Nilotinib

Class: Tyrosine Kinase Inhibitor

Indications :

_Chronic myeloid leukemia (CML)

_ Treatment of newly-diagnosed Philadelphia chromosome-positive CML (Ph+ CML) in chronic phase

_treatment of chronic and accelerated phase Ph+ CML refractory or intolerant to prior therapy (including imatinib)

Available dosage form in the hospital:200 MG TAB

Trade name : Tasigna

Doses:

-Chronic myeloid leukemia (CML), Ph+, newly-diagnosed in chronic phase: Oral: 300 mg twice daily

-CML, Ph+, resistant or intolerant in chronic or accelerated phase: Oral: 400 mg twice daily

-Gastrointestinal stromal tumor (GIST), refractory (unlabeled use): Oral: 400 mg twice daily until disease progression or unacceptable toxicity

Missed doses: If a dose is missed, do not make up, resume with next scheduled dose.

-Dosage adjustment for concomitant CYP3A4 inhibitors/inducers:

-*CYP3A4 inhibitors:* Avoid the concomitant use of a strong CYP3A4 inhibitor with nilotinib. If a strong CYP3A4 inhibitor is required, interruption of nilotinib treatment is recommended; if therapy cannot be interrupted and concurrent use cannot be avoided, consider reducing the nilotinib dose to 300 mg once daily in patients with resistant or intolerant Ph+ CML (chronic or accelerated phase) or to 200 mg once daily in newly-diagnosed chronic phase Ph+ CML, with careful monitoring, especially of the QT interval. When a strong CYP3A4 inhibitor is discontinued, allow a washout period prior to adjusting nilotinib dose upward.

-*CYP3A4 inducers:* Avoid the concomitant use of a strong CYP3A4 inducer with nilotinib (based on pharmacokinetic parameters, an increased nilotinib dose is not likely to compensate for decreased exposure).

Geriatric
Refer to adult dosing.

Renal Impairment:
Not studied in patients with serum creatinine >1.5 times ULN, however, nilotinib and its metabolites have minimal renal excretion; dosage adjustments for renal dysfunction may not be necessary.

Hepatic Impairment:

Note: Dosage adjustment for impairment at treatment initiation (if possible, consider alternative therapies first); recommendations vary by indication.

-*Newly-diagnosed Ph+ CML in chronic phase:* Mild-to-severe impairment (Child-Pugh class A, B, or C): Initial: 200 mg twice daily; may increase to 300 mg twice daily based on patient tolerability

-*Resistant or intolerant Ph+ CML in chronic or accelerated phase:*

-Mild-to-moderate impairment (Child-Pugh class A or B): Initial: 300 mg twice daily; may increase to 400 mg twice daily based on patient tolerability

-Severe impairment (Child-Pugh class C): Initial: 200 mg twice daily; may increase to 300 mg twice daily and then further increased to 400 mg twice daily based on patient tolerability

-*For hepatotoxicity during treatment:*

-If bilirubin >3 times ULN (≥grade 3): Withhold treatment, monitor bilirubin, resume treatment at 400 mg once daily when bilirubin returns to ≤1.5 times ULN (≤grade 1)

-If ALT or AST >5 times ULN (≥grade 3): Withhold treatment, monitor transaminases, resume treatment at 400 mg once daily when ALT or AST returns to ≤2.5 times ULN (≤grade 1)

Adjustment for Toxicity

-Dosage adjustment for hematologic toxicity:

- ANC <1000/mm^3 and/or platelets <50,000/mm^3: Withhold treatment, monitor blood counts
- If ANC >1000/mm^3 and platelets >50,000/mm^3 within 2 weeks: Resume at prior dose
- If ANC <1000/mm^3 and/or platelets <50,000/mm^3 for >2 weeks: Reduce dose to 400 mg once daily

-Dosage adjustment for nonhematologic toxicity:

- Amylase or lipase >2 times ULN (≥grade 3): Withhold treatment, monitor serum amylase or lipase, resume treatment at 400 mg once daily when lipase or amylase returns to ≤1.5 times ULN (≤grade 1)
- Lipase increases in conjunction with abdominal symptoms: Withhold treatment and consider diagnostics to exclude pancreatitis.
- Clinically-significant moderate or severe nonhematologic toxicity: Withhold treatment, upon resolution of toxicity, resume at 400 mg once daily; may escalate back to initial dose (300 mg twice daily or 400 mg twice daily depending on indication) if clinically appropriate.

-Dosage adjustment for QT prolongation: Note: Repeat ECG ~7 days after any dosage adjustment.

- QT_c >480 msec: Withhold treatment, monitor and correct potassium and magnesium levels; review concurrent medications.
    - If QT_cF returns to <450 msec and to within 20 msec of baseline within 2 weeks: Resume at prior dose.
    - If QT_cF returns to 450-480 msec after 2 weeks: Reduce dose to 400 mg once daily.
    - If QT_cF >480 msec after dosage reduction to 400 mg once daily: Discontinue treatment.

Common side effect :

>10%:

Cardiovascular: Peripheral edema (8% to 15%), hypertension (10% to 11%)

Central nervous system: Headache (20% to 35%), fatigue (21% to 32%), fever (11% to 28%), insomnia (7% to 12%)

Dermatologic: Rash (29% to 38%), pruritus (20% to 32%), alopecia (11% to 13%)

Endocrine & metabolic: Hypophosphatemia (grades 3/4: 5% to 17%), hyperglycemia (grades 3/4: 6% to 12%)

Gastrointestinal: Nausea (20% to 37%), vomiting (11% to 29%), diarrhea (14% to 28%), constipation (17% to 26%), lipase increased (1% to ≥10%; grades 3/4: 7% to 18%), abdominal pain (12% to 17%), anorexia (12% to 15%)

Hematologic: Neutropenia (grades 3/4: 12% to 42%; median duration: 15 days), thrombocytopenia (grades 3/4: 10% to 42%; median duration: 22 days), anemia (grades 3/4: 4% to 27%)

Hepatic: Hyperbilirubinemia (≥10%; grades 3/4: 4% to 9%), ALT increased (≥10%; grades 3/4: 4%), AST increased (≥10%; grades 3/4: 1% to 3%)

Neuromuscular & skeletal: Arthralgia (16% to 26%), limb pain (11% to 20%), myalgia (14% to 19%), back pain (14% to 17%), weakness (11% to 16%), bone pain (14% to 15%), muscle spasm (11% to 15%), musculoskeletal pain (11% to 12%)

Respiratory: Cough (14% to 27%), nasopharyngitis (15% to 24%), dyspnea (9% to 15%), upper respiratory tract infection (≤15%), oropharyngeal pain (7% to 11%)

Miscellaneous: Night sweats (12% to 27%), flu-like syndrome (11%)

1% to 10%:

Cardiovascular: Arterial stenosis (5% to 6%), cerebrovascular accident (5% to 6%), peripheral arterial occlusive disease (5% to 6%), angina, arrhythmia (including AV block, atrial fibrillation, bradycardia, cardiac flutter, extrasystoles, and tachycardia), chest pain (including noncardiac), flushing, palpitation, QT interval prolonged

Central nervous system: Dizziness (10%), anxiety, depression, dysphonia, hypoesthesia, malaise, pain, vertigo

Dermatologic: Dry skin (>5% to <10%), acne, bruising, dermatitis (including allergic and acneiform), eczema, erythema, folliculitis, hyperhidrosis, skin papilloma, urticaria

Endocrine & metabolic: Hypokalemia (grades 3/4: ≤9%), hyponatremia (grades 3/4: ≤7%), hyperkalemia (grades 3/4: 2% to 6%), hypocalcemia (grades 3/4: ≤5%), albumin decreased (grades 3/4: ≤4%), diabetes mellitus, hypercalcemia, hypercholesterolemia, hyperlipidemia, hyperphosphatemia, hypomagnesemia

Gastrointestinal: Dyspepsia (4% to 10%), abdominal discomfort, abnormal taste, amylase increased, flatulence, pancreatitis, weight gain/loss

Genitourinary: Pollakuria

Hematologic: Lymphopenia, neutropenic fever, pancytopenia

Hepatic: Alkaline phosphatase increased (grades 3/4: ≤1%), GGT increased

Neuromuscular & skeletal: Paresthesia, peripheral neuropathy

Ocular: Eyelid edema (1%), conjunctivitis, dry eye, eye hemorrhage, periorbital edema, pruritus

Respiratory: Pleural effusion (≤1%), dyspnea (exertional), epistaxis

Pregnancy category: D