Imatinib: Drug information

(For additional information see "Imatinib: Patient drug information" and see "Imatinib: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Gleevec

Brand Names: Canada

ACT-Imatinib; Apo-Imatinib; Gleevec; Teva-Imatinib

Pharmacologic Category

Antineoplastic Agent, BCR-ABL Tyrosine Kinase Inhibitor; Antineoplastic Agent, Tyrosine Kinase Inhibitor

Dosing: Adult

Note: Treatment may be continued until disease progression or unacceptable toxicity. The optimal duration of therapy for chronic myeloid leukemia (CML) in complete remission is not yet determined. Discontinuing CML treatment is not recommended unless part of a clinical trial (Baccarani 2009). Imatinib is associated with a moderate emetic potential; antiemetics may be recommended to prevent nausea and vomiting (Roila 2010).

Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML): Oral:

Chronic phase: 400 mg once daily; may be increased to 600 mg daily, if tolerated, for disease progression, lack of hematologic response after 3 months, lack of cytogenetic response after 6 to 12 months, or loss of previous hematologic or cytogenetic response. An increase to 800 mg daily has been used (Cortes, 2010; Hehlmann, 2014).

Accelerated phase or blast crisis: 600 mg once daily; may be increased to 800 mg daily (400 mg twice daily), if tolerated, for disease progression, lack of hematologic response after 3 months, lack of cytogenetic response after 6 to 12 months, or loss of previous hematologic or cytogenetic response

Ph+ acute lymphoblastic leukemia (ALL) (relapsed or refractory): Oral: 600 mg once daily

Gastrointestinal stromal tumors (GIST) (adjuvant treatment following complete resection): Oral: 400 mg once daily; recommended treatment duration: 3 years

GIST (unresectable and/or metastatic malignant): Oral: 400 mg once daily; may be increased up to 800 mg daily (400 mg twice daily), if tolerated, for disease progression. **Note:** Significant improvement (progression-free survival, objective response rate) was demonstrated in patients with KIT exon 9 mutation with 800 mg (versus 400 mg), although overall survival (OS) was not impacted. The higher dose did not demonstrate a difference in time to progression or OS patients with Kit exon 11 mutation or wild-type status (Debiec-Rychter, 2006; Heinrich, 2009).

Aggressive systemic mastocytosis (ASM) with eosinophilia: Oral: Initiate at 100 mg once daily; titrate up to a maximum of 400 mg once daily (if tolerated) for insufficient response to lower dose

ASM without D816V c-Kit mutation or c-Kit mutation status unknown: Oral: 400 mg once daily

Dermatofibrosarcoma protuberans (DFSP): Oral: 400 mg twice daily

Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL): Oral: 400 mg once daily

HES/CEL with FIP1L1-PDGFRα fusion kinase: Oral: Initiate at 100 mg once daily; titrate up to a maximum of 400 mg once daily (if tolerated) if insufficient response to lower dose

Myelodysplastic/myeloproliferative disease (MDS/MPD) with PDGF receptor gene rearrangements: Oral: 400 mg once daily

Chordoma, progressive, advanced, or metastatic expressing PDGFRB and/or PDGFB (off-label use): Oral: 400 mg twice daily (Stacchiotti 2012)

Desmoid tumors, unresectable and/or progressive (off-label use): Oral: 300 mg twice daily (BSA ≥1.5 m^2), 200 mg twice daily (BSA 1 to 1.49 m^2), 100 mg twice daily (BSA <1 m^2) (Chugh 2010) **or** 400 mg once daily; may increase to 400 mg twice daily if progressive disease on 400 mg daily (Penel 2011)

Melanoma, advanced or metastatic with C-KIT mutation (off-label use): Oral: 400 mg twice daily (Carvajal 2011)

Stem cell transplant (SCT, off-label use) for CML (in patients who have not failed imatinib therapy prior to transplant): Oral:

Prophylactic use to prevent relapse post SCT: 400 mg daily starting after engraftment for 1 year post transplant (Carpenter 2007) **or** 300 mg daily starting on day +35 post SCT (increased to 400 mg within 4 weeks) and continued until 12 months post transplant (Olavarria 2007)

Relapse post SCT: Initial: 400 mg daily; if inferior response after 3 months, dose may be increased to 600 to 800 mg daily (Hess 2005) **or** 400 to 600 mg daily (chronic phase) **or** 600 mg daily (blast or accelerated phase) (DeAngelo 2004)

Dosage adjustment with concomitant strong CYP3A4 inducers: Avoid concomitant use of strong CYP3A4 inducers (eg, dexamethasone, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin); if concomitant use cannot be avoided, increase imatinib dose by at least 50% with careful monitoring.

Dosing: Pediatric

(For additional information see "Imatinib: Pediatric drug information")

Note: Treatment may be continued until disease progression or unacceptable toxicity. The optimal duration of therapy for CML in complete remission is not yet determined. Imatinib is associated with a moderate emetic potential; antiemetics may be recommended to prevent nausea and vomiting (Dupuis, 2011).

Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) (newly diagnosed): Children ≥1 year and Adolescents: Oral: 340 mg/m^2/day (in combination with chemotherapy); maximum: 600 mg daily

Ph+ chronic myeloid leukemia (CML), chronic phase, newly diagnosed: Children ≥1 year and Adolescents: Oral: 340 mg/m^2/day; maximum: 600 mg daily

Dosage adjustment with concomitant strong CYP3A4 inducers: Avoid concomitant use of strong CYP3A4 inducers (eg, dexamethasone, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin); if concomitant use cannot be avoided, increase imatinib dose by at least 50% with careful monitoring.

Dosage adjustment for hepatotoxicity: Refer to "Hepatic Impairment" dosing.

Dosage adjustment for hematologic adverse reactions: Refer to dosing adjustment for toxicity.

Dosage adjustment for nonhematologic adverse reactions: Refer to dosing adjustment for toxicity.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

CrCl 40 to 59 mL/minute: Maximum recommended dose: 600 mg.

CrCl 20 to 39 mL/minute: Decrease recommended starting dose by 50%; dose may be increased as tolerated; maximum recommended dose: 400 mg.

CrCl <20 mL/minute: Use caution; a dose of 100 mg daily has been tolerated in a limited number of patients with severe impairment (Gibbons 2008).

Dosing: Hepatic Impairment

Mild-to-moderate impairment: No dosage adjustment necessary.

Severe impairment: Reduce dose by 25%.

Dosage adjustment for hepatotoxicity (during therapy): If elevations of bilirubin >3 times ULN or transaminases >5 times ULN occur, withhold treatment until bilirubin <1.5 times ULN and transaminases <2.5 times ULN. Resume treatment at a reduced dose as follows (**Note:** The decision to resume treatment should take into consideration the initial severity of hepatotoxicity):

Adults:

If current dose 400 mg daily, reduce dose to 300 mg daily

If current dose 600 mg daily, reduce dose to 400 mg daily

If current dose 800 mg daily, reduce dose to 600 mg daily

Children ≥1 year and Adolescents: If current dose 340 mg/m^2/day, reduce dose to 260 mg/m^2/day

Dosing: Adjustment for Toxicity

Hematologic toxicity:

Chronic phase CML (initial dose 400 mg daily in adults or 340 mg/m^2/day in children); ASM, MDS/MPD, and HES/CEL (initial dose 400 mg daily); or GIST (initial dose 400 mg daily): If ANC <1 x 10^9/L and/or

platelets <50 x 10^9/L: Withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at original starting dose. For recurrent neutropenia and/or thrombocytopenia, withhold until recovery, and reinstitute treatment at a reduced dose as follows:

Children ≥1 year and Adolescents: If initial dose 340 mg/m^2/day, reduce dose to 260 mg/m^2/day.

Adults: If initial dose 400 mg daily, reduce dose to 300 mg daily.

CML (accelerated phase or blast crisis): Adults (initial dose 600 mg daily): If ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L, establish whether cytopenia is related to leukemia (bone marrow aspirate or biopsy). If unrelated to leukemia, reduce dose to 400 mg daily. If cytopenia persists for an additional 2 weeks, further reduce dose to 300 mg daily. If cytopenia persists for 4 weeks and is still unrelated to leukemia, withhold treatment until ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L, then resume treatment at 300 mg daily.

ASM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase: Adults (starting dose 100 mg daily): If ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: Withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at previous dose.

DFSP: Adults (initial dose 800 mg daily): If ANC <1 x 10^9/L and/or platelets <50 x 10^9/L, withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at reduced dose of 600 mg daily. For recurrent neutropenia and/or thrombocytopenia, withhold until recovery, and reinstitute treatment with a further dose reduction to 400 mg daily.

Ph+ ALL:

Pediatrics (Schultz 2009): Hematologic toxicity requiring dosage adjustments was not observed in the study. No major toxicities were observed with imatinib at 340 mg/m^2/day in combination with intensive chemotherapy.

Adults (initial dose 600 mg daily): If ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L, establish whether cytopenia is related to leukemia (bone marrow aspirate or biopsy). If unrelated to leukemia, reduce dose to 400 mg daily. If cytopenia persists for an additional 2 weeks, further reduce dose to 300 mg daily. If cytopenia persists for 4 weeks and is still unrelated to leukemia, withhold treatment until ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L, then resume treatment at 300 mg daily.

Nonhematologic toxicity (eg, severe edema): Withhold treatment until toxicity resolves; may resume if appropriate (depending on initial severity of adverse event).

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Gleevec: 100 mg, 400 mg [scored]

Generic: 100 mg, 400 mg

Generic Equivalent Available (US)

Yes

Administration

Imatinib is associated with a moderate emetic potential; antiemetics may be recommended to prevent nausea and vomiting (Dupuis 2011; Roila 2010).

Should be administered with a meal and a large glass of water. For daily dosing ≥800 mg, the 400 mg tablets should be used in order to reduce iron exposure. Do not crush tablets. Tablets may be dispersed in water or apple juice (using ~50 mL for 100 mg tablet, ~200 mL for 400 mg tablet); stir until dissolved and administer immediately. If necessary, an oral suspension may be prepared (see Extemporaneously Prepared). Avoid skin or mucous membrane contact with crushed tablets; if contact occurs, wash thoroughly. Avoid exposure to crushed tablets.

Adults: Doses ≤600 mg may be given once daily; 800 mg dose should be administered as 400 mg twice daily.

Children: Dosing may be once or twice daily for chronic myeloid leukemia (CML) and once daily for Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL).

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration (NIOSH 2016).

Use

Acute lymphoblastic leukemia: Treatment of relapsed or refractory Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) in adults

Treatment of newly diagnosed Ph+ ALL in children (in combination with chemotherapy)

Aggressive systemic mastocytosis: Treatment of aggressive systemic mastocytosis without D816V c-Kit mutation as determined by an approved test (or c-Kit mutational status unknown) in adults

Chronic myeloid leukemia: Treatment of Ph+ chronic myeloid leukemia (CML) in chronic phase (newly diagnosed) in adults and children

Treatment of Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alfa therapy

Dermatofibrosarcoma protuberans: Treatment of unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP) in adults

Gastrointestinal stromal tumors: Treatment of Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)

Adjuvant treatment of Kit (CD117)–positive GIST following complete gross resection

Hypereosinophilic syndrome and/or chronic eosinophilic leukemia: Treatment of hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) in adult patients who have the FIP1L1–platelet-derived growth factor (PDGF) receptor alpha fusion kinase (mutational analysis or fluorescent in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGF receptor alpha fusion kinase negative or unknown

Myelodysplastic/Myeloproliferative diseases: Treatment of myelodysplastic syndrome/myeloproliferative diseases (MDS/MPD) associated with PDGF receptor gene rearrangements as determined by an approved test in adults

Use: Off-Label

Chordoma; Chronic myeloid leukemia (CML) post-stem cell transplantation (SCT) (allogeneic) (follow-up treatment); Desmoid tumor; Melanoma, advanced or metastatic (C-KIT mutated tumors)

Medication Safety Issues

Sound-alike/look-alike issues:

Imatinib may be confused with axitinib, dasatinib, erlotinib, gefitinib, ibrutinib, idelalisib, nilotinib, nintedanib, PONATinib, SORAfenib, SUNItinib, vandetanib

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

Adverse reactions listed as a composite of data across many trials, except where noted for a specific indication.

>10%:

Cardiovascular: Edema (11% to 86%; includes aggravated edema, anasarca, ascites, pericardial effusion, peripheral edema, pulmonary edema, and superficial edema), facial edema (≤17%), chest pain (7% to 11%), hypotension (Ph+ ALL [pediatric])

Central nervous system: Fatigue (20% to 75%), pain (≤47%), headache (8% to 37%), dizziness (5% to 19%), insomnia (9% to 15%), depression (3% to 15%), taste disorder (≤13%), rigors (10% to 12%), anxiety (8% to 12%), paresthesia (≤12%), chills (≤11%)

Dermatologic: Skin rash (9% to 50%), dermatitis (GIST: ≤39%), pruritus (7% to 26%), night sweats (CML: 13% to 17%), alopecia (7% to 15%), diaphoresis (GIST: ≤13%)

Endocrine & metabolic: Increased lactate dehydrogenase (≤60%), weight gain (5% to 32%), decreased serum albumin (≤21%), hypokalemia (6% to 13%)

Gastrointestinal: Nausea (41% to 73%), diarrhea (25% to 59%), vomiting (11% to 58%), abdominal

pain (3% to 57%), anorexia (≤36%), dyspepsia (11% to 27%), flatulence (≤25%), abdominal distension (≤19%), constipation (8% to 16%), stomatitis (≤16%)

Hematologic & oncologic: Hemorrhage (3% to 53%; grades 3/4: ≤19%), leukopenia (GIST: 5% to 47%; grades 3/4: 2%), hypoproteinemia (≤32%), anemia, neutropenia, thrombocytopenia

Hepatic: Increased serum AST (≤38%), increased serum ALT (≤34%), increased alkaline phosphatase (≤17%), increased serum bilirubin (≤13%), increased serum transaminases (Ph+ ALL [pediatric])

Infection: Influenza (Ph+ CML: ≤14%), infection (Ph+ ALL [pediatric])

Neuromuscular & skeletal: Muscle cramps (16% to 62%), musculoskeletal pain (adults: 38% to 49%; children: 21%), arthralgia (11% to 40%), myalgia (9% to 32%), weakness (≤21%), back pain (≤17%), limb pain (≤16%), ostealgia (≤11%)

Ophthalmic: Periorbital edema (15% to 74%), increased lacrimation (DFSP: 25%; GIST: ≤18%), eyelid edema (Ph+ CML: 19%), blurred vision (≤11%)

Renal: Increased serum creatinine (≤44%)

Respiratory: Nasopharyngitis (1% to 31%), cough (11% to 27%), upper respiratory tract infection (3% to 21%), dyspnea (≤21%), pharyngolaryngeal pain (≤18%), rhinitis (DFSP: 17%), pharyngitis (CML: 10% to 15%), flu-like symptoms (1% to 14%), pneumonia (CML: 4% to 13%), sinusitis (4% to 11%)

Miscellaneous: Fever (6% to 41%)

1% to 10%:

Cardiovascular: Palpitations (≤5%), hypertension (≤4%), cardiac failure (Ph+ CML: 1%), flushing, pleural effusion (Ph+ ALL [pediatric])

Central nervous system: Cerebral hemorrhage (≤9%), hypoesthesia, peripheral neuropathy

Dermatologic: Skin photosensitivity (4% to 7%), xeroderma (≤7%), erythema, nail disease

Endocrine & metabolic: Hypophosphatemia (10%), hyperglycemia (≤10%), weight loss (≤10%), hypocalcemia (GIST: ≤6%), fluid retention (Ph+ CML: 3%; pleural effusion, pericardial effusion, ascites, or pulmonary edema: 2%), hyperkalemia (1%)

Gastrointestinal: Decreased appetite (10%), gastroenteritis (≤10%), gastrointestinal hemorrhage (1% to 8%), gastritis, gastroesophageal reflux, increased serum lipase, xerostomia

Hematologic & oncologic: Lymphocytopenia (≤10%; grades 3/4: 1% to 2%), eosinophilia, febrile neutropenia, pancytopenia, purpura

Neuromuscular & skeletal: Joint swelling

Ophthalmic: Conjunctivitis (5% to 8%), conjunctival hemorrhage, dry eyes

Respiratory: Hypoxia (9%), oropharyngeal pain (Ph+ CML: ≤6%), epistaxis, pneumonitis (Ph+ ALL [pediatric])

<1%, postmarketing, and/or case reports: Actinic keratosis, acute generalized exanthematous

pustulosis, anaphylactic shock, angina pectoris, angioedema, aplastic anemia, arthritis, ascites, atrial fibrillation, avascular necrosis of bones, blepharitis, bullous rash, cardiac arrhythmia, cardiac tamponade, cardiogenic shock, cataract, cellulitis, cerebral edema, cheilitis, cold extremities, colitis, confusion, decreased libido, decreased linear skeletal growth rate (children), dehydration, diverticulitis, DRESS syndrome, drowsiness, dyschromia, dysphagia, embolism, eructation, erythema multiforme, esophagitis, exfoliative dermatitis, folliculitis, fungal infection, gastric ulcer, gastrointestinal obstruction, gastrointestinal perforation, glaucoma, gout, gynecomastia, hearing loss, hematemesis, hematoma, hematuria, hemolytic anemia, hepatic failure, hepatic necrosis, hepatitis, hepatotoxicity, herpes simplex infection, herpes zoster, hypercalcemia, hypermenorrhea, hypersensitivity angiitis, hyperuricemia, hypomagnesemia, hyponatremia, hypothyroidism, IgA vasculitis, increased creatine phosphokinase, increased intracranial pressure, inflammatory bowel disease, interstitial pneumonitis, interstitial pulmonary disease, intestinal obstruction, jaundice, left ventricular dysfunction, lichen planus, lower respiratory tract infection, lymphadenopathy, macular edema, melena, memory impairment, menstrual disease, migraine, myocardial infarction, myopathy, onychoclasis, optic neuritis, oral mucosa ulcer, osteonecrosis (hip), ovarian cyst (hemorrhagic), palmar-plantar erythrodysesthesia, pancreatitis, papilledema, pericarditis, petechia, pleuritic chest pain, polyuria, psoriasis, pulmonary fibrosis, pulmonary hemorrhage, pulmonary hypertension, Raynaud phenomenon, reactivation of HBV, renal failure, respiratory failure, restless leg syndrome, retinal hemorrhage, rhabdomyolysis, ruptured corpus luteal cyst, sciatica, scrotal edema, seizure, sepsis, sexual disorder, Stevens-Johnson syndrome, subconjunctival hemorrhage, subdural hematoma, Sweet syndrome, syncope, tachycardia, telangiectasia (gastric antral), thrombocythemia, thrombosis, tinnitus, toxic epidermal necrolysis, tremor, tumor hemorrhage (GIST), tumor lysis syndrome, urinary tract infection, urticaria, vertigo, vesicular eruption, vitreous hemorrhage

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to imatinib or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: May cause bone marrow suppression (anemia, neutropenia, and thrombocytopenia), usually occurring within the first several months of treatment. Median duration of neutropenia is 2 to 3 weeks; median duration of thrombocytopenia is 2 to 4 weeks. Monitor blood counts weekly for the first month, biweekly for the second month, and as clinically necessary thereafter. In chronic myeloid leukemia (CML), cytopenias are more common in accelerated or blast phase than in chronic phase.

• Cardiovascular effects: Severe heart failure (HF) and left ventricular dysfunction (LVD) have been reported (occasionally). Cardiac adverse events usually occur in patients with advanced age or comorbidities. Carefully monitor patients with preexisting cardiac disease or risk factors for HF or history of renal failure. With initiation of imatinib treatment, cardiogenic shock and/or LVD have been reported in patients with hypereosinophilic syndrome (HES) and cardiac involvement (reversible with systemic steroids, circulatory support and temporary cessation of imatinib). Echocardiogram and serum troponin monitoring may be considered in patients with HES/chronic eosinophilic leukemia (CEL) and in patients with myelodysplastic/myeloproliferative (MDS/MPD) disease or

aggressive systemic mastocytosis associated with high eosinophil levels. Patients with high eosinophil levels and an abnormal echocardiogram or abnormal serum troponin level may benefit from prophylactic systemic steroids (for 1 to 2 weeks) with the initiation of imatinib. In a scientific statement from the American Heart Association, imatinib has been determined to be an agent that may either cause direct myocardial toxicity (rare) or exacerbate underlying myocardial dysfunction (magnitude: moderate) (AHA [Page 2016]).

• Dermatologic reactions: Severe bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported; recurrence has been described with rechallenge. Case reports of successful resumption at a lower dose (with corticosteroids and/or antihistamine) have been described; however, some patients may experience recurrent reactions. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. Symptoms of DRESS include fever, severe skin eruption, lymphadenopathy, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement. If symptoms of DRESS occur, interrupt therapy and consider permanently discontinuing; symptoms regressed upon discontinuation of therapy, however, symptoms recurred in all cases when rechallenged.

• Driving/heavy machinery: Caution is recommended while driving/operating motor vehicles and heavy machinery when taking imatinib; advise patients regarding side effects such as dizziness, blurred vision, or somnolence. Reports of accidents have been received, but it is unclear if imatinib has been the direct cause in any case.

• Fluid retention/edema: Imatinib is commonly associated with fluid retention, weight gain, and edema (risk increases with higher doses and age >65 years); may be occasionally serious and lead to significant complications, including pleural effusion, pericardial effusion, pulmonary edema, and ascites. Monitor regularly for rapid weight gain or other signs/symptoms of fluid retention; rapid unexpected weight gain should be evaluated and managed appropriately. Use with caution in patients where fluid accumulation may be poorly tolerated, such as in cardiovascular disease (HF or hypertension) and pulmonary disease.

• GI toxicity: Imatinib is associated with a moderate emetic potential; antiemetics may be recommended to prevent nausea and vomiting (Dupuis, 2011; Roila, 2010). May cause GI irritation; take with food and water to minimize irritation. There have been rare reports (including fatalities) of GI perforation.

• Hemorrhage: Severe hemorrhage (grades 3 and 4) has been reported with use, including GI hemorrhage and/or tumor hemorrhage. The incidence of hemorrhage is higher in patients with gastrointestinal stromal tumors (GIST) (GI tumors may have been hemorrhage source). Gastric antral vascular ectasia (a rare cause of gastrointestinal bleeding) has also been reported (Alshehry 2014; Saad Aldin 2012). Monitor for GI symptoms with treatment initiation.

• Hepatotoxicity: Hepatotoxicity may occur; fatal hepatic failure and severe hepatic injury requiring liver transplantation have been reported with both short- and long-term use; monitor liver function (transaminases, bilirubin, and alkaline phosphatase) prior to initiation and monthly or as needed thereafter; therapy interruption or dose reduction may be necessary. Transaminase and bilirubin elevations, and acute liver failure have been observed with imatinib in combination with chemotherapy.

• Nephrotoxicity: Imatinib is associated with acute kidney injury and a decline in renal function (may be associated with duration of therapy); monitor renal function periodically during treatment (Marcolino 2011).

• Tumor lysis syndrome: Tumor lysis syndrome (TLS), including fatalities, has been reported in patients with acute lymphoblastic leukemia (ALL), CML eosinophilic leukemias, and GIST. Risk for TLS is higher in patients with a high tumor burden or high proliferation rate; monitor closely. Correct clinically significant dehydration and treat high uric acid levels prior to initiation of imatinib.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended in patients with severe impairment.

• Gastric surgery: Imatinib exposure may be reduced in patients who have had gastric surgery (eg, bypass, major gastrectomy, or resection); monitor imatinib trough concentrations (Liu 2011; Pavlovsky 2009; Yoo 2010).

• Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended for moderate and severe renal impairment (CrCl <40 mL/minute).

• Thyroid disease: Hypothyroidism has been reported in thyroidectomy patients who were receiving thyroid hormone replacement therapy prior to initiation of imatinib; monitor thyroid function. The average onset for imatinib-induced hypothyroidism is 2 weeks; consider doubling levothyroxine doses upon initiation of imatinib (Hamnvik 2011).

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Special populations:

• Elderly: The incidence of edema was increased with age older than 65 years in CML and GIST studies.

• Pediatric: Growth retardation has been reported in children receiving imatinib for the treatment of CML; generally where treatment was initiated in prepubertal children; growth velocity was usually restored as pubertal age was reached (Shima 2011). Monitor growth closely.

Other warnings/precautions:

• Appropriate use: Determine PDGFRb gene rearrangements status (for MDS/MPD), D816V c-Kit mutation status (for aggressive systemic mastocytosis [ASM]), Philadelphia chromosome status for acute lymphoblastic leukemia and chronic myeloid leukemia, Kit (CD117)-positivity for GIST, and FIP1L1–platelet-derived growth factor (PDGF) receptor status for HES or CEL prior to initiating treatment.

Metabolism/Transport Effects

Substrate of CYP1A2 (minor), CYP2C19 (minor), CYP2C8 (minor), CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (major), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** BCRP, CYP2C9 (weak), CYP3A4 (moderate)

Drug Interactions

(For additional information: Launch drug interactions program)

Acetaminophen: May enhance the hepatotoxic effect of Imatinib. *Risk C: Monitor therapy*

AmLODIPine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of AmLODIPine. *Risk C: Monitor therapy*

Apixaban: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Apixaban. *Risk C: Monitor therapy*

Aprepitant: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Aprepitant. *Risk X: Avoid combination*

ARIPiprazole: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of ARIPiprazole. Management: Monitor for increased aripiprazole pharmacologic effects. Aripiprazole dose adjustments may or may not be required based on concomitant therapy and/or indication. Consult full interaction monograph for specific recommendations. *Risk C: Monitor therapy*

Asunaprevir: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Asunaprevir. *Risk X: Avoid combination*

Avanafil: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Avanafil. Management: The maximum avanafil adult dose is 50 mg per 24-hour period when used together with a moderate CYP3A4 inhibitor. Patients receiving such a combination should also be monitored more closely for evidence of adverse effects. *Risk D: Consider therapy modification*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Blonanserin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Blonanserin. *Risk C: Monitor therapy*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Bosentan: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Bosentan. Management: Concomitant use of both a CYP2C9 inhibitor and a CYP3A inhibitor or a single agent that inhibits both enzymes with bosentan is likely to cause a large increase in serum concentrations of bosentan and is not recommended. See monograph for details. *Risk C: Monitor therapy*

Bosutinib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Bosutinib. *Risk X: Avoid combination*

Brexpiprazole: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Brexpiprazole. Management: The brexpiprazole dose should be reduced to 25% of usual if used together with both a moderate CYP3A4 inhibitor and a strong or moderate CYP2D6 inhibitor, or if a moderate CYP3A4 inhibitor is used in a CYP2D6 poor metabolizer. *Risk C: Monitor therapy*

Bromocriptine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Bromocriptine. Management: The bromocriptine dose should not exceed 1.6 mg daily with use of a moderate CYP3A4 inhibitor. The Cycloset brand specifically recommends this dose limitation, but other bromocriptine products do not make such specific recommendations. *Risk D: Consider therapy modification*

Budesonide (Systemic): CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Budesonide (Systemic). *Risk X: Avoid combination*

Budesonide (Topical): CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Budesonide (Topical). Management: Per US prescribing information, avoid this combination. Canadian product labeling does not recommend strict avoidance. If combined, monitor for excessive glucocorticoid effects as budesonide exposure may be increased. *Risk D: Consider therapy modification*

Cannabis: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Cannabis. More specifically, tetrahydrocannabinol and cannabidiol serum concentrations may be increased. *Risk C: Monitor therapy*

Cilostazol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Cilostazol. Management: Consider reducing the cilostazol dose to 50 mg twice daily in adult patients who are also receiving moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Cobimetinib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Cobimetinib. Management: Avoid the concomitant use of cobimetinib and moderate CYP3A4 inhibitors. If concurrent short term (14 days or less) use cannot be avoided, reduce the cobimetinib dose to 20 mg daily. *Risk X: Avoid combination*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Colchicine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Colchicine. Management: Reduce colchicine dose as directed when using with a moderate CYP3A4 inhibitor, and increase monitoring for colchicine-related toxicity. Use extra caution in patients with impaired renal and/or hepatic function. *Risk D: Consider therapy modification*

CycloSPORINE (Systemic): Imatinib may increase the serum concentration of CycloSPORINE (Systemic). *Risk C: Monitor therapy*

CYP2D6 Substrates: Imatinib may increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Imatinib. Management: Avoid concurrent use of imatinib with strong CYP3A4 inducers when possible. If such a combination must be used, increase imatinib dose by at least 50% and monitor the patient's clinical response closely. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Imatinib. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Imatinib. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. **Exceptions:** Alitretinoin (Systemic); Praziquantel; Vinorelbine. *Risk C: Monitor therapy*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dapoxetine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Dapoxetine. Management: The dose of dapoxetine should be limited to 30 mg/day when used together with a moderate inhibitor of CYP3A4. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Deflazacort: CYP3A4 Inhibitors (Moderate) may increase serum concentrations of the active metabolite(s) of Deflazacort. Management: Administer one third of the recommended deflazacort dose when used together with a strong or moderate CYP3A4 inhibitor. *Risk D: Consider therapy modification*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dexamethasone (Systemic): May decrease the serum concentration of Imatinib. Management: Avoid concurrent use of imatinib with dexamethasone when possible. If such a combination must be used, increase imatinib dose by at least 50% and monitor clinical response closely. *Risk D: Consider therapy modification*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Dofetilide: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Dofetilide. *Risk C: Monitor therapy*

Domperidone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Domperidone. *Risk X: Avoid combination*

DOXOrubicin (Conventional): CYP3A4 Inhibitors (Moderate) may increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to moderate CYP3A4 inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

Dronabinol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Dronabinol. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Eletriptan: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eletriptan. Management: The use of eletriptan within 72 hours of a moderate CYP3A4 inhibitor should be avoided. *Risk D: Consider therapy modification*

Eliglustat: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eliglustat. Management: Use should be avoided under some circumstances. See full drug interaction monograph for details. *Risk D: Consider therapy modification*

Enzalutamide: May decrease the serum concentration of CYP3A4 Substrates. Management: Concurrent use of enzalutamide with CYP3A4 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP3A4 substrate should be performed with caution and close monitoring. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: When used concomitantly with moderate inhibitors of CYP3A4, eplerenone dosing recommendations vary by indication and international labeling. See full drug interaction monograph for details. *Risk D: Consider therapy modification*

Everolimus: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Everolimus. Management: Everolimus dose reductions are required for patients being treated for subependymal giant cell astrocytoma or renal cell carcinoma. See prescribing information for specific dose adjustment and monitoring recommendations. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. Management: Monitor patients closely for several days following initiation of this combination, and adjust fentanyl dose as necessary. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Flibanserin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Flibanserin. *Risk X: Avoid combination*

Fludarabine: Imatinib may diminish the myelosuppressive effect of Fludarabine. Imatinib may decrease the serum concentration of Fludarabine. More specifically, imatinib may decrease the formation of fludarabine active metabolite F-ara-ATP Management: Due to the risk for impaired fludarabine response, consider discontinuing imatinib therapy at least 5 days prior to initiating fludarabine conditioning therapy in CML patients undergoing HSCT. *Risk D: Consider therapy modification*

Gemfibrozil: May decrease serum concentrations of the active metabolite(s) of Imatinib. Specifically N-desmethylimatinib concentrations may be decreased. Gemfibrozil may decrease the serum concentration of Imatinib. *Risk C: Monitor therapy*

Grapefruit Juice: May increase the serum concentration of Imatinib. *Risk X: Avoid combination*

GuanFACINE: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of GuanFACINE. Management: Reduce the guanfacine dose by 50% when initiating this combination. *Risk D: Consider therapy modification*

Halofantrine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Halofantrine. *Risk D: Consider therapy modification*

HYDROcodone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of HYDROcodone. *Risk C: Monitor therapy*

HydrOXYzine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of HydrOXYzine. Management: This combination is specifically contraindicated in some non-U.S. labeling. *Risk D: Consider therapy modification*

Ibrutinib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ibrutinib. Management: If a moderate CYP3A inhibitor must be used, consider reducing the dose of ibrutinib to 140mg daily and monitor closely for signs of toxicity. *Risk X: Avoid combination*

Ibuprofen: May decrease the serum concentration of Imatinib. Specifically, ibuprofen may decrease intracellular concentrations of imatinib, leading to decreased clinical response. Management: Consider using an alternative to ibuprofen in patients who are being treated with imatinib. Available evidence suggests other NSAIDs do not interact in a similar manner. *Risk D: Consider therapy modification*

Ifosfamide: CYP3A4 Inhibitors (Moderate) may decrease serum concentrations of the active metabolite(s) of Ifosfamide. *Risk C: Monitor therapy*

Ivabradine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ivabradine. *Risk X: Avoid combination*

Ivacaftor: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ivacaftor. Management: Ivacaftor dose reductions are required; consult full monograph content for specific age- and weight-based recommendations. No dose adjustment is needed when using ivacaftor/lumacaftor with a moderate CYP3A4 inhibitor. *Risk D: Consider therapy modification*

Lansoprazole: May enhance the dermatologic adverse effect of Imatinib. *Risk C: Monitor therapy*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lomitapide: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Lomitapide. *Risk X: Avoid combination*

Lurasidone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Lurasidone. Management: Lurasidone US labeling recommends reducing lurasidone dose by half with a moderate CYP3A4 inhibitor. Some non-US labeling recommends initiating lurasidone at 20 mg/day and limiting dose to 40 mg/day; avoid concurrent use of grapefruit products. *Risk D: Consider therapy modification*

Manidipine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Manidipine. *Risk C: Monitor therapy*

Mirodenafil: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Mirodenafil. *Risk C: Monitor therapy*

Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. *Risk D: Consider therapy modification*

Naldemedine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Naldemedine. *Risk C: Monitor therapy*

Naloxegol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Naloxegol. *Risk X: Avoid combination*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically,

the risk of concurrent infection may be increased. *Risk X: Avoid combination*

NiMODipine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of NiMODipine. *Risk C: Monitor therapy*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Olaparib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Olaparib. Management: Avoid use of moderate CYP3A4 inhibitors in patients being treated with olaparib. If such concurrent use cannot be avoided, the dose of olaparib should be reduced to 200 mg twice daily. *Risk X: Avoid combination*

OxyCODONE: CYP3A4 Inhibitors (Moderate) may enhance the adverse/toxic effect of OxyCODONE. CYP3A4 Inhibitors (Moderate) may increase the serum concentration of OxyCODONE. Serum concentrations of the active metabolite Oxymorphone may also be increased. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Pimozide: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Pimozide. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Propacetamol: May enhance the hepatotoxic effect of Imatinib. *Risk C: Monitor therapy*

Propafenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Propafenone. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine adult dose to a maximum of 500 mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Imatinib. Management: Avoid concurrent use of imatinib with the rifamycin derivatives when possible. If such a combination must be used, increase imatinib dose by at least 50% and monitor the patient's clinical response closely. *Risk D: Consider therapy modification*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Rupatadine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Rupatadine. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

SAXagliptin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of SAXagliptin. *Risk C: Monitor therapy*

Sildenafil: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Sildenafil. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Simeprevir: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Simeprevir. *Risk X: Avoid combination*

Simvastatin: Imatinib may decrease the metabolism of Simvastatin. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

Sonidegib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Sonidegib. Management: Avoid concomitant use of sonidegib and moderate CYP3A4 inhibitors when possible. When concomitant use cannot be avoided, limit CYP3A4 inhibitor use to less than 14 days and monitor for sonidegib toxicity (particularly musculoskeletal adverse reactions). *Risk D: Consider therapy modification*

St John's Wort: May increase the metabolism of Imatinib. *Risk D: Consider therapy modification*

Suvorexant: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Suvorexant. *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Telithromycin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Telithromycin. *Risk C: Monitor therapy*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tetrahydrocannabinol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Tetrahydrocannabinol. *Risk C: Monitor therapy*

Ticagrelor: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ticagrelor. *Risk C: Monitor therapy*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Tolvaptan: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Tolvaptan. *Risk X:*

Avoid combination

Trabectedin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Trabectedin. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Udenafil: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Udenafil. *Risk C: Monitor therapy*

Ulipristal: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ulipristal. Management: This is specific for when ulipristal is being used for signs/symptoms of uterine fibroids (Canadian indication). When ulipristal is used as an emergency contraceptive, patients receiving this combination should be monitored for ulipristal toxicity. *Risk X: Avoid combination*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Venetoclax: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Venetoclax. Management: Reduce the venetoclax dose by at least 50% in patients requiring these combinations. *Risk D: Consider therapy modification*

Vilazodone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Vilazodone. *Risk C: Monitor therapy*

Vindesine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Vindesine. *Risk C: Monitor therapy*

Warfarin: Imatinib may enhance the anticoagulant effect of Warfarin. Imatinib may decrease the metabolism of Warfarin. *Risk D: Consider therapy modification*

Zopiclone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Zopiclone. Management: The starting adult dose of zopiclone should not exceed 3.75 mg if combined with a moderate CYP3A4 inhibitor. Monitor patients for signs and symptoms of zopiclone toxicity if these agents are combined. *Risk D: Consider therapy modification*

Zuclopenthixol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Zuclopenthixol. *Risk C: Monitor therapy*

Food Interactions Food may reduce GI irritation. Grapefruit juice may increase imatinib plasma concentration. Management: Take with a meal and a large glass of water. Avoid grapefruit juice. Maintain adequate hydration, unless instructed to restrict fluid intake.

Pregnancy Implications Adverse events have been observed in animal reproduction studies.

Women of childbearing potential are advised not to become pregnant (female patients and female partners of male patients); highly effective contraception should be used during treatment and for 2 weeks after the last imatinib dose. Case reports of pregnancies while on therapy (both males and females) include reports of spontaneous abortion, minor abnormalities (hypospadias, pyloric stenosis, and small intestine rotation) at or shortly after birth, and other congenital abnormalities including skeletal malformations, hypoplastic lungs, exomphalos, kidney abnormalities, hydrocephalus, cerebellar hypoplasia, and cardiac defects.

Retrospective case reports of women with CML in complete hematologic response (CHR) with cytogenic response (partial or complete) who interrupted imatinib therapy due to pregnancy, demonstrated a loss of response in some patients while off treatment. At 18 months after treatment reinitiation following delivery, CHR was again achieved in all patients and cytogenic response was achieved in some patients. Cytogenetic response rates may not be at as high as compared to patients with 18 months of uninterrupted therapy (Ault 2006; Pye 2008).

Breast-Feeding Considerations Imatinib and its active metabolite are found in human breast milk; the milk/plasma ratio is 0.5 for imatinib and 0.9 for the active metabolite. Based on body weight, up to 10% of a therapeutic maternal dose could potentially be received by a breast-fed infant. Due to the potential for serious adverse reactions in the breast-feeding infant, breast-feeding is not recommended by the manufacturer during treatment and for 1 month after the last imatinib dose.

Dietary Considerations Avoid grapefruit juice.

Monitoring Parameters CBC (weekly for first month, biweekly for second month, then periodically thereafter), liver function tests (at baseline and monthly or as clinically indicated; more frequently [at least weekly] in patients with moderate-to-severe hepatic impairment [Ramanathan 2008]), renal function (at baseline and periodically thereafter), serum electrolytes (including calcium, phosphorus, potassium and sodium levels); bone marrow cytogenetics (in CML; at 6-, 12-, and 18 months), pregnancy test; fatigue, weight, and edema/fluid status; consider echocardiogram and serum troponin levels in patients with HES/CEL, and in patients with MDS/MPD or ASM with high eosinophil levels; in pediatric patients, also monitor serum glucose, albumin, and growth

Gastric surgery (eg, bypass, major gastrectomy, or resection) patients: Monitor imatinib trough concentrations (Liu 2011; Pavlovsky 2009; Yoo 2010)

Thyroid function testing (Hamnvik 2011):

> Preexisting levothyroxine therapy: Obtain baseline TSH levels, then monitor every 4 weeks until levels and levothyroxine dose are stable, then monitor every 2 months
>
> Without preexisting thyroid hormone replacement: TSH at baseline, then every 4 weeks for 4 months, then every 2 to 3 months

Monitor for signs/symptoms of CHF in patients with at risk for cardiac failure or patients with pre-existing cardiac disease. Monitor for signs/symptoms of gastrointestinal irritation or perforation and dermatologic toxicities.

Mechanism of Action Inhibits Bcr-Abl tyrosine kinase, the constitutive abnormal gene product of the

Philadelphia chromosome in chronic myeloid leukemia (CML). Inhibition of this enzyme blocks proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as in fresh leukemic cells in Philadelphia chromosome positive CML. Also inhibits tyrosine kinase for platelet-derived growth factor (PDGF), stem cell factor (SCF), c-Kit, and cellular events mediated by PDGF and SCF.

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: Parent drug and metabolite: ~95% to albumin and alpha$_1$-acid glycoprotein

Metabolism: Hepatic via CYP3A4 (minor metabolism via CYP1A2, CYP2D6, CYP2C9, CYP2C19); primary metabolite (active): N-demethylated piperazine derivative (CGP74588); severe hepatic impairment (bilirubin >3 to 10 times ULN) increases AUC by 45% to 55% for imatinib and its active metabolite, respectively

Bioavailability: 98%; may be decreased in patients who have had gastric surgery (eg, bypass, total or partial resection) (Liu 2011; Pavlovsky 2009; Yoo 2010)

Half-life elimination: Adults: Parent drug: ~18 hours; N-desmethyl metabolite: ~40 hours; Children: Parent drug: ~15 hours

Time to peak: 2 to 4 hours

Excretion: Feces (68% primarily as metabolites, 20% as unchanged drug); urine (13% primarily as metabolites, 5% as unchanged drug)

Pricing: US

Tablets (Gleevec Oral)

100 mg (90): $10112.93

400 mg (30): $12146.92

Tablets (Imatinib Mesylate Oral)

100 mg (90): $9101.64

400 mg (30): $10932.23

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Alvotinib (SG, UA); Celonib (LK); Egitinid (RO); Enliven (BD); Gemivil (JO); Glimatib (VN); Glinib (KR); Glivec (AE, AR, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CU, CY, CZ, DE, DK, EC, EE, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IL, IS, IT, JO, JP, KR, KW, LB, LK, LT, LU, LV, MT, MX, MY, NL, NO, PE, PH, PK, PL, PT, PY, QA, RO, RU, SA, SE, SG, SI, SK, TH, TR, TW, UY, VE, VN); Glivic (NZ); Hlivek (UA); Imakrebin (HK); Imanix (BD, LK); Imarem (MT, TR); Itivas (LV); Kadimer (CR, DO, GT, HN, NI, PA, SV); Lemat (HR); Matinac (EC); Meaxin (LV, PL); Milatus (PE); Nibix (HR, PL); Survtyk (CR, DO, GT, HN, NI, PA, SV); Timab (EC); Tinibat (VN); Tyrokin (BD); Tyronib (BD); Unitinib (LK); Zeite (PY); Zeltinib (EC)

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