KIMONIL® CAPSULE

KIMONIL®
NILOTINIB

KIMONIL® (NILOTINIB) CAPSULE FOR ORAL USE
Read this patient information carefully before you start taking Kimonil® because it answers some common questions about Kimonil®. This medication is prescribed for your current condition, therefore do not use it in similar cases and do not recommend it to others.
To report SUSPECTED ADVERSE REACTIONS, contact Noavaran Daroui Kimia Co. at +982166433514 or send email to medical@kimia-pharma.co

Read this patient Information carefully before you start taking Kimonil® because it contains important information for you. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

Composition
Each capsule Kimonil® 150 mg contains: Nilotinib (as HCl) 150 mg.
Each capsule Kimonil® 200 mg contains: Nilotinib (as HCl) 200 mg.

Mechanism of action
Nilotinib is an inhibitor of the BCR-ABL kinase.

Pharmacokinetic
Absorption
Relative bioavailability of Kimonil® capsule is approximately 50%, as compared to an oral drink solution (pH of 1.2 to 1.3). Peak concentrations of Kimonil® are reached 3 hours after oral administration.
Median steady-state trough concentration of Kimonil® was decreased by 53% in patients with total gastrectomy compared to patients who had not undergone surgeries.
Effect of Food
Compared to the fasted state, the systemic exposure (AUC) increased by 82% when the dose was given 30 minutes after a high fat meal.
Single dose administration of two 200 mg Kimonil® capsules each dispersed in 1 teaspoon of applesauce and administered within 15 minutes was shown to be bioequivalent to a single dose administration of two 200 mg intact capsules.
Distribution
The blood-to-serum ratio of Kimonil® is 0.68. Serum protein binding is approximately 98%.
Metabolism
Kimonil® is primarily metabolized via CYP3A4-mediated oxidation and to a minor extent by CYP2C8. Kimonil® is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of Kimonil®.
Excretion
After a single dose of radiolabeled Kimonil®, more than 90% of the administered dose was eliminated within 7 days: 93% of the dose in feces. Parent drug accounted for 69% of the dose.
Elimination
The mean (CV%) apparent elimination half-life is estimated to be approximately 17 hours (69%) and the mean (CV%) apparent clearance approximates 29 L/h (61%).

Indication
Kimonil® is a kinase inhibitor indicated for the treatment of:
- Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+CML resistant to or intolerant to prior therapy that included imatinib.
- Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

Dosage and Administration
- Recommended Adult Dose: Newly diagnosed Ph+ CML-CP: 300 mg orally twice daily. Resistant or intolerant Ph+ CML-CP and CML-AP: 400 mg orally twice daily.
- Recommended Pediatric Dose: Newly Diagnosed Ph+ CML-CP or Ph+CML-CP resistant or intolerant to prior TKI therapy: 230 mg/m^2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).
- Reduce starting dose in patients with baseline hepatic impairment.
- Eligible newly diagnosed adult patients with Ph+ CML-CP who have received Kimonil® for a minimum of 3 years and have achieved a sustained molecular response (MR4.5) and patients with Ph+ CML-CP resistant or intolerant to imatinib who have received Kimonil® for at least 3 years and have achieved a sustained molecular response (MR4.5) may be considered for treatment discontinuation.

Side effects / Adverse reactions
It should be noted that these side effects do not occur in all patients. These are not all the possible side effects of Kimonil®. For more information, ask your healthcare provider or pharmacist.
Kimonil® can cause serious side effects, including:
- **Low blood cell counts.** Low blood cell counts (red blood cells, white blood cells, and platelets) are common with Kimonil®, but can also be severe. Your healthcare provider will check your blood counts regularly during treatment with Kimonil®. Call your healthcare provider or get medical help right away if you develop any signs or symptoms of low blood counts including:
  - fever
  - chills or other signs of infection
  - unexplained bleeding or bruising
  - unexplained weakness
  - shortness of breath
- **Decreased blood flow to the leg, heart, or brain.** People who have recently been diagnosed with Ph+ CML and take Kimonil® may develop decreased blood flow to the leg, the heart, or brain.
Get medical help right away if you suddenly develop any of the following symptoms:
  - chest pain or discomfort
  - numbness or weakness
  - problems walking or speaking
  - leg pain
  - your leg feels cold
  - change in the skin color of your leg
- **Pancreas inflammation (pancreatitis).** Tell your healthcare provider right away if you develop any symptoms of pancreatitis including sudden stomach area pain with nausea and vomiting.
- **Liver problems.** Kimonil® can increase your risk of liver problems. People who have had liver problems in the past may be at risk for getting liver problems with Kimonil®. Call your healthcare provider or get medical help right away if you develop any symptoms of liver problems including:
  - stomach area (abdominal) pain
  - yellow skin and eyes
  - dark-colored urine
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. Your healthcare provider may do blood tests to check you for TLS. TLS can cause you to have:
  - **kidney failure and the need for dialysis treatment**
  - **an abnormal heart beat**
- **Bleeding problems.** Serious bleeding problems and death have happened during treatment with Kimonil®. Tell your healthcare provider right away if you develop any signs and symptoms of bleeding during treatment with Kimonil®.
- **Fluid retention.** Your body may hold too much fluid (fluid retention). Symptoms of fluid retention include shortness of breath, rapid weight gain, and swelling.
- **Abnormal growth and development in children.** Effects on growth and development have happened in children with chronic phase Ph+ CML during treatment with Kimonil®. Some children and adolescents may have slower than normal growth during treatment with Kimonil®.
- **QTc prolongation: Kimonil® can cause a possible life-threatening heart problem called QTc prolongation.** QTc prolongation causes an irregular heartbeat, which may lead to sudden death.
Your healthcare provider should check the electrical activity of your heart with a test called an electrocardiogram (ECG):
  - before starting Kimonil®
  - 7 days after starting Kimonil®
  - with any dose changes
  - regularly during Kimonil® treatment

Prior to Kimonil® administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies.

Call your healthcare provider right away if you have aforementioned symptoms.
The most common side effects of Kimonil® in adults and children include:

- nausea, diarrhea, rash, headache, tiredness, itching, vomiting, cough, constipation, muscle and joint pain, runny or stuffy nose, sneezing, sore throat, fever, night sweats

Side effects in adult patients attempting treatment free remission:
If you and your healthcare provider decide that you can stop taking Kimonil® and try treatment free remission (TFR), you may have more muscle and bone (musculoskeletal) symptoms than before you stopped treatment. Symptoms may include:
- muscle pain, arm and leg pain, joint pain, bone pain, spine pain

Tell your healthcare provider if you or your child have any side effect that bothers you or does not go away.

Drug interaction
Strong CYP3A Inhibitors
Concomitant use with a strong CYP3A inhibitor increases Kimonil® concentrations compared to Kimonil® alone, which may increase the risk of Kimonil® toxicities. Avoid concomitant use of strong CYP3A inhibitors with Kimonil®. If patients must be coadministered a strong CYP3A4 inhibitor, reduce Kimonil® dose.
Strong CYP3A Inducers
Concomitant use with a strong CYP3A inducer decreases Kimonil® concentrations compared to Kimonil® alone, which may reduce Kimonil® efficacy. Avoid concomitant use of strong CYP3A inducers with Kimonil®.
Proton Pump Inhibitors
Concomitant use with a proton pump inhibitor (PPI) decreases Kimonil® concentrations compared to Kimonil® alone, which may reduce Kimonil® efficacy. Avoid concomitant use of PPI with Kimonil®.
Avoid coadministration of Kimonil® with agents that may prolong the QT interval, such as anti-arrhythmic drugs.
Kimonil® is contraindicated in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

Warnings
Before taking Kimonil®, tell your healthcare provider about all of your medical conditions including if you:
- have heart problems
- have had a stroke or other problems due to decreased blood flow to the brain
- have problems with decreased blood flow to your legs
- have irregular heartbeat
- have QTc prolongation or a family history of it
- have liver problems
- have had pancreatitis
- have low blood levels of potassium or magnesium in your blood
- have a severe problem with lactose (milk sugar) or other sugars. Kimonil® capsules contain lactose. Most people who have mild or moderate lactose intolerance can take Kimonil®.
- have bleeding problems
- had a surgical procedure involving the removal of the entire stomach (total gastrectomy)
- are pregnant or plan to become pregnant. Kimonil® can harm your unborn baby. Tell your healthcare provider right away if you are pregnant, or if you become pregnant during treatment with Kimonil®.
- are breastfeeding or plan to breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over- the counter medicines, vitamins, and herbal supplements. Kimonil® can interact with many medicines and supplements and increase your chance for serious and life-threatening side effects.
If you need to take antacids (medicines to treat heartburn) do not take them at the same time that you take Kimonil®. If you take:
- **a medicine to block the amount of acid produced in the stomach (H2 blocker):** Take these medicines **about 10 hours before** you take Kimonil®, **or about 2 hours after** you take Kimonil®.
- **an antacid that contains aluminum hydroxide, magnesium hydroxide, and simethicone to reduce the amount of acid in the stomach:** Take these medicines **about 2 hours before or about 2 hours after** you take Kimonil®.
- Sudden deaths have been reported in patients receiving Kimonil®. Do not administer Kimonil® to patients with hypokalemia, hypomagnesemia, or long QT syndrome.

Missed dose
If you miss a dose, just take your next dose at your regular time. Do not take 2 doses at the same time to make up for a missed dose.

Overdose
If you take too much Kimonil®, call your healthcare provider or go to the nearest hospital emergency room right away. Symptoms may include vomiting and drowsiness.

Pregnancy and lactation
Kimonil® can harm your unborn baby. Tell your healthcare provider right away if you are pregnant, or if you become pregnant during treatment with Kimonil®.
In females who are able to become pregnant:
- Your healthcare provider should do a pregnancy test before you start treatment with Kimonil®.
- Use effective birth control (contraception) during treatment with Kimonil® and for at least 14 days after the last dose.
- It is not known if Kimonil® passes into your breast milk. Do not breastfeed during treatment and for at least 14 days after your last dose of Kimonil®.

Patient information
- Take Kimonil® exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking Kimonil® unless your healthcare provider tells you.
- Kimonil® is a long-term treatment.
- Your healthcare provider will tell you how many Kimonil® capsules to take and when to take them.
- If your child takes Kimonil®, your healthcare provider will change the dose as your child grows.
- **Kimonil® must be taken on an empty stomach.**
  - **Avoid eating food for at least 2 hours before the dose is taken, and**
  - **Avoid eating food for at least 1 hour after the dose is taken.**
- Swallow Kimonil® capsules whole with water. If you cannot swallow Kimonil® capsules whole, tell your healthcare provider.
- **If you cannot swallow Kimonil® capsules whole:**
- **Open the Kimonil® capsules and sprinkle the contents in 1 teaspoon of applesauce (puréed apple).**
  - **Do not use more than 1 teaspoon of applesauce.**
  - **Only use applesauce. Do not sprinkle Kimonil® onto other foods.**
- **Swallow the mixture right away (within 15 minutes).**
- Do not drink grapefruit juice, eat grapefruit, or take supplements containing grapefruit extract at any time during treatment.
- During treatment with Kimonil® your healthcare provider will do tests to check for side effects and to see how well Kimonil® is working for you. The tests will check your:
  - heart
  - blood cells (white blood cells, red blood cells, and platelets). Your blood cells should be checked every 2 weeks for the first 2 months and then monthly.
  - electrolytes (potassium, magnesium)
  - pancreas and liver function
  - bone marrow samples

Your healthcare provider may change your dose. Your healthcare provider may have you stop Kimonil® for some time or lower your dose if you have side effects with it.
- Your healthcare provider will monitor your CML during treatment with Kimonil® to see if you are in a remission. After at least 3 years of treatment with Kimonil®, your healthcare provider may do certain tests to determine if you continue to be in remission. Based on your test results, your healthcare provider may decide if you may be eligible to try stopping treatment with Kimonil®. This is called Treatment Free Remission (TFR).
- Your healthcare provider will carefully monitor your CML during and after you stop taking Kimonil®. Based on your test results, your healthcare provider may need to re-start your Kimonil® if your CML is no longer in remission.
- It is important that you are followed by your healthcare provider and undergo frequent monitoring to find out if you need to re-start your Kimonil® treatment because you are no longer in TFR. Follow your healthcare provider's instructions about re-starting Kimonil® if you are no longer in TFR.

Storage
- Keep away from light and moisture. Store below 30°C.
- Safely throw away medicine that is out of date or no longer needed.
- Keep out of the reach of children.
- Use appropriate precautions for handling and disposal of cytotoxic drugs.

Packaging
Bottle of 30 Capsules

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