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

The medicine is dispensed with a doctor's prescription only

SIMVACOR 20, 40, 80

Film-coated Tablets

Composition:

Each **Simvacor 20** film-coated tablet contains: simvastatin 20 mg
Each **Simvacor 40** film-coated tablet contains: simvastatin 40 mg
Each **Simvacor 80** film-coated tablet contains: simvastatin 80 mg

For the list of inactive and allergenic ingredients in the preparation, please see section 6 "Further information". Also see in section 2 "Important information about some of the ingredients of the medicine".

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

This leaflet contains concise information about **Simvacor.** If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

The medicine is not intended for children and adolescents under 20 years of age.

1. WHAT IS THE MEDICINE INTENDED FOR?

Simvacor lowers levels of LDL and other fatty components in the blood and raises HDL levels – in patients with hyperlipidemia (high blood fat level). In patients with coronary heart disease and hypercholesterolemia, **Simvacor** reduces the overall mortality risk by lowering the mortality from heart diseases; reduces the risk of non-fatal myocardial infarction; reduces the risk of myocardial revascularization procedures (e.g., bypass surgery or balloon angioplasty), and reduces the risk of stroke and transient ischemic attack (TIA).

Therapeutic group: Statins, HMG-CoA reductase enzyme inhibitors.

How Simvacor works:

Simvacor contains the active ingredient simvastatin. **Simvacor** is used to lower blood levels of total cholesterol, levels of the "bad" cholesterol (LDL cholesterol), and levels of fatty compounds called triglycerides. In addition, **Simvacor** raises the levels of the "good" cholesterol (HDL cholesterol).

Cholesterol is one of the fatty components found in the blood. The total cholesterol is made up mainly of LDL and HDL cholesterol. LDL cholesterol is often called the "bad" cholesterol, because it may build up on the walls of the arteries and form plaque. With time, plaque buildup may cause narrowing of the arteries. This narrowing may slow or block blood flow to vital organs such as the heart or brain. Blocking of the blood flow may lead to a heart attack or stroke. HDL cholesterol is often called the "good" cholesterol, because it helps prevent plaque buildup in the arteries and prevents heart disease. Triglycerides are another type of fat found in the blood that may increase the risk of heart disease.

You need to follow a low-cholesterol diet while taking this medicine.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to simvastatin, or to any of the additional ingredients contained in the medicine (see section 6 “Further Information” and in section 2 “Important information about some of the ingredients of the medicine”).
- You currently have liver problems.
- You are pregnant or breastfeeding.
- You are taking medicines that contain one or more of the following active ingredients:
  - itraconazole, ketoconazole, posaconazole or voriconazole (used to treat fungal infections).
  - erythromycin, clarithromycin or telithromycin (used to treat infections).
  - HIV protease inhibitors, e.g., indinavir, nelfinavir, ritonavir and saquinavir (HIV protease inhibitors used to treat HIV infections).
  - boceprevir or telaprevir (used to treat hepatitis C infection).
  - nefazodone (used to treat depression).
  - cobicistat.
  - gemfibrozil (used to lower cholesterol).
  - ciclosporin (used in patients after a transplantation).
  - danazol (an artificial hormone used to treat endometriosis, a condition in which parts of the endometrium tissue grow outside of the uterus).
- If you are taking lomitapide (a medicine used to treat a severe and rare condition of hereditary cholesterol), do not take more than 40 mg **Simvacor**.

Ask your doctor if you are uncertain if your medicine appears above.

Special warnings regarding use of the medicine

Before treatment with Simvacor, tell the doctor:

- About all your medical problems, including allergies.
- If you consume large amounts of alcohol.
- If you suffered in the past from liver disease; treatment with **Simvacor** may not be appropriate for you.
- If you are due to undergo surgery. It may be necessary to stop taking **Simvacor** for a short period of time.
- If you are suffering from severe respiratory failure.
- If you are of Asian origin; you may need a different dosage.
- If you are taking, or have taken in the last 7 days, a medicine called fusidic acid (a medicine for treating bacterial infection), orally or by injection. The combination of fusidic acid with **Simvacor** may lead to serious muscle problems (rhabdomyolysis).
- If you have or have had myasthenia gravis (a disease with general muscle weakness including in some cases muscles used when breathing), or ocular myasthenia (a disease causing eye muscle weakness) as statins may sometimes aggravate the condition or lead to the occurrence of myasthenia (see section 4 "Side Effects").

Contact your doctor immediately if you experience unexplained muscle pain, tenderness or muscle weakness. This is because in rare cases,

muscle problems may be severe, including muscle breakdown resulting in kidney damage, and, in very rare cases, to death.

The risk of muscle breakdown is higher in patients taking high doses of **Simvacor**, particularly an 80 mg dosage. In addition, the risk of muscle breakdown is higher in certain patients. Talk to your doctor if any of the following apply to you:

- You consume large amounts of alcohol.
- You have kidney problems.
- You have thyroid problems.
- You are 65 years old or older.
- You are female.
- You had muscle problems in the past during treatment with cholesterol-lowering medicines called statins or fibrates.
- You or a family member has a hereditary muscle disease.

Furthermore, tell the doctor or pharmacist if you have constant muscle weakness. Additional tests and medicines may be required to diagnose and treat this matter.

Tests and follow-up

If you have any symptoms of liver problems, the doctor will refer you to a blood test before you start using the medicine and during the treatment period with the medicine. This is to test your liver function. After starting treatment with **Simvacor**, you may be referred by the doctor for a liver function blood test.
Your doctor will monitor you closely, if you have diabetes or you are at risk of developing diabetes. You are at risk of developing diabetes if you have high levels of sugars and fats in your blood, excess weight and high blood pressure.

Drug interactions

If you are taking, or have recently taken, other medicines including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.
Taking **Simvacor** with one of the medicines listed below can increase the risk of muscle problems (some are mentioned in section 2 “Do not use the medicine if”):

- **If you need to take fusidic acid orally to treat a bacterial infection, you will need to temporarily stop taking Simvacor. The doctor will instruct you when you can safely resume taking Simvacor. Taking Simvacor concomitantly with fusidic acid may rarely cause muscle weakness, muscle tenderness or muscle pain (rhabdomyolysis). For more information about rhabdomyolysis see section 4 “Side effects”.**
- Ciclosporin (often given to patients after transplants).
- Danazol (an artificial hormone used to treat endometriosis, a condition in which parts of the endometrial tissue grow outside the uterus).
- Medicines with active ingredients such as itraconazole, ketoconazole, fluconazole, posaconazole or voriconazole (used to treat fungal infections).
- Fibrates with active ingredients such as gemfibrozil or bezafibrate (used to lower cholesterol).
- Erythromycin, clarithromycin or telithromycin (used to treat bacterial infections).

- HIV protease inhibitors such as indinavir, nelfinavir, ritonavir and saquinavir (used to treat HIV).
- Antiviral medicines for the treatment of hepatitis C such as boceprevir, telaprevir, elbasvir or grazoprevir (used to treat hepatitis C viral infection).
- Nefazodone (used to treat depression).
- Medicines containing the active ingredient cobicistat.
- Amiodarone (used to treat irregular heartbeat).
- Verapamil, diltiazem or amlodipine (used to treat high blood pressure, chest pain attributed to heart disease or other heart conditions).
- Lomitapide (a medicine used to treat a severe and rare condition of hereditary cholesterol).
- Daptomycin (a medicine used to treat complicated infections of the skin and skin tissues and bacteremia). It is possible that the side effects affecting the muscles will be stronger when taking this medicine during treatment with **Simvacor**. The doctor may decide that you should temporarily stop taking **Simvacor**.
- Colchicine (used to treat gout).
- Ticagrelor (anticoagulant medicine).

In addition to the medicines listed above, tell the doctor or pharmacist if you are taking, or have recently taken, other medicines, including non-prescription medicines. In particular, tell the doctor if you are taking one of the following medicines:
- Medicines with an active ingredient to prevent blood clotting, such as warfarin, phenprocoumon or acenocoumarol (anticoagulants).
- Fenofibrate (also used to lower cholesterol).
- Niacin (also used to lower cholesterol).
- Rifampicin (used to treat tuberculosis).

Tell all doctors prescribing a new medicine for you that you are taking **Simvacor**.

Use of the medicine and food

Grapefruit juice contains one or more ingredients that affect the way the body breaks down certain medicines, including **Simvacor**. **Avoid consuming grapefruit juice.**

Pregnancy and breastfeeding

Do not use Simvacor if you are pregnant, trying to become pregnant or think you are pregnant. If you become pregnant during the course of treatment with **Simvacor**, stop taking it and contact your doctor immediately.
Do not take **Simvacor** if you are breastfeeding, since it is not known whether the medicine passes into breast milk.
Consult the doctor or pharmacist before taking any medicine.

Driving and operating machinery

Simvacor is not expected to affect your ability to drive or operate machinery. However, keep in mind that some people may feel dizzy after taking **Simvacor**.

Important information about some of the ingredients of the medicine

Simvacor contains a sugar called lactose. If you have been told by the doctor that you are suffering from an intolerance to certain sugars, consult the doctor before using the medicine (see section 6 “Further information”).
Simvacor contains less than 1 mmol (23 mg) sodium per tablet, namely, the tablet is essentially “sodium-free”.

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. The dosage and treatment regimen will be determined by the doctor only.
The usual dosage is generally:
The recommended starting dosage is 10 or 20 mg once a day, in the evening, with or without food.
Swallow the medicine with a bit of water.
Because of the increased risk of muscle problems, the 80 mg dosage is only recommended for patients taking the 80 mg dosage chronically (e.g., 12 months or more) without muscle damage and who do not need to take certain other medicines together with **Simvacor**, which may increase their risk of developing muscle damage.
Your doctor may prescribe lower dosages for you, especially if you are taking certain medicines from those listed above, or if you have certain kidney conditions.
If you are also taking bile acid sequestrants (medicines for lowering cholesterol) such as cholestyramine, you should take **Simvacor** at least two hours before or four hours after taking the bile acid sequestrants.

Do not exceed the recommended dose.

Tests and follow-up:

- During treatment with **Simvacor**, liver function tests should be performed.
- If you have diabetes or are at risk of developing diabetes, your doctor will monitor you closely while you are being treated with this medicine. You may be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.
- Refer to your doctor regularly to check your cholesterol level and to check for side effects. Your doctor should perform blood tests to check your liver before you start taking **Simvacor** and to check if you have any symptoms of liver problems while taking **Simvacor**.

Crushing/halving/chewing:

Simvacor 40 – **Do not halve the tablet.** There is no information regarding crushing or chewing the tablet.
Simvacor 20, **Simvacor 80** – If necessary, the tablet can be halved for immediate use. There is no information regarding crushing or chewing the tablet.

If you accidently took a higher dose or if a child has accidentally swallowed the medicine, immediately proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take Simvacor

Do not take a double dose. Take the next dose at the usual time and consult the doctor.
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 your doctor.

If you stop taking Simvacor

Continue taking **Simvacor** unless your doctor has told you to stop. If you stop taking **Simvacor**, your cholesterol may rise again.

Do not take medicines in the dark! Check the label and dose <u>each time</u> 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 **Simvacor** 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.

Rare serious side effects – effects that occur in 1-10 users in 10,000 users:

<u>Stop using the medicine and refer immediately to a doctor or proceed to a hospital emergency room if any of the following effects occur:</u>

- Muscle pains, tenderness, weakness, cramps or muscle rupture (very rare). On rare occasions, these muscle problems may be serious, including muscle breakdown, which results in kidney damage and, in very rare cases, even to death.
- Hypersensitivity reactions (allergy), including: swelling of the face, tongue or throat which may cause breathing difficulties (angioedema).
- Severe muscle pain, usually in the shoulders or hips (polymyalgia rheumatica).
- Rash accompanied by weakness of limbs and neck muscles.
- Rash that may occur in the skin and mouth ulcers (lichenoid drug eruptions) (very rare).
- Joint pains or inflammation.
- Inflammation of the blood vessels (vasculitis).
- Unusual bruising, skin rash and swelling (dermatomyositis), hives, skin sensitivity to sunlight, fever, flushing.
- Shortness of breath (dyspnea) and generally feeling unwell.
- Lupus-like condition (including rash, joint problems, and effects on blood cells).
- Inflammation of the liver, accompanied by the following symptoms: yellowing of the skin and eyes, itching, dark-colored urine or pale-colored stools, feeling tired or weak, loss of appetite, fatal and non-fatal liver failure (very rare).

- Inflammation of the pancreas (pancreatitis), usually accompanied by severe abdominal pains.

Very rare serious side effects – effects that occur in less than one user in 10,000:

- Severe allergic reaction that causes breathing difficulties or dizziness (anaphylaxis).
- Gynecomastia (breast enlargement in men).

Rare side effects – effect that occur in 1-10 in 10,000 users:

- Low count of red blood cells (anemia).
- Numbness or weakness in the arms and feet.
- Headaches, dizziness, tingling sensation.
- Blurred vision, impaired vision.
- Digestive system disturbances (abdominal pain, constipation, flatulence, indigestion, diarrhea, nausea, vomiting).
- Rash, itching, hair loss.
- Weakness.
- Sleeping problems (very rare).
- Poor memory (very rare), memory loss, confusion.

Side effects whose frequency is unknown (effects whose frequency has not yet been determined):

- Erection problems.
- Depression.
- Tendon problems, sometimes with complications to the extent of rupturing of the tendon.
- Permanent muscle weakness.
- Myasthenia gravis (a disease causing general muscle weakness including in some cases muscles used when breathing).
- Ocular myasthenia (a disease causing eye muscle weakness).

Talk to your doctor if you experience weakness in your arms or legs that worsens after periods of activity, double vision or drooping of your eyelids, difficulty swallowing, or shortness of breath.

Possible side effects when using statins:

- Sleep disturbances including nightmares.
- Difficulties in sexual functioning.
- Breathing problems including persistent cough and/or shortness of breath or fever.
- Diabetes. This is more likely if you have high levels of sugars and fats in the blood, excess weight and high blood pressure. Your doctor will monitor you during the course of treatment with this medicine.

Laboratory value results:

Elevations in some laboratory blood tests of liver function and the muscle enzyme (creatine kinase) have been observed.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the 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/
Additionally, you can report to "Unipharm Ltd.".

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine should be kept in a safe place out of the reach and sight of children and/or infants 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) that appears on the package. The expiry date refers to the last day of that month.
- Storage conditions: Store below 25°C and in a place protected from light.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Lactose, Pregelatinized Starch, Microcrystalline Cellulose, Carmellose Sodium LS, Ascorbic Acid, Citric Acid, Magnesium Stearate, Butylated Hydroxyanisole, Opadry Coatings.
Each **Simvacor 20** film-coated tablet contains 138 mg lactose.
Each **Simvacor 40** film-coated tablet contains 276 mg lactose.
Each **Simvacor 80** film-coated tablet contains 552 mg lactose.

What the medicine looks like and the contents of the package:
Simvacor is packaged in trays (blisters) that are inserted into a carton package. Each package has 5, 7, 10, 15, 20, 25, 30 or 100 tablets.
Not all package sizes may be marketed.
Simvacor 20: round, biconvex, orange film-coated tablets, with a break line on one side.
Simvacor 40: beige, oblong, capsule-shaped film-coated tablets.
Simvacor 80: oval, elongated, orange film-coated tablets, with a break line on one side.
Registration holder and address: Unipharm Ltd., P.O. Box 16545, Tel Aviv, 6116401.
Manufacturer and address: Unipharm Ltd., "Mevo Carmel" Industrial Park.

Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:
Simvacor 20: 121 26 30128 01
Simvacor 40: 121 95 30222 01
Simvacor 80: 121 96 30223 01

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