Patient package insert according to pharmacists' regulations (Preparations) - 1986

This medicine is to be supplied upon physician's prescription only.

REVLIMID® 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg, 25mg
Hard Capsules

Composition:
Active ingredient:
Each hard capsule contains: Lenalidomide 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg or 25mg

Inactive ingredients and allergens - See section 6 in the leaflet **"Additional information".**

Read this package insert carefully in its entirety before using this medicine. This leaflet contains summary information about this medicine. If you have any further questions, refer to the physician or a pharmacist.

This medicine has been prescribed for treating your illness. Do not pass it on to others. It may harm them, even if it seems to you that their condition is similar to yours.
The safety and efficacy of this medicine in unknown for children and adolescents under 18 years of age.

1. What is this medicine intended for?

Revlimid is used to treat adult patients who have low red blood cells counts, a condition called myelodysplastic syndrome (MDS). Revlimid can increase the number of healthy red blood cells that the body produces by reducing the number of abnormal cells. This can reduce the number of blood transfusions needed. It is possible that no transfusions will be needed.

Revlimid is used in newly diagnosed patients with multiple myeloma when you are unable to be treated with a bone marrow transplant. If you are aged 75 years or older or have moderate to severe kidney problems - your physician will check you carefully before starting treatment.
In newly diagnosed multiple myeloma patients there are two types of treatment:

- Revlimid together with an anti-inflammatory medicine called 'dexamethasone'.
- Revlimid together with a chemotherapy medicine called 'melphalan' and an immunosuppressant medicine called 'prednisone'.

You will take these other medicines at the start of treatment and then continue to take Revlimid on its own.

Revlimid in combination with dexamethasone is used to treat adult patients who have been diagnosed with multiple myeloma who have received at least one prior therapy.

Revlimid is used for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

Revlimid 7.5mg is used:
in combination with dexamethasone, to treat adult patients who have been diagnosed with multiple myeloma who have received at least one prior therapy.

Revlimid should not be used to treat people who have chronic lymphocytic leukemia (CLL) unless they are participants in a controlled clinical trial.

Therapeutic group: Immunomodulating agents

2. Before using this medicine

Do not use this medicine if:

Women:

- Do not use this medicine **if you are pregnant or are planning to become pregnant.** Revlimid may be dangerous to the fetus therefore if you are a woman of childbearing potential do not take this drug without using two reliable forms of contraception (please see section 2 – "Special warnings regarding the use of the medicine").
- You should wait 4 weeks after the end of the treatment before trying to get pregnant.
- Do not breastfeed during Revlimid therapy, during any breaks (discontinuations) in your therapy and for 4 weeks after stopping Revlimid therapy.

Men:
- Do not use this medicine **if you are not able or willing to use a condom in every sexual intercourse with a women of childbearing potential** (please see section 2 – "Special warnings regarding the use of the medicine").
- Do not donate semen or sperm while taking Revlimid, during any breaks (discontinuations) in your therapy, and for 4 weeks after stopping Revlimid therapy.

All patients:
- Do not take Revlimid if you are allergic (hypersensitive) to lenalidomide or any of the other ingredients of Revlimid (please see section 6 **"Additional information"**).
- Do not donate blood during Revlimid therapy, during any breaks (discontinuations) in your therapy, and for 4 weeks after stopping therapy.

Special warnings regarding the use of the medicine:

Before starting Revlimid treatment, tell your physician if:
- You have kidney problems or receive kidney dialysis treatment
- Have liver problems
- You had a heart attack, stroke, have ever had a blood clot, or if you smoke, have high blood pressure or high cholesterol levels.
- You had a history of blood clots or if you take medicines that can increase the risk for blood clots. Blood clots in the arteries, veins, and lungs happen more often in people who take REVLIMID. This risk is even higher for people with multiple myeloma who take the medicine dexamethasone with REVLIMID. Heart attacks and strokes also happen more often in people who take REVLIMID with dexamethasone. To reduce this increased risk, most people who take REVLIMID will also take a blood thinner medicine.
- You have a high total amount of tumour throughout the body, including your bone marrow. This could lead to a condition where the tumours break down and cause unusual levels of chemicals in the blood which can lead to kidneys failure (this condition is called Tumour Lysis Syndrome).
- You have any sign of infection, such as a cough or fever.
- You had an allergic reaction whilst taking thalidomide such as rash, itching, swelling, dizziness or trouble breathing.

You are intolerant to some sugars (the medicine contains lactose). If you have myelodysplastic syndromes, you may be more likely to get a more advanced condition called acute myeloid leukaemia (AML). In addition, we do not know how Revlimid affects the chances of you getting AML. Your physician may therefore do tests to check for signs which may better predict the likelihood of getting AML during your treatment with Revlimid.

The safety and efficacy of this medicine in unknown for children and adolescents under 18 years of age.

Your physician will enroll you in the Risk Management/Pregnancy Prevention Programme (RMP/PPP). This program intends to help your physician advise you concerning the risks involved in Revlimid therapy and ensures that you are aware of the precautions that you should take before, during and after therapy.

Women of childbearing potential: You will have pregnancy tests under the supervision of your physician (before treatment, then monthly during the treatment, during dose interruptions and 4 weeks after the treatment has finished) except in the following cases:
If you have undergone hysterectomy,
If you have undergone a bilateral oophorectomy,
If you have been postmenopausal naturally for at least 24 consecutive months
Or in any other case indicated by your physician.

*__Secession of menses due to anti-cancer therapy, do not exclude the potential to become pregnant.__

You must use 2 methods of birth control at the same time every time for 4 weeks before starting therapy, during therapy, during dose interruptions and for 4 weeks after stopping therapy unless continuous abstinence from heterosexual sexual contact is the chosen method. Your physician will advise you on appropriate methods of contraception.

Men: If your female partner is able to become pregnant or is pregnant, you must use condom, during Revlimid therapy, and for 4 weeks after the end of therapy, even if you have undergone a successful vasectomy.
In the case of a male patient with an allergy to latex or polyurethane, at least one effective form of contraception should be used by any female sexual partner. Contraception should be started in this

partner at least 4 weeks prior to the start of a sexual relationship with the patient, and continued throughout Revlimid therapy and for an additional 4 weeks following discontinuation of therapy.
You should not donate semen or sperm during therapy, during any breaks (discontinuations) in your therapy, and for 4 weeks after the end of therapy.

All patients:
Before and during the treatment with Revlimid you will have regular blood tests as the medicine may cause a fall in the blood cells that help to fight infection and help the blood to clot (please see section 3 – "How to use this medicine – tests and follow up").
You should not donate blood during Revlimid therapy, during any breaks (discontinuations) in your therapy and for 4 weeks after the end of therapy.

Tell the physician or a pharmacist if you are taking or have recently taken other medicines, including non-prescription medicines or food supplements.
It is especially important to inform your physician or pharmacist if you are taking:
- Erythropoietic agents (treating anemia), or other agents that may increase the risk of thrombosis in blood vessels such as hormone replacement therapy and oral contraceptives (birth control pills)
- Warfarin – close monitoring of warfarin blood concentration is advised during the combined treatment with dexamethasone
- Digoxin – periodic monitoring of digoxin blood concentration is advised during the treatment with Revlimid.

Taking this medicine with food
The medicine can be taken either with or without food.

Pregnancy and breastfeeding
Do not use this medicine if you are pregnant or are planning to become pregnant. Revlimid may be dangerous to the fetus therefore if you are a woman of childbearing potential do not take this drug without using effective forms of contraception (please see section 2 – "Special warnings regarding the use of the medicine").
If you do become pregnant during Revlimid therapy, you must stop the therapy and inform your physician immediately.

You should wait 4 extra weeks after the end of the treatment before trying to get pregnant.
Do not breastfeed during Revlimid therapy, during any breaks (discontinuations) in your therapy and for 4 weeks after stopping Revlimid therapy.

Driving and using machines:

The use of this medicine may cause dizziness, tiredness, sleepiness or blurred vision and therefore caution should be exercised when driving a vehicle, operating dangerous machinery or performing any other activity that requires alertness.

Important information on some of the product ingredients:
If you are intolerant to lactose or other sugars, please inform your physician. Revlimid contains lactose. If you are aware of lactose intolerance or you were told to have intolerance to any sugars please consult your physician before starting treatment.

3. How to use this medicine?

Always use according to physician prescription. If you are not sure, ask your physician or a pharmacist.

Directions for use:
Do not open, chew or break the hard capsule! This medicine should be swallowed whole, with water, once a day. You should take the medicine at about the same time each day. The medicine can be taken either with or without food.

Dosage:
Dosage is according to physician's instructions only. The usual dose is:
- Newly diagnosed multiple myeloma (NDMM): 25mg once daily, for 21 days. This medicine is given in repeated 28-day cycles.
- Multiple Myeloma (MM): 25mg once daily for 21 days. This medicine is given in repeated 28-day cycles.
- Myelodysplastic Syndromes (MDS): 10mg once daily.
- Mantle Cell lymphoma (MCL): 25mg once daily for 21 days. This medicine is given in repeated 28-day cycles.

Do not exceed the recommended dosage. Take this medicine at specified time as prescribed by your physician. It is important not to skip any dose.

Tests and Follow up:

- Before and during the treatment with Revlimid you will have regular blood tests as the medicine may cause a fall in the blood cells that help to fight infection and help the blood to clot. Your physician will ask you to have a periodic blood tests:
  - If you are being treated for del 5q myelodysplastic syndromes (MDS) your blood counts should be checked weekly during the first 8 weeks of treatment with REVLIMID, and at least monthly until the end of the treatment.
  - If you are being treated for multiple myeloma, your blood counts should be checked every 2 weeks for the first 12 weeks and then at least monthly until the end of the treatment.
  - If you are being treated for mantle cell lymphoma (MCL) you should have complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter.

Your physician may adjust your dose of Revlimid or stop your treatment depending on the results of your blood tests and your general condition.

- Women of childbearing potential: You should perform pregnancy testing under your physician supervision (before starting therapy and then monthly during therapy, during dose interruptions and 4 weeks after stopping therapy). Please see section 2 – "Special warnings regarding the use of the medicine".

- If you are newly diagnosed with multiple myeloma, your physician may also assess your treatment based on your age and other conditions you may already be experiencing.

If you have taken an overdose:
If you have taken an overdose, or if a child accidentally swallowed this medicine, refer immediately to a physician or a hospital emergency room and bring the medicine package with you.

If you forgot to take your medicine:
If you forget to take the medicine at your regular time and less than 12 hours have passed: take your hard capsule immediately.
If more than 12 hours have passed: do not take your hard capsule. Take your next hard capsule at the usual time the next day.

If you stop taking the medicine:
Do not discontinue use of this medicine without consulting your physician.

How can you contribute to the success of the treatment?
Complete the full course of treatment as instructed by the physician.
Even if there is an improvement in your health, do not discontinue use of this medicine without consulting your physician or a pharmacist.

Do not take medicines in the dark! Check the label and the dose every time you take this medicine.
Wear glasses if you need them.
If you have any additional questions regarding the use of the medicine, consult the physician or a pharmacist.

4. Side Effects:

Like all medicines, Revlimid can cause side effects, although not everybody gets them. Do not be alarmed by the list of side effects. You may not experience any of them.

Increased risk of death in people who have chronic lymphocytic leukemia (CLL). People with CLL who take REVLIMID have an increased risk of death compared with people who take the medicine chlorambucil. REVLIMID may cause you to have serious heart problems that can lead to death, including atrial fibrillation, heart attack, or heart failure. You should not take REVLIMID if you have CLL unless you are participating in a controlled clinical trial.

Serious side effects which may affect more than 1 in 10 people

Revlimid may reduce the number of white blood cells that fight infection and also the blood cells which help the blood to clot (platelets) which may lead to bleeding disorders e.g. nosebleeds and bruising.

Revlimid may also cause blood clots in the veins (thrombosis), arteries or lungs that can lead to pulmonary embolism, heart attack or stroke.
Therefore **you must tell your physician immediately** or get medical help if you experience:

- signs or symptoms of a blood clot in the lung, arm, or leg may include: shortness of breath, chest pain, or arm or leg swelling**.**
- signs or symptoms of a heart attack may include: chest pain that may spread to the arms, neck, jaw, back, or stomach-area (abdomen), feeling sweaty, shortness of breath, feeling sick or vomiting.
- signs or symptoms of stroke may include: sudden numbness or weakness, especially on one side of the body, severe headache or confusion, or problems with vision, speech, or balance.
- fever, chills, sore throat, cough, mouth ulcers or any other symptoms of infection including within the blood stream (sepsis).
- bleeding or bruising in the absence of injury.

Additional serious side effects:

Risk of new cancers (malignancies). People with multiple myeloma who receive melphalan (a type of chemotherapy) and a blood stem cell transplant with the addition of REVLIMID have a higher risk of developing new cancers, including certain blood cancers (acute myelogenous leukemia or AML) and a type of lymphoma called Hodgkin lymphoma. Talk with your healthcare provider about your risk of developing new cancers if you take REVLIMID. Your healthcare provider will check you for new cancers during your treatment with REVLIMID.

Severe liver problems, including liver failure and death. Tell your healthcare provider right away if you develop any of the following symptoms of liver problems:

- yellowing of your skin or the white part of your eyes (jaundice)
- dark or brown (tea colored) urine
- pain on the upper right side of your stomach area (abdomen)
- bleeding or bruising more easily than normal
- feeling very tired

Your healthcare provider will do blood tests to check your liver function during your treatment with REVLIMID.

Serious skin reactions. Serious skin reactions can happen with REVLIMID and may cause death. Call your healthcare provider right away if you have any skin reaction while taking REVLIMID.

Tumor lysis syndrome (TLS). TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure and sometimes death. Your healthcare provider may do blood tests to check you for TLS.

Worsening of your tumor (tumor flare reaction). Tell your healthcare provider if you get any of these symptoms of tumor flare reaction while taking REVLIMID: tender swollen lymph nodes, low-grade fever, pain, or rash.

Other side effects are given below
It is important to note that a small number of patients with multiple myeloma may develop additional types of cancer, and it is possible that this risk may be increased with Revlimid treatment, therefore your physician should carefully evaluate the benefit and risk when you are prescribed Revlimid.

Very common side effects may affect more than 1 in 10 people:

- A fall in the number of white blood cells (the cells that fight infection), platelets (the cells that help the blood to clot, which may lead to bleeding disorders) and red blood cells (anaemia leading to tiredness and weakness)
- Constipation, diarrhoea, nausea, rashes, vomiting, muscle cramps, muscle aches, back, bone or limb pain, tiredness, generalized swelling including swelling of the limbs
- Fever and flu like symptoms including fever, muscle ache, headache, and chills
- Numbness, tingling or burning sensation to the skin, pains in hands or feet, dizziness, tremor, taste disturbance
- Chest pain spreading to the arms, neck, jaw, back or stomach, feeling sweaty and breathless, feeling sick or vomiting, which may be symptoms of a heart attack (myocardial infarction)
- Decreased appetite, low levels of potassium in the blood
- Leg pain (which could be a symptom of thrombosis), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs called pulmonary embolism)
- Infection of the lung and the upper respiratory tract, shortness of breath, nosebleed
- Blurred vision
- Clouding of your eye (cataract)
- Kidney problems

- Changes to a protein in the blood that can cause swelling of the arteries (vasculitis)
- Increases in your blood sugar level (diabetes)
- Dry skin
- Abdominal pain
- Mood change, difficulty sleeping
- Headache

Common side effects may affect up to 1 in 10 people:
- Difficulty breathing
- Infections of all types
- Bleeding from the gums, stomach, or bowels, bruising
- Increased blood pressure or a fall in blood pressure, slow, fast or irregular heart beat
- Increased pigmentation of skin, increased hair growth
- Skin eruptions, skin cracking, flaking, redness, decreased tactile sensitivity
- Hives, itching, dry skin, increased sweating, night sweats, dehydration
- Sore inflamed nasal membranes, mouth or stomach, dry mouth, difficulty swallowing, cough, hoarseness
- Abdominal pain
- Production of much more or much less urine than usual (which may be a symptom of kidney failure), passing blood in the urine, painful urination
- Shortness of breath especially when lying down (which may be a symptom of heart failure)
- Difficulty in obtaining an erection
- Stroke, fainting
- Muscle weakness
- Joint swelling or joint pain
- Changes to blood thyroid hormone, low levels of calcium, phosphate or magnesium in the blood
- Depression, hallucinations, mood swings
- Cataract
- Deafness
- Abnormal liver test results
- Impaired balance, movement difficulty
- Ringing in the ears (tinnitus)

Uncommon side effects may affect up to 1 in 100 people:
- Confusion and decreased consciousness
- Bleeding within the skull
- Circulatory problems
- Loss of vision
- Loss of sex drive (libido)
- Passing large amount of urine with bone pain and weakness, which may be symptoms of a kidney disorder (Fanconi syndrome)
- Inflammation of the large intestine (colitis and caecitis), both of which may be manifested as abdominal pain, bloating, or diarrhoea
- Irritable bowel syndrome
- Renal tubular necrosis (a type of kidney impairment) which may be evident by production of much more or much less urine than usual
- Skin discoloration, sensitivity to sunlight
- Certain types of tumour of skin
- Types of allergic reaction that may be manifested as hives, rashes, swelling of eyes, mouth or face, difficulty of breathing, or itching (hypersensitivity/angioedema)
- Fractures of bones, arthritis, low blood sugar

Rare side effects may affect up to 1 in 1,000 people:
- Serious allergic reaction that may begin as rash in one area but spread with extensive loss of skin over the whole body (Stevens-Johnson syndrome and/or toxic epidermal necrolysis)
- Tumour lysis syndrome - metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the break-down products of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heartbeat, seizures, and sometimes death

Not known: frequency cannot be estimated from the available data:
- Sudden, or mild but worsening pain in the upper abdomen and/or back, which remains for a few days, possibly accompanied by nausea, vomiting, fever and a rapid pulse − these symptoms may be due to inflammation of the pancreas.
- Wheezing, shortness of breath or a dry cough, which may be symptoms caused by inflammation of the tissue in the lungs.

- Yellow pigmentation to the skin, mucus membrane or eyes (jaundice), pale coloured stools, dark coloured urine, skin itch, rash, pain or swelling of the abdomen –these may be symptoms of injury to the liver (hepatic disorder).

If you get a side effect not mentioned in this leaflet or the side effects get worse, talk to your physician. Side effects can be reported to the Ministry of Health by pressing on the link "Reporting side effects of drug treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il) using an online form. Please also contact the registration holder by email: drugsafety@neopharmgroup.com

5. How to store this medicine?

- Avoid Poisoning! This medicine and all other medicines must be stored in a safe place out of the sight and reach of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly being instructed to do so by a physician!
- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
- This medicine has been prescribed for the treatment of your ailment, in another patient, it may cause harm. **Do not give this medicine to your relatives, neighbors or acquaintances.**

Storage Conditions
Do not store above 25°C.

Even if kept in their original container and stored as recommended, medicines may be kept for a limited period only. Please note the expiry date of the medicine! In case of doubt, consult the pharmacist who dispensed the medicine to you.
Do not store different medications in the same package.
All unused Revlimid capsules should be returned to the pharmacist or physician.

6. Additional Information

In addition to the active ingredient, this medicine also contains:

Lactose:
Revlimid 2.5mg - Lactose Anhydrous 73.5mg
Revlimid 5mg - Lactose Anhydrous 147mg
Revlimid 7.5mg - Lactose Anhydrous 144.5mg
Revlimid 10mg - Lactose Anhydrous 294mg
Revlimid 15mg - Lactose Anhydrous 289mg
Revlimid 20mg - Lactose Anhydrous 244.5mg
Revlimid 25mg - Lactose Anhydrous 200mg

Inactive ingredients:
Microcrystalline Cellulose, Lactose Anhydrous, Croscarmellose Sodium, Magnesium Stearate, Gelatine, Titanium Dioxide, Indigo Carmine (Revlimid 10mg, 15mg and 20mg), Yellow Iron Oxide (Revlimid 10mg and 20mg), Black Ink.

Registration holder:
Neopharm Scientific Ltd.,
Hashiloach st. 6, P.O.Box 7063, Petach-Tiqva 4917001.

Registration No:
Revlimid® 2.5mg: 151-24-33894
Revlimid® 5mg: 140-45-31660
Revlimid® 7.5mg: 151-25-33896
Revlimid® 10mg: 140-46-31661
Revlimid® 15mg: 140-47-31662
Revlimid® 20mg: 151-26-33965
Revlimid® 25mg: 140-48-31663

Manufacturers name and address:
Celgene International Sarl, Boudry, Switzerland for Celgene Europe Limited, Stockley Park, Uxbridge, UK or for Celgene Corporation, Summit NJ, USA.

The format of this leaflet has been defined by the Ministry of Health; its content has been checked and approved on August 2015.

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