TRUSTINIB® F. C. TABLET

TRUSTINIB®
TRAMETINIB

TRUSTINIB® (TRAMETINIB) F. C. TABLET FOR ORAL USE
Read this patient information carefully before you start taking Trustinib® because it answers some common questions about Trustinib®. 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 Trustinib® 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 Trustinib® 0.5 mg contains: Trametinib (as dimethyl sulfoxide) 0.5 mg.
Each film-coated tablet Trustinib® 2 mg contains: Trametinib (as dimethyl sulfoxide) 2 mg.

Mechanism of action
Trametinib is a reversible inhibitor of MEK1 and MEK2 activation and of MEK1 and MEK2 kinase activity. Trametinib inhibits cell growth of various BRAF V600 mutation-positive tumors.

Pharmacokinetic
Absorption
The median time to achieve peak plasma concentrations (T_{max}) is 1.5 hours. The mean absolute bioavailability of a single oral dose of Trustinib® 2 mg is 72%.
Distribution
Trustinib® is 97.4% bound to human plasma proteins. The apparent volume of distribution (Vc/F) is 214 L.
Metabolism
Trustinib® is metabolized predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways *in vitro*.
Elimination
The estimated elimination half-life of Trustinib® is 3.9 to 4.8 days. The apparent clearance is 4.9 L/h.
Excretion
Following oral administration of [^{14}C]-trametinib, greater than 80% of excreted radioactivity was recovered in the feces while less than 20% of excreted radioactivity was recovered in the urine with less than 0.1% of the excreted dose as parent.

Indication
Trustinib® is indicated as a single agent for the treatment of BRAF-inhibitor treatment-naïve patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA approved test.
Trustinib® is indicated, in combination with Dabrafenib, for:
- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.
- the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use:
- Trustinib® is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition.

It is not known if Trustinib® used in combination with Dabrafenib is safe and effective in children younger than 6 years of age. It is not known if Trustinib® used alone is safe and effective in children.

Dosage and Administration
The recommended dosage of Trustinib® in adult patients is 2 mg orally once daily. The recommended dosage for Trustinib® in pediatric patients is based on body weight. Take Trustinib® at least 1 hour before or at least 2 hours after a meal.

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 Trustinib®. For more information, ask your healthcare provider or pharmacist.
Trustinib® can cause serious side effects, including:

- **risk of new skin cancers. Trustinib®, when used with Dabrafenib, may cause skin cancers,** called cutaneous squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, or melanoma.
  Talk to your healthcare provider about your risk for these cancers.
  Check your skin and tell your healthcare provider right away about any skin changes, including a:
  - new wart
  - skin sore or reddish bump that bleeds or does not heal
  - change in size or color of a mole

  Your healthcare provider should check your skin before treatment with Trustinib® and Dabrafenib, every 2 months during treatment with Trustinib® and Dabrafenib and for up to 6 months after you stop taking Trustinib® and Dabrafenib to look for any new skin cancers.
  Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that develop during treatment with Trustinib® with Dabrafenib.
- **bleeding problems.** Trustinib® can cause serious bleeding problems, especially in your brain or stomach, which can be life threatening. Concomitant antiplatelet or anticoagulant therapy increases the risk of hemorrhage. Call your healthcare provider and get medical help right away if you have any signs of bleeding, including:
  - headaches, dizziness, or feeling weak
  - cough up blood or blood clots
  - vomit blood or your vomit looks like "coffee grounds"
  - red or black stools that look like tar
- **inflammation of the intestines, or tears (perforation) of the stomach or intestines.** This side effect can be life threatening. Tell your healthcare provider right away if you have any of the following symptoms:
  - bleeding. See "bleeding problems" above.
  - fever
  - diarrhea (loose stools) or more bowel movements than usual
  - nausea
  - stomach-area (abdomen) pain or tenderness
- **blood clots.** Trustinib® can cause blood clots in your arms or legs, which can travel to your lungs and can be life threatening. Get medical help right away if you have the following symptoms:
  - sudden shortness of breath or trouble breathing
  - chest pain
  - pain in your legs with or without swelling
  - swelling in your arms or legs
  - a cool pale arm or leg
- **heart problems, including heart failure.** Your healthcare provider should check your heart function before and during treatment with Trustinib®. Call your healthcare provider right away if you have any of the following signs and symptoms of a heart problem:
  - feeling like your heart is pounding or racing
  - shortness of breath
  - swelling of your ankles and feet
  - feeling lightheaded
- **eye problems.** Trustinib® can cause severe eye problems that might lead to blindness. Call your healthcare provider right away if you get these symptoms of eye problems:
  - blurred vision, loss of vision, or other vision changes
  - see color dots
  - halo (seeing blurred outline around objects)
  - eye pain, swelling, or redness
- **lung or breathing problems.** Tell your healthcare provider if you have any new or worsening symptoms of lung or breathing problems, including:
  - shortness of breath
  - cough
- **fever.** Fever is common during treatment with Trustinib® and Dabrafenib, but it may also be serious. When taking Trustinib® with Dabrafenib, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever. **Call your healthcare provider right away if you get a fever during treatment with Trustinib®.** Your healthcare provider may temporarily or permanently stop your treatment, or change your dose of Trustinib® with Dabrafenib if you have fevers. Your healthcare provider will treat you as needed for your fever and any signs and symptoms of infection, and should check your kidney function during and after you have had severe fever.
- **serious skin reactions.** Skin rash is a common side effect of Trustinib®. Trustinib® can also cause other skin reactions. In some cases, these rashes and other skin reactions can be severe or serious, and may need to be treated in a hospital or can be life threatening. **Tell your healthcare provider right away if you develop any of the following signs or symptoms of a severe skin reaction, including:**
  - blisters or peeling of your skin
  - mouth sores
  - enlarged lymph nodes
  - blisters on your lips, or around your mouth or eyes
  - high fever or flu-like symptoms
- **increased blood sugar (hyperglycemia).** Some people may develop high blood sugar or worsening diabetes during treatment with Trustinib® and Dabrafenib. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with Trustinib® and Dabrafenib. Your diabetes medicine may need to be changed. Tell your healthcare provider if you have any of the following symptoms of severe high blood sugar:
  - increased thirst
  - urinating more often than normal or urinating an increased amount of urine

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

The most common side effects of Trustinib® when taken alone include:
- diarrhea. Call your healthcare provider if you get severe diarrhea.
- rash
- swelling of the face, arms, or legs

The most common side effects of Trustinib® when taken with Dabrafenib in people with melanoma that has spread to other parts of the body or cannot be removed by surgery include:
- diarrhea. Call your healthcare provider if you get severe diarrhea.
- vomiting
- high blood pressure (hypertension)
- fever
- rash
- swelling of the face, arms, or legs
- nausea
- chills

The most common side effects of Trustinib® when taken with Dabrafenib to help prevent melanoma from coming back after the cancer has been removed by surgery include:
- tiredness
- nausea
- headache
- rash
- vomiting
- joint aches
- muscle aches
- chills
- diarrhea. Call your healthcare provider if you get severe diarrhea.
- fever

The most common side effects of Trustinib® when taken with Dabrafenib in people with NSCLC include:
- fever
- tiredness
- nausea
- vomiting
- diarrhea. Call your healthcare provider if you get severe diarrhea.
- dry skin
- decreased appetite
- rash
- chills
- bleeding
- cough
- shortness of breath
- swelling of your face, arms, and legs

The most common side effects of Trustinib® when taken with Dabrafenib in adults with solid tumors that cannot be removed by surgery or have spread to other parts of the body include:
- fever
- bleeding
- tiredness
- cough
- nausea
- vomiting
- rash
- constipation
- chills
- diarrhea
- muscle and joint aches
- headache
- swelling of your arms, and legs

The most common side effects of Trustinib® when taken with Dabrafenib in children with solid tumors that cannot be removed by surgery or have spread to other parts of the body include:
- fever
- acne
- rash
- headache
- vomiting
- tiredness
- nausea
- dry skin
- diarrhea. Call your healthcare provider if your child gets severe diarrhea.
- bleeding
- stomach-area (abdomen) pain
- constipation
- cough
- skin infection around fingernails or toenails

Trustinib® can cause new or worsening high blood pressure (hypertension). Your healthcare provider should check your blood pressure during treatment with Trustinib®. Call your healthcare provider right away if you develop high blood pressure, your blood pressure worsens, or you have severe headache, lightheadedness, blurry vision, or dizziness.

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

Drug interactions
Trustinib® is indicated for use in combination with Dabrafenib. Refer to the Dabrafenib labeling for additional risk information that applies to combination use treatment.

Effect of other medicinal products on Trustinib®
Strong inhibition of hepatic P-gp may result in increased levels of Trustinib®, caution is advised when co-administering Trustinib® with medicinal products that are strong inhibitors of P-gp (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole).

Warnings
Before you take Trustinib®, tell your healthcare provider about all of your medical conditions, including if you:
- have had bleeding problems or blood clots
- have stomach problems
- have inflammation of the colon
- have heart problems
- have eye problems
- have lung or breathing problems
- have high blood pressure (hypertension)
- have liver or kidney problems
- have diabetes
- are breastfeeding or plan to breastfeed.
- are pregnant or plan to become pregnant. Trustinib® can harm your unborn baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Missed dose
If you miss a dose, take it as soon as you remember. If it is less than 12 hours before your next scheduled dose, skip the missed dose. Just take the next dose at your regular time.

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

Pregnancy and lactation
Females who are able to become pregnant:
- Your healthcare provider will do a test to see if you are pregnant before starting treatment with Trustinib®.
- You should use effective birth control (contraception) during treatment with Trustinib® and for 4 months after your last dose of Trustinib®.
- Use with Dabrafenib may render hormonal contraceptives less effective and therefore an alternative method of contraception, such as a barrier method, should be used when Trustinib® is used in combination with Dabrafenib. Talk to your healthcare provider about birth control methods that may be right for you during this time.
- Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with Trustinib®.

Males (including those who have had a vasectomy) with a female partner who is able to become pregnant:
- Use condoms during sexual intercourse during treatment with Trustinib® and for at least 4 months after your last dose of Trustinib®.

Trustinib® may cause fertility problems in females. This could affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.

It is not known if Trustinib® passes into your breast milk.
- Do not breastfeed during treatment and for 4 months after your last dose of Trustinib®. Talk to your healthcare provider about the best way to feed your baby during this time.

Patient information
- Take Trustinib® exactly as your healthcare provider tells you to take it. Do not change your dose or stop Trustinib® unless your healthcare provider tells you.
- Your healthcare provider may change your dose of Trustinib®, temporarily stop, or completely stop your treatment with Trustinib® if you develop certain side effects.
- Take Trustinib® one time a day, about every 24 hours.
- Take Trustinib® at least 1 hour before or 2 hours after a meal.
- You may experience dizziness and visual disturbances during treatment with Trustinib®. Therefore, be cautious about driving a car or operating machinery.

Storage
- Store Trustinib® tablets in the refrigerator between 2 °C to 8 °C. Once opened, bottle may be stored for 30 days at not more than 30 °C.
- Keep Trustinib® dry and away from moisture and light. Do not throw away the desiccant pack.
- Keep Trustinib® in its original bottle. Do not place tablets in a pill box.
- Keep out of the reach of children.
- 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 Trustinib® tablets.

Packaging
Bottle of 30 F. C. Tablets

MANUFACTURED BY:
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References
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204114s024lbl.pdf
https://www.ema.europa.eu/en/documents/product-information/mekinist-epar-product-information_en.pdf
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