Kimonil®
Nilotinib

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Composition
Each capsule Kimonil® 200 mg contains: nilotinib (as Hcl) 200 mg
Each capsule Kimonil® 150 mg contains: nilotinib (as Hcl) 150 mg

Description
Kimonil is used to treat a certain type of blood cancer (chronic myelogenous leukemia-CML).

Pharmacokinetic
Absorption
Peak Plasma Time: 3 hrs.
Distribution
Protein Binding: 98%
Metabolism
Oxidation and hydroxylation by liver None of the metabolites contribute significantly to the pharmacological activity of kimonil.
Elimination
Half-Life: 15-17 hrs.
Excretion
Feces 93%

Dosage and Administration
Adult ≥ 18 years

1. Newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase:
300 mg orally twice daily.
2. Resistant or intolerant Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase and accelerated phase:
400 mg orally twice daily.

Pediatric
Safety and effectiveness have not been established.

Dosage Adjustment
1. Elevated serum lipase or amylase (≥ grade 3)
• Withhold treatment and monitor serum lipase or amylase; resume treatment at 400 mg once daily if serum lipase or amylase return to grade 1 or lower.
2. Elevated bilirubin or hepatic transaminases (≥ grade 3): Withhold treatment and monitor bilirubin or hepatic transaminases; resume at 400 mg once daily if bilirubin/transaminases return to grade 1 or lower.
3. Neutropenia and thrombocytopenia
• If ANC (Absolute neutrophil Count) $<10^9$/L or Platelet counts$<50 * 10^9$/L Withhold treatment and monitor blood cell counts.
• Within 2 weeks of recovery: Resume original dose if ANC $>10^9$/L and Platelet$>50 * 10^9$/L If levels remain low for 2 weeks, Reduce dose to 400 mg once daily.
4. QT interval Prolongation (QTc>480 msec)
• Withhold drug and analyze serum potassium and magnesium; if below lower limit of normal, correct with supplements to within normal limits.
• Resume within 2 weeks at prior dose if QTc returns to <450 msec and to within 20 msec of baseline.
• If QTcF (Fridericia correction of QT interval) is between 450 msec and 480 msec after 2 weeks, reduce kimonil dose to 400 mg once daily.
• Discontinue if QTc returns to >480 msec despite reducing the dose to 400 mg daily.
• Repeat ECG ~7 days after any dose adjustment.
5. Coadministration with strong CYP3A4 inducers
• Avoid coadministration
6. Coadministration with strong CYP3A4 inhibitors
• Avoid if possible; for patients who cannot avoid use of strong CYP3A4 inhibitors, monitor closely for prolongation of the QT interval.
• If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, consider a dose reduction to 300 mg once daily. In patients with resistant or intolerant Philadelphia chromosome-positive CML or to 200 mg once daily in patients with:
  • Newly diagnosed Philadelphia chromosome-positive CML in chronic phase.
  • If the strong inhibitor is discontinued, a washout period should be allowed before the kimonil dose is adjusted upward to the indicated dose.
7. Hepatic Impairment
• Newly diagnosed Ph+ CML (chronic phase at 300 mg twice daily) Mild, moderate, or severe hepatic impairment: Start initial dose at 200 mg twice daily; if tolerated, may increase to 300 mg twice daily.
• Resistant or intolerant Ph+ CML (chronic phase or accelerated phase at 400 mg twice daily)
In Mild or moderate hepatic impairment, Start initial dose at 300 mg twice daily; if tolerated, may increase to 400 mg twice daily.
In Severe hepatic impairment, Start initial dose at 200 mg twice daily; if tolerated, may increase to 300 mg twice daily, and then 400 mg twice daily based on tolerability.

Monitoring
Perform CBCs every 2 weeks for the first 2 months and then monthly thereafter.
Check electrolytes (e.g., calcium, magnesium, phosphate, potassium, sodium) at baseline and periodically thereafter.
Check lipid profile periodically. Obtain ECGs at baseline, 7 days after initiation, and periodically thereafter, as well as following dose adjustments.
Check hepatic function tests and serum lipase monthly and monitor patients with hepatic impairment closely for QT interval prolongation.

Precautions/Warnings
• Myelosuppression:
Thrombocytopenia, neutropenia, and anemia.
• QT Prolongation
• Elevated Serum Lipase
• Hepatotoxicity
• Electrolyte Serum Lipase abnormalities.
• Tumor Lysis Syndrome
• Total Gasrectomy
• History of Pancreatitis
• Lactolose intolerance
• Cardiac Disorders
• Hepatic function impairment
• Sudden Deaths:
Sudden deaths have been reported in patients with CML treated with kimonil in clinical studies (0.3%). The relative early occurrence of some of the deaths relative to the initiation of kimonil suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.

Contraindication
Hypokalemia, Hypomagnesaemia, or Long QT syndrome.

Adverse Effects
Rash, Headache, Nausea, Pruritus, Fatigue, Pyrexia, Diarrhea, Constipation, Vomiting, Arthralgia, Cough, Extremity pain, Asthenia, Muscle spasms, Myalgia, Abdominal pain, Bone pain, Back pain, Dyspnea, Nasopharyngitis, Peripheral edema.

Drug Interactions
CYP3A4 Inducers, CYP3A4 inhibitors, Gastric Anti acids, Imatinib, Nevirapine, Warfarin, P-glycoprotein inhibitors.

HOW TO USE
Advise patients to take kimonil twice daily, approximately 12 hours apart, and do not take kimonil with food. Instruct patients to swallow kimonil capsules whole with water. Advise patients to take kimonil on an empty stomach at least 2 hours after a meal. Instruct patients not to consume food for at least 1 hour after the dose is taken. Advise patients not to consume grapefruit products and other foods that are known to inhibit CYP3A4 at any time during kimonil treatment.
Advise patients who are unable to swallow capsules that the contents of each capsule may be dispersed in 1 teaspoon of applesauce (pureed apple) and swallowed immediately (within 15 minutes). Inform patients that kimonil and certain other medicines, including nonprescription medications or herbal supplements, such as St. John's wort, can interact with each other.
Advise patients to continue taking kimonil every day for as long as their health care provider tells them. Kimonil is a long-term treatment; advise patients not to change the dose or discontinue treatment without first consulting their health care provider. Advise patients that the use of kimonil during pregnancy may cause harm to the fetus and advise them not to take kimonil during pregnancy unless necessary. Instruct women of childbearing potential to use effective contraceptives if taking kimonil. Advise sexually active women taking kimonil to use adequate contraception.

MISSED DOSE
Advise patients not to take a makeup dose if a dose is missed, but to resume taking the next prescribed daily dose.

Pregnancy & Lactation
Pregnancy Category: D
This is not recommended for use during pregnancy. It may harm an unborn baby.
Lactation: avoid to breast, present in milk in animal studies.

STORAGE
Keep away from light and moisture, Store below 30°C. Do not store in the bathroom. Keep all medicine away from children and pets.

Presentation Kimonil®
Bottle of 30 Capsules

Refrence
Drug facts and comparisons 2015 edition, Tyrosine kinase inhibitor, page 3779-3784
BNF 68, part 8.1.5 other antineoplastic drugs, pages 596, 598, 604.

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