with DASATINIB. Advise patients to seek medical attention if these symptoms are bothersome or persistent.
Fatigue
Inform patients that they may experience fatigue with DASATINIB. Advise patients to seek medical attention if this symptom is bothersome or persistent. Rash Inform patients that they may experience skin rash with DASATINIB. Advise patients to seek medical attention if this symptom is bothersome or persistent.
Lactose
Inform patients that DASATINIB contains 94.5 mg mg of lactose monohydrate in a 70 mg daily dose, 67.5 mg of lactose monohydrate in a 50-mg daily dose.
Missed Dose
Advise patients that if they miss a dose of DASATINIB, they should take the next scheduled dose at its regular time. The patient should not take two doses at the same time.

10. DETAILS OF MANUFACTURER
BDR Pharmaceuticals International Pvt. Ltd.
R. S. No. 578, Near Effluent Channel Road,
Vill. Luna, Tal. Padra, Dist. Vadodara-391 440. Gujarat.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
G/25/2071 issued on February 2020.

12. DATE OF REVISION
March, 2020

Marketed by :
APRAZER
Aprazer Healthcare Pvt. Ltd.
B-256, 2nd Floor, Naraina Phase-1,
New Delhi-110028, India
Web.: www.aprazerhealthcare.com
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