SIMERTA® F. C. TABLET

SIMERTA®
OSIMERTINIB

SIMERTA® (OSIMERTINIB) F. C. TABLET FOR ORAL USE
Read this patient information carefully before you start taking Simerta® because it answers somecommon questions about Simerta®. 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 Simerta® 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 Simerta® 40 mg contains: Osimertinib (as mesylate) 40 mg.
Each film-coated tablet Simerta® 80 mg contains: Osimertinib (as mesylate) 80 mg.

Mechanism of action
Osimertinib is a kinase inhibitor of epidermal growth factor receptor (EGFR), which binds irreversibly to certain mutant forms of EGFR (T790M, L858R, and exon 19 deletions). *In vitro*, Osimertinib also inhibited the activity of HER2, HER3, HER4, ACK1, and BLK at clinically relevant concentrations.

Pharmacokinetic
Absorption
The median time to C_{max} of Simerta® was 6 hours (range 3-24 hours).
Distribution
The mean volume of distribution at steady-state (V_{ss}/F) of Simerta® was 918 L. Plasma protein binding of Simerta® was 95%.
Metabolism
The main metabolic pathways of Simerta® were oxidation (predominantly CYP3A) and dealkylation *in vitro*. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after Simerta® oral administration.
Elimination
Simerta® plasma concentrations decreased with time and a population estimated mean half-life of Simerta® was 48 hours, and oral clearance (CL/F) was 14.3 (L/h).
Excretion
Simerta® is primarily eliminated in the feces (68%) and to a lesser extent in the urine (14%). Unchanged Simerta® accounted for approximately 2% of the elimination.

Indication
Simerta® is indicated for:
- adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- in combination with pemetrexed and platinum-based chemotherapy, the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

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

Dosage and administration
- Adjuvant treatment of early-stage NSCLC: 80 mg orally once daily, with or without food, until disease recurrence, or unacceptable toxicity, or for up to 3 years.
- Metastatic NSCLC: 80 mg orally once daily, with or without food, until disease progression or unacceptable toxicity.
- Locally advanced or metastatic NSCLC: 80 mg orally once daily administered in combination with pemetrexed and platinum-based chemotherapy, with or without food, until disease progression or unacceptable toxicity due to Simerta®.

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 Simerta®. For more information, ask your healthcare provider or pharmacist.
Simerta® may cause serious side effects including:
- **Lung problems (Interstitial lung disease (ILD)/pneumonitis).** Simerta® may cause lung problems that may be life-threatening. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening lung symptoms, including trouble breathing, shortness of breath, cough, or fever.
- **Heart problems, including heart failure.** Simerta® may cause heart problems that may be life-threatening. Your healthcare provider should check your heart function before you start taking Simerta® and during treatment as needed. Tell 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, dizziness, feeling lightheaded, or feeling faint.
- **Eye problems.** Simerta® may cause eye problems. Tell your healthcare provider right away if you have symptoms of eye problems which may include watery eyes, sensitivity to light, eye pain, eye redness, or vision changes. Your healthcare provider may send you to see an eye specialist (ophthalmologist) if you get eye problems with Simerta®.
- **Skin problems (Erythema Multiforme Major, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis).** Simerta® may cause skin problems. Tell your healthcare provider right away if you develop skin reactions that look like rings (target lesions), severe blistering or peeling of the skin.
- **Inflammation of the blood vessels in your skin.** Simerta® may cause blood vessel problems in your skin. Tell your healthcare provider right away if you develop purple spots or redness of the skin that does not fade in color when pressed (non-blanching) on your lower arms, lower legs, or buttocks or large hives on the main part of your body (trunk) that do not go away within 24 hours and look bruised.
- **Blood and bone marrow problems.** Simerta® may cause a condition where your bone marrow cannot make enough new blood cells (aplastic anemia), and which may be life-threatening. Your healthcare provider will monitor your blood cell counts before you start and during treatment with Simerta®. **Tell your healthcare provider right away** if you develop any signs or symptoms of blood and bone marrow problems, including:
  - o a new fever or fever that does not go away (temperature 100.4°F (38°C) or higher)
  - o easy bruising or bleeding that will not stop
  - o unusually pale skin
  - o weakness
  - o infection
  - o tiredness

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

The most common side effects of Simerta® when given alone include:
- o low white blood cell counts
- o low red blood cell counts (anemia)
- o dry skin
- o inflamed and sore mouth (Stomatitis)
- o Nose bleed
- o low platelet counts
- o muscle, bone, or joint pain
- o mouth sores
- o loss of appetite
- o Hair thinning
- o diarrhea
- o rash
- o tiredness
- o cough
- o changes in your nails, including: redness, tenderness, pain, inflammation, brittleness, separation from the nailbed, and shedding of nail
- o Increase of a substance in the blood called creatinine (produced by your body and removed by the kidney).
- o Increase of a substance in the blood called creatine phosphokinase (an enzyme released into the blood when muscle is damaged).
- o Hand-foot syndrome – this may include redness, swelling, tingling or burning sensation with cracking of the skin on the palms of hands and/or soles of feet.

The most common side effects of Simerta® in combination with pemetrexed and platinum-based chemotherapy include:
- o low white blood cell counts
- o diarrhea
- o low platelet counts
- o mouth sores
- o rash
- o dry skin
- o increase of a substance in the blood called creatinine
- o changes in your nails, including: redness, tenderness, pain, inflammation, brittleness, separation from the nailbed, and shedding of nail

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 Simerta® 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 Simerta® if you are taking any of the following medicines.
The following medicines may reduce how well Simerta® works:
- Phenytoin, carbamazepine or phenobarbital – used for seizures or fits.
- Rifabutin or rifampicin – used for tuberculosis (TB).
- St. John's Wort (*Hypericum perforatum*) – an herbal medicine used for depression.

Simerta® may affect how well the following medicines work and/or increase side effects of these medicines:
- Rosuvastatin – used to lower cholesterol.
- Oral hormonal contraceptive pill– used to prevent pregnancy.
- Bosentan – used for high blood pressure in the lungs.
- Efavirenz and etravirine – used to treat HIV infections/AIDS.
- Modafinil – used for sleep disorders.
- Dabigatran – used to prevent blood clots.
- Digoxin – used for irregular heart beat or other heart problems.
- Aliskiren – used for high blood pressure.

If you are taking any of the medicines listed above, tell your healthcare provider before taking Simerta®. Your healthcare provider will discuss appropriate treatment options with you.

Warnings
Before you take Simerta®, tell your healthcare provider about all of your medical conditions, including if you:
- have lung or breathing problems (signs and symptoms of Interstitial lung disease (ILD)/pneumonitis) other than your lung cancer.
- have heart problems, including a condition called long QTc syndrome.
- have problems with your electrolytes, such as sodium, potassium, calcium or magnesium.
- have a history of eye problems.
- have reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and be preceded by fever and flu-like symptoms (signs and symptoms of Erythema Multiforme Major, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis).
- are pregnant or plan to become pregnant. Simerta® can harm your unborn baby.
- are breastfeeding or plan to breastfeed.

Tell your healthcare provider about all the medicines you take or treatments you receive, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take a heart or blood pressure medicine. You should not start or stop any medicine before you talk with the healthcare provider that prescribed Simerta®. Simerta® and other medicines may affect each other causing serious side effects.

Missed dose
If you miss a dose of Simerta®, do not make up for the missed dose. Take your next dose at your regular time.

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

Pregnancy and lactation
Simerta® can harm your unborn baby.
- Tell your healthcare provider right away if you become pregnant during treatment with Simerta® or think you may be pregnant.
- **Females** who are able to become pregnant should have a pregnancy test before starting treatment with Simerta®. You should use effective birth control (contraception) during treatment with Simerta® and for 2 months after the final dose of Simerta®.
- Simerta® may interfere with how well oral hormonal contraceptives work. Discuss with your healthcare provider the most appropriate methods of contraception.
- **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with Simerta® and for 4 months after the final dose of Simerta®.
- It is not known if Simerta® passes into your breast milk. Do not breastfeed during treatment with Simerta® and for 2 weeks after your final dose of Simerta®. Talk to your healthcare provider about the best way to feed your baby during this time.

Patient information
- Take Simerta® exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with Simerta® if you have side effects.
- Take Simerta® 1 time each day.
- You can take Simerta® with or without food.
- **If you cannot swallow Simerta® tablets whole:**
  - o Place your dose of Simerta® in a container that contains 60 mL (2 ounces) of water. **Do not** use carbonated water or any other liquids.
  - o Stir the Simerta® tablet and water until the Simerta® tablet is in small pieces (the tablet will not completely dissolve). Do not crush, heat, or use ultrasound to prepare the mixture.
  - o Drink the Simerta® and water mixture right away.
  - o Add 120 mL to 240 mL (4 to 8 ounces) of water into the container and drink to make sure that you take your full dose of Simerta®.
- **If you have a nasogastric (NG) tube:**
  - o Follow the same instructions for mixing Simerta® tablets in a container that contains 15 mL of water. **Do not** use carbonated water or any other liquids.
  - o Stir the Simerta® tablets and water until the Simerta® tablets are in small pieces (the tablets will not completely dissolve). Do not crush, heat, or use ultrasound to prepare the mixture.
  - o Add another 15 mL of water into the container to make sure no pieces of Simerta® tablet remain.
  - o Give the Simerta® tablet and water mixture using the NG tube manufacturer instructions within 30 minutes.
  - o Add another 30 mL of water into the syringe and give the water and any remaining Simerta® through the NG tube to make sure that all of the medicine is given. Repeat this step until no pieces remain in the syringe. This will help to ensure that the full prescribed dose of the Simerta® is given.

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

Packaging
Bottle of 30 F. C. Tablets

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MANUFACTURED BY:
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References
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https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf
BNF 84 (British National Formulary) September 2022- March 2023