LOKEMIDE® (IBRUTINIB) CAPSULE AND TABLET

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LOKEMIDE® (IBRUTINIB) CAPSULE AND TABLET FOR ORAL USE
Read this patient information carefully before you start taking Lokemide® because it answers some common questions about Lokemide®. 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 Lokemide® 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 Lokemide® 70 mg contains: Ibrutinib 70 mg.
Each capsule Lokemide® 140 mg contains: Ibrutinib 140 mg.
Each film-coated tablet Lokemide® 420 mg contains: Ibrutinib 420 mg.

Mechanism of action
Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK).

Pharmacokinetic
Absorption
Absolute bioavailability of Lokemide® in fasted condition was 2.9% in healthy subjects. Lokemide® is absorbed after oral administration with a median T_{max} of 1 hour to 2 hours. The administration of Lokemide® with a high-fat and high-calorie meal increased Lokemide® C_{max} by 2- to 4-fold and AUC by approximately 2-fold, compared with administration of Lokemide® after overnight fasting.
Distribution
The volume of distribution (Vd) was 683 L, and the apparent volume of distribution at steady state (Vd,ss/F) was approximately 10,000 L.
Metabolism
Lokemide® is primarily metabolized by cytochrome P450 (CYP) 3A and to a minor extent by CYP2D6.
Elimination
The half-life of Lokemide® is 4 hours to 6 hours.
Excretion
After a single oral administration of radiolabeled Lokemide®, 80% excreted in the feces and less than 10% eliminated in urine.

Indication
Lokemide® is a kinase inhibitor indicated for the treatment of:
- Adult patients with Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL).
- Adult patients with Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL) with 17p deletion.
- Adult patients with Waldenström's Macroglobulinemia (WM).
- Adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

It is not known if Lokemide® is safe and effective in children under 1 year of age. Lokemide® should not be used in children and adolescents.

Dosage and administration
- CLL / SLL and WM: 420 mg taken orally once daily.
- cGVHD:
  - Patients 12 years and older: 420 mg taken orally once daily.
  - Patients 1 to less than 12 years of age: 240 mg/m² taken orally once daily (up to a dose of 420 mg).

Take Lokemide® tablets or capsules orally once daily with a glass of water. Do not open, break, or chew the capsules. Do not cut, crush, or chew the tablets.

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 Lokemide®. For more information, ask your healthcare provider or pharmacist.
Lokemide® may cause serious side effects including:
- **Bleeding problems.** During treatment with Lokemide® bleeding problems are common and can also be serious and life-threatening.
  The risk of bleeding may increase if you are also taking a blood thinner medicine (e.g. vitamin K antagonists (warfarin), anticoagulant agents (heparin), antiplatelet agents, acetyl salicylic acid and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen or naproxen and supplements (e.g. fish oil, vitamin E or flaxseed). If co-administration is unavoidable, the risks and benefits of anticoagulant or antiplatelet therapy should be considered by your healthcare provider.
  Tell your healthcare provider if you have any signs of bleeding, including:
  - blood in your stools or black stools (looks like tar)
  - increased bruising
  - pink or brown urine
  - dizziness
  - unexpected bleeding, or bleeding that is severe or that you cannot control
  - weakness
  - confusion
  - vomit blood or vomit looks like coffee grounds
  - cough up blood or blood clots
  - change in your speech
  - headache that lasts a long time or severe headache

- **Infections.** These infections can be serious and may be life-threatening. Tell your healthcare provider right away if you have fever, chills, weakness, confusion, or other signs or symptoms of an infection during treatment with Lokemide®.
- **Heart problems (Cardiac Arrhythmias).** Serious and life-threatening heart rhythm problems (ventricular arrhythmias, atrial fibrillation and atrial flutter) and heart failure have happened in people treated with Lokemide®, especially in people who have an infection, an increased risk for heart disease (including hypertension, diabetes mellitus and advanced age), or have had heart rhythm problems in the past. Your heart function will be checked before and during treatment with Lokemide®. Tell your healthcare provider if you get any symptoms of heart problems, such as feeling as if your heart is beating fast and irregular, lightheadedness, dizziness, shortness of breath, swelling of the feet, ankles or legs, chest discomfort, or you faint. If you develop any of these symptoms, your healthcare provider may do tests to check your heart and may change your Lokemide® regimen.
- **Hypertension.** New or worsening high blood pressure has happened in people treated with Lokemide®. Your healthcare provider may start blood pressure medicine for you or change current medicines to treat your blood pressure.
- **Decrease in blood cell counts (neutropenia, thrombocytopenia and anaemia).** Your healthcare provider should do monthly blood tests to check your blood counts.
- **Leukostasis.** Cases of leukostasis have been reported in patients treated with Lokemide®.
- **Haemophagocytic lymphohistiocytosis (HLH).** HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation such as fever.
- **Second Primary Malignancies.** New cancers have happened during treatment with Lokemide®, including cancers of the skin or other organs.
- **Tumor Lysis Syndrome (TLS).** TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure, and sometimes can be life-threatening. Your healthcare provider may do blood tests to check you for TLS.
- **Splenic rupture.** Cases of splenic rupture have been reported following discontinuation of Lokemide® treatment. Tell your healthcare provider if you have any signs of left upper abdominal or shoulder tip pain.
- **Hepatic problem.** Cases of hepatotoxicity, hepatitis B reactivation, and cases of hepatitis E, which may be chronic, have occurred in patients treated with Lokemide®. Hepatic failure, including life-threatening events, has occurred in patients treated with Lokemide®.
- **Interstitial Lung Disease (ILD).** Cases of ILD have been reported in patients treated with Lokemide®.
- **Cerebrovascular accidents.** Cases of life-threatening cerebrovascular accident like stroke with and without concomitant cardiac accidents and/or hypertension have been reported in patients treated with Lokemide®.

Call your healthcare provider right away if you have aforementioned symptoms.

The most common side effects of Lokemide® in adults with B-cell malignancies (CLL / SLL and WM) include:
- diarrhea
- rash
- tiredness
- bruising
- muscle and bone pain
- nausea

The most common side effects of Lokemide® in adults or children 1 year of age and older with cGVHD include:
- tiredness
- low platelet count
- mouth sores (stomatitis)
- stomach pain
- bruising
- muscle and joint pain
- bleeding
- pneumonia
- diarrhea
- muscle spasms
- nausea
- headache
- low red blood cell count (anemia)
- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath

Other most common side effects of Lokemide®:
- feeling dizzy
- swollen hands, ankles or feet
- breaking of the nails
- indigestion
- blurred vision
- Constipation
- high blood pressure
- redness of the skin
- Vomiting
- sudden kidney damage
- inflammation within the lungs that may lead to permanent damage
- increased level of "creatinine" in the blood.
- nose bleeds, small red or purple spots caused by bleeding under the skin
- blood in your stomach, gut, stools or urine, heavier periods, or bleeding that you cannot stop from an injury
- high level of "uric acid" in the blood, which may cause gout
- weakness, numbness, tingling or pain in your hands or feet or other parts of the body

Diarrhea is a common side effect in people who take Lokemide®. Drink plenty of fluids during treatment with Lokemide® to help reduce your risk of losing too much fluid (dehydration) due to diarrhea. Tell your healthcare provider if you have diarrhea that does not go away.

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

Drug interaction
Since the drug interactions with Lokemide® is not limited to the following medicines tell your healthcare provider or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and other medicines you bought without a prescription.
Tell your healthcare provider before taking Lokemide® if you are taking any of the following medicines. The following medicines may reduce how well Lokemide® works:
The effects of Lokemide® or other medicines may be influenced if you take Lokemide® together with any of the following medicines:
- medicines called antibiotics to treat bacterial infections – clarithromycin, telithromycin, ciprofloxacin, erythromycin, rifampicin or azithromycin
- medicines for fungal infections – posaconazole, ketoconazole, itraconazole, fluconazole or voriconazole
- medicines for HIV infection – ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, fosamprenavir or efavirenz
- medicines to prevent nausea and vomiting associated with chemotherapy – aprepitant
- medicines for depression – nefazodone, fluvoxamine
- medicines called kinase inhibitors for treatment of other cancers – crizotinib or imatinib
- medicines called calcium channel blockers for high blood pressure or chest pain – diltiazem or verapamil
- medicines called statins to treat high cholesterol - rosuvastatin
- heart medicines/anti-arrhythmics – amiodarone or dronedarone
- medicines to prevent seizures or to treat epilepsy, or medicines to treat a painful condition of the face called trigeminal neuralgia – carbamazepine or phenytoin.
- a medicine to treat leukemia – venetoclax
- a herbal medicine for depression – St. John's Wort

If you are taking digoxin, a medicine used for heart problems, or methotrexate, a medicine used to treat other cancers and to reduce the activity of the immune system (e.g., for rheumatoid arthritis or psoriasis), it should be taken at least 6 hours before or after Lokemide®.

Lokemide® with food
Do not take Lokemide® with grapefruit or Seville oranges (bitter oranges) – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because it can increase the amount of Lokemide® in your blood.

Warnings
Before taking Lokemide®, tell your healthcare provider about all of your medical conditions, including if you:
- have kidney problems.
- have had recent surgery or plan to have surgery. Your healthcare provider may stop Lokemide® for any planned medical, surgical, or dental procedure at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
- have bleeding problems.
- have or had heart rhythm problems, smoke, or have a medical condition that increases your risk of heart disease, such as high blood pressure, high cholesterol, or diabetes.
- have an infection.
- have liver problems.
- are pregnant or plan to become pregnant. Lokemide® may harm your unborn baby.
- are breastfeeding or plan to breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription medicines and over-the-counter medicines, vitamins, and herbal supplements. Do not start new medicines during treatment with Lokemide® without first talking with your healthcare provider. Lokemide® and other medicines may affect each other causing serious side effects.
Tell your doctor immediately if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be life-threatening (Progressive Multifocal Leukoencephalopathy or PML).

Tell your doctor immediately if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

Missed dose
If you miss a dose of Lokemide® take it as soon as you remember on the same day. Take your next dose of Lokemide® at your regular time on the next day. Do not take extra doses of Lokemide® to make up for a missed dose.

Overdose
If you take too much Lokemide®, call your healthcare provider or go to the nearest hospital emergency room right away.

Pregnancy and lactation
Lokemide® may harm your unborn baby.
- If you are pregnant or planning to become pregnant, tell your healthcare provider about taking Lokemide®.
- If you are able to become pregnant, your healthcare provider will do a pregnancy test before starting treatment with Lokemide®. Tell your healthcare provider if you are pregnant or think you may be pregnant during treatment with Lokemide®.
- **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with Lokemide® and for three months after the last dose.
- **Males** with female partners who are able to become pregnant should use effective birth control, such as condoms, during treatment with Lokemide® and for one month after the last dose.
- It is not known whether Lokemide® or its metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Do not breastfeed during treatment with Lokemide® and for 1 week after the last dose.

Patient information
- Take Lokemide® exactly as your healthcare provider tells you to take it. Do not change your dose of Lokemide® or stop taking Lokemide® unless your healthcare provider tells you to.
- You should not drink grapefruit juice, eat grapefruit, or eat Seville oranges (often used in marmalades) during treatment with Lokemide®. These products may increase the amount of Lokemide® in your blood.
- Take Lokemide® 1 time a day with a glass of water at about the same time each day.
- Swallow Lokemide® capsules or tablets whole. Do not open, break or chew the capsules. Do not cut, crush, or chew the tablets.
- Use caution before driving or using machinery.
- Healthy people should not touch Lokemide® capsules or tablets without protection like gloves.
- Lokemide® **capsule** does not contain lactose (a type of sugar). However, Lokemide® **tablet** contains lactose. If you have been told by your healthcare provider that you have an intolerance to some sugars, contact your healthcare provider before taking this medicine.

Storage
- Keep away from light and moisture. Store below 30°C.
- Keep out of the reach of children.
- Keep in the original container with the lid tightly closed. **Do not** transfer the capsules or tablets to a different container.
- Keep the desiccant in the bottle. Do not eat or throw away the desiccant pack.
- Safely throw away medicine that is out of date or that you no longer need. Ask your pharmacist how to safely throw away Lokemide® capsules or tablets.
- Use appropriate precautions for handling and disposal of cytotoxic drugs.

Packaging
Lokemide® 70 mg: Bottle of 28 Capsules.
Lokemide® 140 mg: Bottle of 90 Capsules.
Lokemide® 420 mg: Bottle of 30 F. C. Tablets.

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