VERZALIB® F. C. TABLET

VERZALIB®
ABEMACICLIB

VERZALIB® (ABEMACICLIB) F. C. TABLET FOR ORAL USE
Read this patient information carefully before you start taking Verzalib® because it answers some common questions about Verzalib®. 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 Verzalib® 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 film coated tablet Verzalib® 50 mg contains: Abemaciclib 50 mg.
Each film coated tablet Verzalib® 100 mg contains: Abemaciclib 100 mg.
Each film coated tablet Verzalib® 150 mg contains: Abemaciclib 150 mg.
Each film coated tablet Verzalib® 200 mg contains: Abemaciclib 200 mg.

Mechanism of action
Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6).

Pharmacokinetic
Absorption
The absolute bioavailability of Verzalib® after a single oral dose of 200 mg is 45% (19% CV). The median T_{max} of Verzalib® is 8.0 hours (range: 4.1-24.0 hours).

Distribution
Verzalib® is bound to human plasma proteins in a concentration independent manner (the mean bound fraction: 96.3%). In patients with advanced cancer, including breast cancer, concentrations of Verzalib® and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV).

Metabolism
Hepatic metabolism is the main route of clearance for Verzalib®. Verzalib® is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4.

Elimination
The geometric mean hepatic clearance (CL) of Verzalib® in patients was 26.0 L/h (51% CV), and the mean plasma elimination half-life for Verzalib® in patients was 18.3 hours (72% CV).

Excretion
After a single 150 mg oral dose of radiolabeled Verzalib®, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.

Indication
Verzalib® is a kinase inhibitor indicated:

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence.
- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
- in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

When Verzalib® is used in combination with fulvestrant, tamoxifen, or an aromatase inhibitor, also read the Patient Information for the prescribed product. Ask your healthcare provider if you are not sure.

It is not known if Verzalib® is safe and effective in children.

Dosage and Administration
Verzalib® tablets are taken orally with or without food.
- Recommended starting dose in combination with fulvestrant, tamoxifen, or an aromatase inhibitor: 150 mg twice daily.
- Recommended starting dose as monotherapy: 200 mg twice daily.
- Dosing interruption and/or dose reductions may be required based on individual safety and tolerability.

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 Verzalib®. For more information, ask your healthcare provider or pharmacist.

Verzalib® may cause serious side effects including:

- **Diarrhea.** Diarrhea is common with Verzalib® treatment and may sometimes be severe. Diarrhea may cause you to develop dehydration or an infection. The most common time to develop diarrhea is during the first month of Verzalib® treatment. If you develop diarrhea during treatment with Verzalib®, your healthcare provider may tell you to temporarily stop taking Verzalib®, stop your treatment, or decrease your dose.
  - **If you have any loose stools,** start taking an antidiarrheal medicine (such as loperamide), drink more fluids, and tell your healthcare provider right away.
- **Low white blood cell counts (neutropenia).** Low white blood cell counts are common during treatment with Verzalib® and may cause serious infections that can be life-threatening. Your healthcare provider should check your white blood cell counts before and during treatment. If you develop low white blood cell counts before and during treatment with Verzalib®. Your healthcare provider may tell you to temporarily stop taking Verzalib®, decrease your dose, or wait before starting your next month of treatment. **Tell your healthcare provider right away if you have signs and symptoms of low white blood cell counts or infections, such as fever and chills.**
- **Lung problems.** Verzalib® may cause severe or life-threatening inflammation of the lungs during treatment that can be life-threatening. If you develop lung problems during treatment with Verzalib®, your healthcare provider may tell you to temporarily stop taking Verzalib®, decrease your dose, or stop your treatment. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
  - trouble breathing or shortness of breath
  - chest pain
  - cough with or without mucus
- **Liver problems.** Verzalib® can cause serious liver problems. Your healthcare provider should do blood tests to check your liver before and during treatment with Verzalib®. If you develop liver problems during treatment with Verzalib®, your healthcare provider may reduce your dose or stop your treatment. Tell your healthcare provider right away if you have any of the following signs and symptoms of liver problems:
  - pain on the upper right side of your stomach area (abdomen)
  - bleeding or bruising more easily than normal
  - feeling very tired
  - loss of appetite

Complete blood counts should be monitored prior to the start of Verzalib® therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated.

- **Blood clots in your veins, or in the arteries of your lungs.** Verzalib® may cause serious blood clots that have been life-threatening. If you develop blood clots during treatment with Verzalib®, your healthcare provider may tell you to temporarily stop taking Verzalib®. Tell your healthcare provider right away if you get any of the following signs and symptoms of a blood clot:
  - pain or swelling in your arms or legs
  - chest pain
  - rapid heart rate
  - shortness of breath
  - rapid breathing

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

The most common side effects of Verzalib® include:
- low red blood cell counts (anemia)
- hair thinning or hair loss (alopecia)
- low white blood cell counts (leukopenia)
- low platelet count (thrombocytopenia)
- infections
- headache
- decreased appetite
- vomiting
- nausea
- tiredness
- abdominal pain

Drug interaction
- **CYP3A Inhibitors**
  Strong and moderate CYP3A4 inhibitors increased the exposure of Verzalib® plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.
  - *Ketoconazole*
    Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of Verzalib® by up to 16-fold.
  - *Other Strong CYP3A Inhibitors*
    In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzalib® dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole, followed by careful monitoring of toxicity. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzalib® dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzalib® discontinues a strong CYP3A inhibitor, increase the Verzalib® dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. Patients should avoid grapefruit products.
  - *Moderate CYP3A Inhibitors*
    With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzalib® dose in 50 mg decrements as demonstrated in the following table, if necessary. No dose adjustment is necessary for patients treated with moderate or weak CYP3A4 inhibitors. There should, however, be close monitoring for signs of toxicity.
    Examples of strong CYP3A4 inhibitors include, but not limited to: clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole or voriconazole.

Dose Level	Verzalib® Dose Combination with Fulvestrant, Tamoxifen, or an Aromatase Inhibitor	Verzalib® Dose for Monotherapy
Recommended starting dose	150 mg twice daily	200 mg twice daily
First dose reduction	100 mg twice daily	150 mg twice daily
Second dose reduction	50 mg twice daily	100 mg twice daily
Third dose reduction	not applicable	50 mg twice daily

- **Strong and Moderate CYP3A Inducers**
  Coadministration of strong or moderate CYP3A inducers (rifampicin, carbamazepine, phenytoin, and St. John's wort) decreased the plasma concentrations of Verzalib® plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.

Warnings
Before taking Verzalib®, tell your healthcare provider about all of your medical conditions, including if you:
- have fever, chills, or any other signs of an infection.
- have a history of blood clots in your veins.
- have lung or breathing problems.
- have liver or kidney problems.
- are pregnant or plan to become pregnant. Verzalib® can 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. Verzalib® may affect the way other medicines work, and other medicines may affect how Verzalib® works, causing serious side effects.
Especially tell your healthcare provider if you take a medicine that contains ketoconazole.

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

Overdose
In the event of a Verzalib® overdose, fatigue and diarrhea may occur. If you take too much Verzalib®, call your healthcare provider or go to the nearest hospital emergency room right away.

Pregnancy and lactation
Verzalib® can harm your unborn baby.
Females who are able to become pregnant:
- Your healthcare provider will do a pregnancy test before you start treatment with Verzalib®.
- You should use effective birth control (contraception) during treatment with Verzalib® and for at least 3 weeks after the last dose of Verzalib®.
- Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with Verzalib®.

Verzalib® may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.
It is not known if Verzalib® passes into your breast milk. Do not breastfeed during treatment with Verzalib® and for at least 3 weeks after the last dose of Verzalib®.

Patient information
- Take Verzalib® exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose if needed. Do not stop taking Verzalib® or change the dose without talking to your healthcare provider.
- Verzalib® may be taken with or without food.
- Swallow Verzalib® tablets whole. Do not chew, crush, or split the tablets before swallowing. Do not take Verzalib® tablets if they are broken, cracked, or damaged.
- Take your doses of Verzalib® at about the same time every day.
- Avoid taking ketoconazole during treatment with Verzalib®. Tell your healthcare provider if you take a medicine that contains ketoconazole.
- Avoid taking Verzalib® if you have rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
- Avoid grapefruit and products that contain grapefruit during treatment with Verzalib®. Grapefruit may increase the amount of Verzalib® in your blood.
- Tiredness and dizziness are very common side effects. If you feel unusually tired or dizzy, take special care when driving or using machines.

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

Packaging
Bottle of 60 F. C. Tablets

MANUFACTURED BY:
Noavaran Daroui Kimia Co., Tehran, Iran.
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www.kimia-pharma.co

References
https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208716s010s011lbl.pdf
https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_en.pdf
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