PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

CAPRELSA 100 mg Film-Coated Tablets

Active ingredient:

Each tablet contains: vandetanib 100 mg

For a list of inactive and allergenic ingredients in the preparation, see section 6 "Further information".

Read this leaflet carefully in its entirety before using the medicine.

Keep this leaflet, you may need it again. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

If a side effect occurs, if one of the side effect worsens, or if you experience a side effect not mentioned in this leaflet, please refer to your doctor straight away.

In addition to the leaflet, Caprelsa has a patient safety information card. This card includes important safety information, which you should know and follow before starting and during treatment with Caprelsa. Read the patient safety information card and the patient leaflet before starting treatment with the preparation. Keep the card for further reference if necessary.

1. WHAT IS THE MEDICINE INTENDED FOR?

Caprelsa is intended for the treatment of metastatic medullary thyroid cancer, cancer that cannot be removed by surgery or has spread to other parts of the body.

Caprelsa works by slowing down the growth of new blood vessels in tumors (in cancer), which prevents the supply of food and oxygen to the tumor. Caprelsa may also act directly on cancer cells, to kill them or slow down their growth.

Therapeutic group:

Protein kinase inhibitor.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient vandetanib or to any of the additional ingredients contained in the medicine (see section 6 "Further information").
- You have a congenital heart disorder called 'congenital long QT syndrome', which is seen on an electrocardiogram (ECG).
- You are breastfeeding.
- You are taking any of the following medicines: arsenic, cisapride (to treat heartburn), intravenous erythromycin and moxifloxacin (for the treatment of infectious inflammation), toremifene (to treat breast cancer), mizolastine (to treat allergies), Class IA and Class III antiarrhythmics (used to control heart rhythm).

Do not use the preparation if any of the above apply to you. If you are not sure, please consult with the doctor.

Special warnings regarding use of the medicine:

Before treatment with Caprelsa, tell the doctor if:

- You are sensitive to the sun.
  People taking Caprelsa may be more sensitive to the sun, sensitivity that will manifest as a sunburn. While you are taking Caprelsa, protect yourself from sun exposure and always use sunscreen and wear long clothes to avoid exposure to the sun.
- You have high blood pressure.
- You have or have had in the past, an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- You need to have a surgical procedure. Your doctor may consider stopping Caprelsa if you will be undergoing a major surgical procedure as Caprelsa may affect wound healing. Caprelsa may be restarted once adequate wound healing is established.
- You have any kidney problems.

Severe Cutaneous Adverse Reactions (SCARs), including Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), have been reported in association with vandetanib treatment. Stop using Caprelsa and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4 "side effects".

Monitoring of your blood and your heart:

The doctor will perform blood tests to check the levels of potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH), as well as the electrical activity of the heart (ECG). The doctor will perform these tests at the following times:

- Before starting treatment with Caprelsa.
- Regularly during Caprelsa treatment.
- 1, 3 and 6 weeks after starting Caprelsa treatment.
- 12 weeks after starting Caprelsa treatment.
- Every 3 months thereafter.
- If the doctor changes your dosage of Caprelsa.
- If you started taking medicines that affect the heart.
- As instructed by your doctor.

Children and adolescents:

Caprelsa is not intended for children and adolescents under the age of 18.

Tests and follow-up:

See Warnings section.

Drug interactions:

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. This is because Caprelsa may affect the way certain medicines work and certain medicines may affect the way Caprelsa works.

In particular, inform the doctor if you are taking any of the following medicines:

- Itraconazole, ketoconazole, ritonavir, clarithromycin, rifampicin and moxifloxacin (medicines used to treat infections).
- Carbamazepine and phenobarbital (used to treat epilepsy).
- Ondansetron (to treat nausea and vomiting).
- Cisapride (to treat heartburn), pimozide (a psychiatric medicine used to treat repetitive and uncontrolled movements of the body and verbal outbursts), halofantrine and lumefantrine (to treat malaria).
- Methadone (to treat addiction), haloperidol, chlorpromazine, sulpiride, amisulpride and zuclopenthixol (to treat mental illness).
- Pentamidine (to treat infection).
- Vitamin K antagonists and dabigatran (blood thinners).
- Cyclosporine and tacrolimus (for the prevention of transplant rejection), digoxin (for heart rate disorders), metformin (to treat diabetes).
- Proton pump inhibitors (to treat heartburn).

Use of the medicine and food:

The medicine can be taken with or without food.

Pregnancy and breastfeeding:

- Do not take Caprelsa if you are pregnant. Consult the doctor before starting treatment with Caprelsa if you are pregnant, breastfeeding, think you are pregnant or are planning a pregnancy. This is because Caprelsa may harm the unborn child. The doctor will explain to you the risks and benefits of Caprelsa treatment at this time.
- Women of child-bearing age must use effective contraception when taking Caprelsa, and for at least four months after stopping to take Caprelsa.
- To keep your baby safe, do not breastfeed during treatment with Caprelsa.

Driving and using machinery:

Exercise caution when driving a car or using machines and machinery, since Caprelsa may cause tiredness, weakness or blurred vision.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

Dosage:

The dosage and treatment regimen will be determined by the doctor only.

The usual dosage of Caprelsa is generally 300 mg each day.

Do not exceed the recommended dosage.

Method of administration:

Be sure to take the tablets at the same time each day.

Swallow the tablet with water.

There is no information regarding crushing or halving the tablets.

If you have trouble swallowing the tablet:

The tablet can be mixed with water as follows:

- Take half a glass of water (non-carbonated); only use water, and do not use any other liquids.
- Place the tablet in the water.
- Stir the tablet until it has dispersed into the water. This may take up to about 10 minutes.
- Drink straight away.

In order to make sure that no remnants of the medicine remain in the glass, add approximately half a glass of water to the empty glass with the remains of the medicine and drink.

If you have accidentally taken a higher dosage:

If you have accidentally taken an overdose or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you experience a side effect:

If you experience any side effects, please inform the doctor. Your doctor may tell you to take a lower dosage of Caprelsa. Your doctor may also prescribe other medicines to treat the side effects. See the list of side effects in section 4 "side effects.

If you forget to take the medicine:

Take action according to the time left until your next dose.

- If **12 hours or more remain until the time for the next dose**, take the missed dose as soon as you remember. Then take the next dose at the normal time.
- If **less than 12 hours remain until it is time for the next dose**, skip the missed dose. Then take the next dose at the normal time.

Do not take a double dose to make up for a forgotten dose.

Adhere to the treatment regimen as recommended by the doctor. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Caprelsa may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them. If you have a side effect, your doctor may tell you to take a lower dosage of Caprelsa. Your doctor may also prescribe you other medicines to treat the side effects.

Refer to the doctor straight away if you experience one or more of the following side effects – you may need urgent medical treatment:

- Fainting, dizziness or heart rhythm changes. These may be signs of a change in the electrical activity of your heart. These effects have been seen in 8% of patients taking Caprelsa for metastatic medullary thyroid cancer. Your doctor may recommend you to take Caprelsa at a

lower dosage or to stop taking Caprelsa. Caprelsa has uncommonly been associated with life-threatening changes in heart rhythm.
- Stop using Caprelsa and seek medical attention immediately if you notice any of the following symptoms: reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Severe diarrhoea.
- Serious breathlessness, or sudden worsening of breathlessness, possibly accompanied by a cough or high fever. This may be caused by an inflammation of the lungs called interstitial lung disease. This effect is uncommon (occurs in less than 1 in 100 users), but can be life-threatening.
- Seizures, headache, confusion or difficulty concentrating. These may be signs of a syndrome called RPLS (reversible posterior leukoencephalopathy syndrome). This syndrome generally passes when stopping treatment with Caprelsa. RPLS is uncommon (occurs in less than 1 in 100 users).

Inform the doctor immediately if you experience any of the side effects listed above.

Additional side effects

Very common side effects (occur in more than 1 in 10 users):
- Diarrhoea. Your doctor may prescribe a medicine to treat the diarrhoea, but if the diarrhoea gets worse, please tell your doctor straight away
- Abdominal pain
- Skin rash or acne
- Depression
- Tiredness
- Nausea
- Abdominal pain (indigestion)
- Nail problems
- Vomiting
- Loss of appetite (anorexia)
- Weakness (asthenia)
- High blood pressure. Your doctor may prescribe a medicine to treat blood pressure
- Headache
- Tiredness (fatigue)
- Trouble sleeping (insomnia)
- Inflammation of the nasal passages
- Inflammation of the main air passages to the lungs
- Upper respiratory tract infections
- Urinary tract infection
- Numbness or tingling sensation in the skin
- Abnormal sensation in the skin
- Dizziness
- Pain
- Edema (swelling caused by excess fluids)
- Stones or calcium deposits in the kidneys or urinary tract (nephrolithiasis)
- Blurred vision, including mild changes in the eyes which can lead to blurred vision
- Sensitivity of the skin to sunlight. While using Caprelsa, protect yourself from exposure to the sun and always use sunscreen and long clothes when going outside.

Common side effects (occur in less than 1 in 10 users):
- Dehydration
- Severe high blood pressure
- Weight loss
- Stroke, cerebral insufficiency or another condition in which the blood flow to the brain is inadequate
- A type of rash that affects the hands and feet (hand-foot syndrome)
- Sore mouth (stomatitis)
- Dry mouth
- Pneumonia
- Toxins in the blood - a complication of infection
- Flu
- Inflammation of the urinary bladder
- Inflammation of the sinuses
- Inflammation of the larynx/voice box
- Inflammation of the follicles, especially hair follicles
- Skin pustular infection (“furuncle”)
- Fungal infection
- Kidney infection
- Loss of body fluids (dehydration)
- Anxiety
- Tremor
- Drowsiness, sleepiness
- Fainting
- Feeling unsteady
- Increased pressure in the eye (glaucoma)
- Bloody cough
- Inflammation of the lung tissue
- Difficulty swallowing
- Constipation
- Inflammation of the lining of the stomach (gastritis)
- Gastrointestinal bleeding
- Gallstones (cholelithiasis)
- Painful urination
- Kidney failure
- Frequent and urgent urination
- Fever
- Nose bleed (epistaxis)
- Dry eyes
- Eye irritation (conjunctivitis)
- Visual impairment
- Halo vision
- Seeing flashes of light (photopsia)
- Corneal defect (keratopathy)
- A type of diarrhoea (colitis)
- Loss of hair from the head and body (alopecia)
- Changes in sense of taste (dysgeusia).

Uncommon side effects (occur in less than 1 in 100 users):
- Heart failure (a condition in which the heart cannot pump the blood well; signs include breathlessness and swelling of the ankle)
- Inflammation of the appendix (appendicitis)
- Bacterial infection
- Inflammation of the diverticula (diverticula – small bulging pouches that can form in the digestive system)
- Bacterial skin infections
- Abdominal wall abscess
- Malnutrition
- Involuntary muscle contractions (convulsions)
- Rapidly alternating muscular contraction and relaxation (clonus)
- Swelling of the brain
- Clouding of the lens of the eye
- Heart rhythm disorders
- Reduced heart function
- Lung function disorders
- Pneumonia caused by the respiration of a foreign substance into the lungs
- Bowel obstruction
- Bowel perforation
- Inability to control bowel movements
- Abnormal color of urine
- Lack of urine
- Impaired ability to heal properly
- Inflammation of the pancreas (pancreatitis)
- Blistering of skin (bullous dermatitis).

Side effects of unknown frequency (frequency can not be estimated from the available data):
- Enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysm and artery dissection).
- Reddish non-elevated, target like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, which can be preceded by fever and flu-like symptoms. These serious skin rashes can be potentially life threatening (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- A skin reaction that causes red spots or patches on the skin that may look like a target or “bulls-eye” with a dark red center surrounded by paler red rings (erythema multiforme).

Side effects that may be seen in laboratory tests:
- Protein or blood in the urine (seen in a urine test)
- Heart rhythm changes (shown in an ECG). Your doctor may tell you to stop taking Caprelsa or to take a lower dosage of Caprelsa
- Abnormal liver and pancreatic functions that are seen in blood tests. Usually without symptoms, but the doctor may want to monitor these values
- Decreased levels of calcium in the blood. The doctor may prescribe or change your current treatment with thyroid hormones
- Decreased levels of potassium in the blood
- Increased levels of calcium in the blood
- Increased red blood cell levels.

If a side effect occurs, if one of the side effect worsens, or if you suffer from a side effect not mentioned in this leaflet, please refer to your doctor straight away.

Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il), which directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il

5. HOW SHOULD THE MEDICINE BE STORED?
- Avoid poisoning! This medicine and any other medicine should be stored in a safe place, out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Store the preparation in a cool place below 30°C.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- Do not discard medicines in the household waste bin or wastewater. Ask your pharmacist how to dispose of medicines you no longer need. These measures will help protect the environment.

6. FURTHER INFORMATION
In addition to the active ingredient, the medicine also contains:
Dibasic calcium phosphate dihydrate, microcrystalline cellulose, crospovidone, povidone, magnesium stearate, hypromellose 2910, macrogol 300 and titanium dioxide (E171).

What the medicine looks like and contents of the package:
White, round, film-coated tablets with “Z100” imprinted on one side.
Caprelsa comes in a blister pack of 30 tablets.

License holder and importer’s name and address:
sanofi-aventis Israel ltd., 10 Beni Gaon Street, P.O.B. 8090, Netanya.
Revised in February 2023 according to MOH guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
149 23 33769
This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, please ask your doctor.