



Drug Profile of Dasatinib

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Abstract

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus not comply with prescription that results in high incidence of non-compliance and ineffective therapy. Immediate release tablets are gaining prominence as new drug delivery systems. These dosage forms dissolve or disintegrate in oral cavity within a minute without the need of water or chewing. In this study, an effort has been made to formulate immediate release tablets using different disintegrants drug. Considering the merits of Dasatinib, we are proposing to choose it as an anticancer drug.

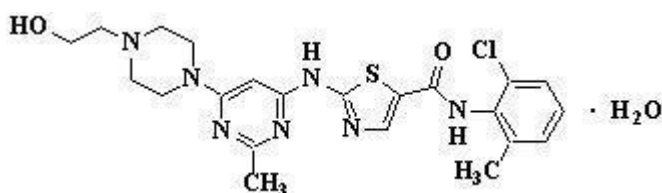
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Introduction

Drug Name: Dasatinib

Category: Anti cancer agent

Chemical structure:



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

Molecular Formula: C₂₂H₂₆ClN₇O₂S • H₂O

Molecular Weight: 506.02 (monohydrate), 488.01 (anhydrous)

Half life: 1.3 to 5 hrs

Dosage forms and Strengths: Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg.

Description: crystalline white powder

Solubility: It is poorly soluble in water and slightly soluble in acetone, acetonitrile, ethanol, methanol, polyethylene glycol.

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Melting point: 280°–286° C

Mechanism of Action: Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFR β . Dasatinib is predicted to bind to multiple conformations of the ABL kinase. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. 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.

Pharmacokinetics

Absorption: Maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 and 6 hours following oral administration.

Distribution: It has a large apparent volume of distribution (2505 L). This indicates that the drug is extensively distributed in extra vascular space. Protein binding is 96 %.

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. Other enzymes involved are Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes.

Excretion: Dasatinib is excreted mainly in faeces (85%) and urine (4%).

Uses: It is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.

It is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

Side Effects

Hematologic:

Thrombocytopenia

Anemia

Neutropenia

Hemorrhage

Neutropenia

General:

Pain

Fatigue

Abdominal pain

Mucosal inflammation

Decreased weight

Chest pain

Gastrointestinal:

Gastrointestinal side effects including diarrhea (49%), nausea (34%), vomiting (22%), anorexia (19%), gastrointestinal bleeding (14%), and constipation (14%) have been reported.

Nervous system:

Nervous system side effects including headache (40%), neuropathy (including peripheral neuropathy) (13%), and CNS bleeding (2%) have been reported

Musculoskeletal:

Musculoskeletal side effects including musculoskeletal pain (39%), arthralgia (19%), and myalgia (12%) have been reported.

Respiratory:

Respiratory side effects have included dyspnea (32%), cough (28%), upper respiratory tract infection/inflammation (26%), bacterial, viral, and fungal pneumonia (11%), pulmonary edema (4%), and pulmonary hypertension (1%).

Metabolic:

Metabolic side effects including hypophosphatemia (up to 23%) and hypocalcemia (up to 20%) have been reported. Appetite disturbances and hyperuricemia have been reported frequently. Hypoalbuminemia has been reported infrequently.

Hepatic:

Hepatic side effects including elevated SGPT (ALT) (up to 11%), elevated SGOT (AST) (up to 8%), elevated bilirubin (up to 8%), and elevated transaminase have been reported. Cholecystitis, cholestasis, and hepatitis have been reported infrequently.

Cardiovascular:

Cardiovascular side effects including arrhythmia (11%) and pericardial effusion (4%) have been reported. Palpitations, flushing, hypotension, hypertension, angina pectoris, cardiomegaly, and myocardial infarction have been reported frequently. Pericarditis, ventricular tachycardia, acute coronary syndrome, myocarditis, and QT prolongation have been reported infrequently. Congestive heart failure/cardiac dysfunction (4%) has included ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, and congestive cardiomyopathy, ejection fraction decreased, and left ventricular failure.

Dermatologic:

Dermatologic side effects including pruritus (11%) have been reported. Hyperhidrosis, alopecia, dry skin, acne, urticaria, dermatitis (including eczema), photosensitivity reaction, nail disorder, and pigmentation disorder have been reported frequently. Skin ulcer, acute febrile neutrophilic dermatosis, bullous conditions, livedo reticularis, panniculitis, palmar-plantar erythrodysesthesia syndrome have been reported infrequently. Skin rash (35%) has included erythema, exfoliative rash, generalized erythema, milia, rash, erythematous rash, follicular rash, generalized rash, macular rash, maculopapular rash, papular rash, pruritic rash, pustular rash, skin exfoliation, systemic lupus erythematosus rash, vesiculosa urticaria, drug eruption, and vesicular rash.

Renal:

Renal side effects including elevated creatinine (up to 2%) have been reported. Urinary frequency and renal failure have been reported frequently. Proteinuria has been reported infrequently.

Other:

Other side effects including infection (including bacterial, viral, fungal, and non-specified), herpes virus infection, sepsis (including fatal outcomes), enterocolitis infection, tinnitus, vertigo, and contusion have been reported frequently. Blood creatine phosphokinase increased has also been reported.

Psychiatric:

Psychiatric side effects including insomnia, depression, anxiety, confusional state, and affect lability have been reported frequently. Decreased libido has been reported infrequently.

Genitourinary:

Genitourinary side effects including gynecomastia have been reported frequently. Irregular menstruation has been reported infrequently.

Hypersensitivity:

Hypersensitivity side effects have infrequently included erythema nodosum.

Ocular:

Ocular side effects including visual disorder, conjunctivitis, and dry eyes have been reported frequently.

Oncologic:

Oncologic side effects including tumor lysis syndrome have been reported frequently.

Drug Interactions

CYP3A4 Inhibitors: May increase dasatinib drug levels and should be avoided. If co administration cannot be avoided, monitor closely.

CYP3A4 Inducers: May decrease dasatinib drug levels. If co administration cannot be avoided, consider increasing dasatinib dose.

Antacids: May decrease dasatinib drug levels. Avoid simultaneous administration. If needed, administer the antacid at least 2 hours prior to or 2 hours after the dose of dasatinib

H2 Antagonists/Proton Pump Inhibitors: May decrease dasatinib drug levels.

Storage: Dasatinib should be stored at room temperature between 15-300°C (59-86 F).

Conclusion

Various formulation trails of dasatinib tablets were conducted using three super disintegrants like Croscarmellose sodium, sodium starch glycolate and crospovidone. These three super disintegrants were used at three different concentrations like 2.5%, 3.5% and 4.5%. Performed 9 formulation trials were done. In that various preformulation parameters were conducted that which has given two good results that which were present within the limit as per B.P.

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