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

The medicine is dispensed with a doctor's prescription only

Cotellic® 20 mg

Film-coated tablets

Composition:
Each film-coated tablet contains:
Cobimetinib 20 mg

For information on the inactive ingredients, see section 6 - "Further Information".

Read this leaflet carefully in its entirety before using the medicine.
- This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
- Keep this leaflet. You may need to read it again.
- 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.
- **In addition to the leaflet, there is a patient safety information card for Cotellic. This card includes important safety information, that you should know, and act upon it accordingly, before starting and during treatment with Cotellic. Read the patient safety information card and the patient leaflet before starting use of this preparation. Keep the card for additional reference, if necessary.**

Cotellic is intended for treatment in adults over the age of 18.

1) What is the medicine intended for?

Cotellic is intended for the treatment of a type of skin cancer called metastatic melanoma, or melanoma which can not be surgically removed, in combination with vemurafenib in patients with the V600 mutation in the protein called BRAF.

How does the medicine work?
The medicine targets a protein called "MEK" that is important in regulating the development of the cancer cell. When **Cotellic** is given in combination with vemurafenib (a medicine which targets the mutated "BRAF" protein), it further slows down or stops the development of the cancer.

Therapeutic group
Anti-neoplastics - protein kinase inhibitors

2) Before using the medicine

Do not use the medicine if:
- You are sensitive (allergic) to the active ingredient (cobimetinib), or to any of the additional ingredients contained in the medicine (listed in section 6 - "Further Information").

  If you are not sure, refer to your doctor before starting treatment with **Cotellic**.

Special warnings regarding use of the medicine
*Before treatment with **Cotellic**, inform the doctor if you have:*

Bleeding
Cotellic can cause severe bleeding, especially in the brain or stomach (see section 4 – "Side Effects", in the section discussing severe bleeding). Tell the doctor **immediately** if you have any unusual bleeding or any of the following symptoms: headaches, dizziness, feeling weak, blood in the stools or black stools and vomiting blood.

Eye problems
Cotellic can cause eye problems [see section 4 – "Side Effects", in the section discussing eye (vision) problems].
Tell your doctor **immediately** if the following symptoms occur: blurred vision, distorted vision, partial vision loss, or any other change in your vision during treatment. Your doctor will examine your eyes in the event of new problems, or worsening of your preexisting vision problems, during the course of treatment with **Cotellic**.

Heart problems
Cotellic can lower the amount of blood pumped by your heart, (see section 4 – "Side Effects", in the section discussing heart problems). Your doctor will instruct you to perform tests before and during treatment with **Cotellic** to test the ability of your heart to pump blood. Tell your doctor **immediately** if it feels like your heart is pounding strongly, racing or beating unevenly, or if you experience dizziness, light-headedness, shortness of breath, tiredness, or swelling in the legs.

Liver problems
During treatment, **Cotellic** can increase the levels of certain liver enzymes in your blood. Your doctor will instruct you to perform blood tests to check the levels of these enzymes and to monitor your liver function.

Muscle problems
Cotellic can cause increased levels of creatine phosphokinase, an enzyme that is found mainly in the muscle, heart and brain. This condition can be a sign of muscle damage (rhabdomyolysis) (see section 4 – "Side Effects", in the section discussing muscle problems). The attending doctor will refer you for blood tests to monitor for this condition. Tell the attending doctor **immediately** if you get any of the following symptoms: muscle aches, muscle spasms, weakness, dark- or red-colored urine.

Diarrhea
Tell your doctor **immediately** if you get diarrhea. Severe diarrhea can cause loss of body fluids (dehydration). Follow your doctor's instructions to know what to do to prevent or treat diarrhea.

Children and adolescents
Cotellic is not intended for treatment of children and adolescents. The safety and efficacy of **Cotellic** in patients under 18 years of age, have not been established.

Cotellic and other medicines
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 **Cotellic** can affect the way other medicines work. In addition, other medicines can have an effect on the way **Cotellic** works.

Before treatment with **Cotellic**, tell your doctor if you are taking the following medicines:

Medicine	Purpose of the medicine
itraconazole, clarithromycin, erythromycin, telithromycin, voriconazole, rifampicin, posaconazole, fluconazole, miconazole	to treat certain bacterial or fungal infections
ritonavir, cobicistat, lopinavir, delavirdine, amprenavir, fosamprenavir	to treat HIV infection (human immunodeficiency virus)
telaprevir	to treat hepatitis C
nefadozone	to treat depression
amiodarone	to treat irregular heart rate
diltiazem, verapamil	to treat high blood pressure
imatinib	to treat cancer
carbamazepine, phenytoin	to treat convulsions (seizures)
St. John's wort (*Hypericum* plant extract)	a herbal medicine to treat depression. This medicine is not available without a prescription

Use of the medicine with food and drink
Avoid taking the medicine with grapefruit juice, since grapefruit juice may increase the amount of medicine in your blood.
Cotellic can be taken with or without food.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to become pregnant, consult your doctor before using this medicine.
- **Cotellic** is not recommended for use during pregnancy - although the effects of **Cotellic** have not been studied in pregnant women, the medicine may cause irreversible harm to an unborn baby or to birth defects.
- If you become pregnant during treatment with **Cotellic** or in the three months after the last treatment, tell your doctor **immediately**.
- It is not known whether the medicine is secreted into breast milk. Your doctor will discuss with you the benefits and risks of taking **Cotellic**, if you are breast-feeding.

Contraception
Women of childbearing potential must use two types of effective methods of contraception [such as a condom or other barrier method to prevent the passage of sperm (with spermicide, if available)] during treatment and for at least three months after treatment has finished. Ask your doctor about contraceptive methods most suitable for you.

Driving and using machines
Cotellic can affect your ability to drive or use machines.
Avoid driving or using machines if you have problems with your vision or other problems that might affect your functioning, e.g., if you feel dizzy or tired. Consult your doctor if you are not sure.

Important information about some of the ingredients in this medicine
Cotellic tablets contain lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, consult your doctor before starting treatment with this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet and therefore is considered 'sodium-free'.

3) How should you use the medicine?

Always use this medicine according to the doctor's instructions.
Check with your doctor or pharmacist if you are not sure.

Usual dosage
The dosage and treatment regimen will be determined by the doctor only.
The usual dosage is generally three tablets (a total of 60 mg) per day.
- Take the tablets every day for 21 days (called a "treatment period").
- After 21 days, do not take any **Cotellic** tablets for 7 days. During this 7 day break in **Cotellic** treatment, keep taking the medicine vemurafenib as instructed by your doctor.
- Start your next **Cotellic** treatment period (21 days of treatment) after the 7 day break.
- If you have side effects, your doctor may decide to lower your dosage, to temporarily or permanently stop the treatment. Always take the medicine exactly as your doctor instructs you. Do not exceed the recommended dose.

Taking the medicine
- Swallow the tablets whole with water.
- **Cotellic** can be taken with or without food.
- Avoid taking the medicine with grapefruit juice.

Tests and follow-up
- Your doctor will instruct you to perform tests before and during treatment with **Cotellic**, to assess your heart's ability to pump blood.
- Your doctor will instruct you to perform blood tests to check the levels of liver enzymes, and in order to monitor your liver function.
- Your doctor will check your eyes to determine if you have any new or worsening problems with your sight, during treatment with **Cotellic**.

If you vomit after taking the medicine, do not take an additional dosage of **Cotellic** on the same day. Continue taking the medicine as normal, the next day.

If you accidentally took a Cotellic dosage higher than instructed by the doctor, refer to the doctor **immediately**. Take the medicine package and this leaflet with you.
If you took an overdose, or if a child has accidentally swallowed the medicine, **immediately** refer to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forget to take Cotellic at the scheduled time, follow the instructions below:
- If it is more than 12 hours before the time for taking the next dose, take the missed dose as soon as you remember.
- If there are fewer than 12 hours until the time for the next dose, do not take the missed dose; skip it. Wait and take the next dose at the usual time.
- If you forgot to take this medicine at the scheduled time, do not take a double dose, in order to make up for a missed dose.

If you stop taking Cotellic
Adhere to the treatment 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.

How can you contribute to the success of the treatment?
Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.
If you have further questions regarding use of this medicine, consult your doctor or pharmacist.

4) Side effects

As with any medicine, use of **Cotellic** 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 side effects, your doctor may decide to lower the dosage, or to stop treatment temporarily or permanently.
Please refer to the package leaflet of the medicine vemurafenib as well, which is given in combination with **Cotellic**.

Serious side effects

Refer to the doctor immediately if you notice any of the side effects listed below or if these get worse during treatment:
- **Severe bleeding** (common side effects which may affect up to one in ten users):
  Cotellic can cause severe bleeding, especially in the brain or stomach. Depending on the area of the bleeding, symptoms may include:
  - headaches, dizziness or weakness
  - vomiting blood
  - abdominal pain
  - red- or black-colored stools
- **Eye (vision) problems** (very common side effects which may affect more than one in ten users):
  Cotellic can cause eye problems, some of which may be a result of a condition called "serous retinopathy", which results from a build-up of fluid under the retina in the eye. Symptoms of "serous retinopathy" include:
  - blurred vision
  - vision disturbances or distortions
  - partial vision loss
  - any other changes to your vision
- **Heart problems** (common side effects which may affect up to one in ten users):
  Cotellic can lower the amount of blood pumped by your heart. The symptoms include:
  - dizziness
  - feeling light-headed
  - feeling short of breath
  - tiredness
  - feeling like your heart is pounding strongly, racing or beating unevenly
  - swelling in the legs
- **Muscle problems** (uncommon side effects which may affect up to one in hundred users):
  Cotellic can result in the breakdown of muscle (rhabdomyolysis). The symptoms may include:
  - muscle aches
  - muscle spasms and weakness
  - dark- or red-colored urine
- **Diarrhea** (very common side effect: may affect more than one in ten users):
  Refer to your doctor **immediately** if you get diarrhea, and follow your doctor's instructions for what to do in order to help prevent or treat diarrhea.

Additional side effects
Refer to your doctor if you notice any of the following side effects:

Very common side effects (may affect more than one in ten users):
- increased skin sensitivity to sunlight
- skin rash
- nausea
- fever
- chills
- increased liver enzyme levels, shown in blood tests
- abnormal blood test results relating to values of creatine phosphokinase, an enzyme found mainly in heart, brain and skeletal muscle
- vomiting
- skin rash with a flat discolored area or raised bump like acne
- high blood pressure
- anemia (low level of red blood cells)
- bleeding
- abnormal thickening of the skin
- swelling usually in the legs (peripheral edema)
- itchy or dry skin.

Common side effects (may affect up to one in ten users):
- some types of skin cancer (such as basal cell carcinoma, cutaneous squamous cell carcinoma and keratoacanthoma)
- dehydration, when your body does not have enough fluid
- decreased levels of phosphate or sodium (shown in blood tests)
- increased sugar level (shown in blood tests)
- increased liver pigment (called "bilirubin") in the blood. Signs of this include yellowing of the skin or eyes
- inflammation of the lungs that may cause difficulty breathing and can be life-threatening (called "pneumonitis").

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, you should consult with your doctor.

Reporting side effects
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) that 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 kept in a closed place out of the reach of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the blister and the package. The expiry date refers to the last day of that month.
- Storage conditions: do not store the medicine above 30°C.
- Do not discard the medicine via household waste or wastewater. Ask the pharmacist how to discard the medicine in order to protect the environment.

6) Further information

In addition to the active substance, the medicine also contains (please see section 2 "Important information about some of the ingredients in this medicine"):
Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, film-coating mixture (polyvinyl alcohol, titanium dioxide, macrogol/PEG 3350, talc).

What does the medicine look like and what are the contents of the package?
Cotellic 20 mg – film-coated, white, round tablets with "COB" debossed on one side.
There is one package size available: 63 tablets (three blisters of 21 tablets).

License holder and address: Roche Pharmaceuticals (Israel) Ltd., P.O.B. 6391, Hod Hasharon 4524079.

Manufacturer name and address: F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 156.38.34546.00

Revised in January 2023 according to MOH guidelines.