PACKAGE LEAFLET: Information for the patient

SIPROLIP

Film-coated tablets – 10 mg, 20 mg, 40 mg

(Simvastatin)

Read this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT SIPROLIP IS AND WHAT IT IS USED FOR?

Siprolip is a drug used to reduce high blood lipids (cholesterol) from the class of cholesterol synthesis enzyme inhibitor. The active substance of Siprolip, simvastatin, reduces cholesterol production in the liver. For simvastatin has been shown that in patients at high risk for coronary heart disease, it reduces the risk of suffering a heart attack or stroke.

Siprolip is used:

in addition of a diet in:

- patients with hypercholesterolemia (primary or mixed hyperlipidemia) when diet and other measures such as physical training or weight loss alone are not sufficient;
- patients with homozygous familial hypercholesterolemia, along with other treatments or if such are not suitable;

for the prevention of cardiovascular diseases:

- in patients whose cholesterol levels in the blood are normal or elevated, with established atherosclerotic cardiovascular disease or diabetes, along with other preventive measures.

2. BEFORE YOU TAKE SIPROLIP

Do not take Siprolip:

- if you are hypersensitive (allergic) to simvastatin or to any of the excipients of Siprolip,
- if you have liver problems or an unexplained continuous high level of certain liver enzymes (serum transaminases),
- if you are pregnant or breast-feeding,
- if you are treated with certain substances which strongly inhibit the normal excretion of simvastatin from the body, such as: itraconazole, ketoconazole, miconazole, posaconazole, voriconazole, HIV protease inhibitors (such as: indinavir, nelfinavir, ritonavir, saquinavir etc.), erythromycin, clarithromycin, telithromycin, drugs used to treat hepatitis C virus infection as: boceprevir, telaprevir etc., nefazodone, cobicistat, gemfibrozil, ciclosporin and danazol (see section 2 “Taking Siprolip with other medicines"),
- if you are taking or have taken, in the last 7 days, a medicine called fusidic acid (antibacterial), orally or by injection; the combination of fusidic acid and Siprolip can lead to serious muscle problems (rhabdomyolysis).

Do not take more than 40 mg Siprolip daily if you are taking concomitantly lomitapide (a drug used to treat a serious and rare genetic cholesterol condition).

Take special care with Siprolip

Tell your doctor about all existing and previous health problems.

During treatment with Siprolip your doctor will monitor you closely if you have a blood sugar disease (diabetes) or the risk that you will develop a blood sugar disease. The risk of developing a blood sugar disease is when you have elevated blood sugar and blood fat levels, are overweight and have high blood pressure.

Myasthenia or ocular myasthenia

If you have or have had myasthenia (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).

Musculoskeletal disorders

Like other statins, simvastatin, the active ingredient of Siprolip, occasionally produces a disease of the skeletal muscles (myopathy) that causes muscle pain, tenderness or weakness, associated with a marked increase in certain laboratory tests (creatine kinase [CK]). Sometimes the myopathy is manifested with rhabdomyolysis (breakdown of skeletal muscle cells) with or without acute renal failure, very rarely with fatalities.

The risk of myopathy is increased with increasing dose of simvastatin.

Heavy physical exertion can lead sometimes to increased creatine kinase (CK) laboratory values. Therefore, this laboratory value can not be measured following strenuous exercise or in the presence of any plausible alternative causing an increase, as this makes difficult the assessment of values. If the values of creatine kinase are significantly increased (more than five times the upper limit of normal), the measurement should be repeated after 5-7 days to confirm the results.

If during treatment with Siprolip you notice unexplained muscle pain, tenderness or weakness of the muscles, please contact your doctor immediately.

Your doctor will check your laboratory results in order to clarify the possible emergence of a muscle disease (myopathy). The treatment with Siprolip should be discontinued in pronounced increase of your laboratory values (creatine kinase more than five times the upper limit of normal), or if the doctor has determined or suspected a myopathy. If daily impairments consist of severe muscle pain, consideration should be given to stop the treatment, even if the creatine kinase is less than five times the upper limit of normal.

Treatment with Siprolip should be temporarily stopped a few days prior to surgery and when any serious medical disease is present.

Treatment with Siprolip should be done only after careful benefit-risk assessment and under close medical supervision if:

- you are already more than 65 years;
- you have kidney dysfunction;
- you have an untreated hypothyroidism;
- you have hereditary myopathy in your own or family medical history;
- you already had a myopathy during treatment with statins or fibrates;
- there is alcohol abuse;
- you are female;

- you are Asian (because a different dose may be applicable to you).

Liver dysfunction
In clinical studies, in some adult patients who received simvastatin, lasting increases (to more than three times the upper limit of normal) in certain liver function tests (serum transaminases) were observed. After interruption or termination of therapy, the values usually fell slowly back to baseline levels.

The doctor should check your liver function (determination of transaminases) at the beginnig of treatment and thereafter as required (see Section 4 “Possible side effects"). Additional controls should be carried out at a daily dose of 80 mg of simvastatin (before increasing the dose, three months after increasing the dose to 80 mg and periodically thereafter [e.g. semi-annually] in the first year).

In case of significant increases of your liver enzymes, your doctor should repeat the test immediately and check these values regularly. If the increases progress, particularly if they rise to three times the upper limit of normal and persist, the drug should be discontinued.

Special care is needed when you have suffered previously of liver disease or you take a significant quantity of alcohol.

As with other drugs used to reduce high blood lipids, during treatment with simvastatin, moderate elevations of serum transaminases were observed (less than three times the upper limit of normal). These deviations occurred soon after initiation of treatment with simvastatin, were often transient, not accompanied by any symptoms and treatment discontinuation was not necessary.

Breathing problems
Talk to your doctor or pharmacist before treatment with Siprolip if you suffer from breathing problems.

Children
Safety and efficacy were investigated at 10 - to 17-year-old boys and also in girls, whose first menstruation (menstrual period) lied back at least 1 year (see Section 3 “How to take Siprolip?”).

Simvastatin has not been studied in children under 10 years. More information on this topic can be obtained from your doctor.

Elderly people

For elderly patients, no dose adjustment is required.

Treatment with Siprolip should be used with caution and under medical supervision if you are already over 65 years old.

Taking Siprolip with other medicines

Please tell your doctor or pharmacist if you take / use or have recently taken / used other medicines even if they were medicines taken without a prescription. In case of new prescriptions inform the doctor that you are already taking Siprolip.

Co-administration of the following drugs or groups of preparations with Siprolip can affect the effect of Siprolip and / or of the other drug.

To avoid the side effects, particularly on the muscles or the liver, and to achieve the desired effect, in each case, the dose of Siprolip and / or of the other medicines may need to be adjusted. The discontinuation of treatment or switching to a different treatment may be needed. You should tell your doctor, especially if you are taking any or more of the medicines listed below.

Caution is needed during concomitant treatment of the below mentioned drugs or medication groups with Siprolip:

- <u>Medicines for the treatment of lipid metabolic disorders that even when administered alone can cause disorders of skeletal muscles</u>:

  Gemfibrozil, other fibrates, niacin (nicotinic acid; ≥ 1 g/day) and lomitapide.

  Gemfibrozil should not be taken concomitantly with Siprolip because it increases simvastatin blood levels.

  Do not take more than 40 mg Siprolip daily if you are treated with lomitapide (used to treat a serious and rare genetic cholesterol condition).

  If any of the fibrates (except fenofibrate), is taken together with Siprolip, the dose of simvastatin should not exceed 10 mg daily (see Section 3 “How to take Siprolip?”).

  There is no evidence for fenofibrate that the risk of such a disease by co-administration is higher than the combined risks of each drug.

  Nevertheless, caution is required because each of these drugs alone can cause myopathy.

  For other fibrates there are no adequate data available.

- Medicines that increase the risk for muscular damage by interfering with the normal excretion of simvastatin from the body:
  Siprolip must not be taken with the following medicines: itraconazole, ketoconazole, miconazole, posaconazole or voriconazole (medicines against pathogenic fungi), erythromycin, clarithromycin, and telithromycin (antibiotics), HIV protease inhibitors such as: indinavir, nelfinavir, ritonavir, saquinavir etc. (used to treat AIDS), drugs used to treat hepatitis C virus infection such as: boceprevir, telaprevir etc., cobicistat (used to treat AIDS), ciclosporin (immunosuppressant drug), danazol (drug used to treat endometriosis) and nefazodone (an antidepressant). If treatment with the above drugs is necessary, treatment with Siprolip should be discontinued.
  The dose of 20 mg Siprolip daily should not be exceeded in patients treated concomitantly with products containing elbasvir or grazoprevir.
  The combination of fusidic acid (orally or by injection) with Siprolip is contraindicated because it can lead to serious muscle problems (rhabdomyolysis).

- Verapamil, amiodarone, amlodipine, ranolazine and also diltiazem (medicines used for the treatment of various cardiovascular diseases):
  The risk of myopathy is increased when high doses of simvastatin are co-administered with these drugs. Therefore, in patients taking amiodarone, verapamil, amlodipine or ranolazine the dose of 20 mg simvastatin daily should not be exceeded (see Section 3 “How to take Siprolip?“), provided the benefits do not outweigh the increased risk of myopathy.
  Patients being treated with diltiazem and 80 mg simvastatin per day, have a slightly increased risk of myopathy. Therefore, in patients taking diltiazem, a dose of 20 mg simvastatin per day should not be exceeded.
  For the risk of muscle damage see also above under "Take special care with Siprolip, Musculoskeletal disorders".

- Medicines to prevent blood clotting (oral anticoagulants) and antiplatelets:
  If you are treated simultaneously with medicines of coumarin derivatives (such as warfarin, phenprocoumon, acenocoumarol) to reduce blood clotting, a slight increase in anticoagulant effect may occur. It should therefore be determined at the beginning and during the treatment with Siprolip, and at dose change or discontinuation of Siprolip your prothrombin time, if you are taking such anticoagulant drugs. Thereafter, the prothrombin time can be checked in the usual intervals.

Should your health conditions make it necessary to take such drugs, your doctor will decide whether the benefits of concomitant therapy outweigh the risks involved or whether a different treatment is possible or whether the treatment with Siprolip can be interrupted. If concomitant treatment with Siprolip is displayed, specific dosage recommendations should be noted (see Section 3 “How to take Siprolip?”). Only your doctor can make in such a case, the decision about your treatment.

In patients that are taking ticagrelor (antiplatelet drug) should not be exceeded the dose of 40 mg Siprolip daily.

Caution should be taken also in the combination of Siprolip with some other drugs such as: fluconazole, rifampicin and colchicine.

In case of unexplained muscle pain, muscle tenderness or muscle weakness, please contact immediately your doctor.

Taking Siprolip with food and drink

Tell your doctor if you consume large amounts of alcohol.
Grapefruit juice contains one or more components that alter the metabolism of some drugs, including Siprolip and thus increase the risk of diseases of the muscles. During treatment with Siprolip you should avoid drinking grapefruit juice.

Pregnancy and breastfeeding

Ask your doctor or pharmacist for advice before taking / using any medicine.
Siprolip should not be used during pregnancy.
Siprolip should not be taken by women who are pregnant, planning to become pregnant or think that may be pregnant. If a woman treated with Siprolip becomes pregnant, she must stop the treatment and contact her doctor immediately.
Since it is not known whether simvastatin, the active ingredient of Siprolip, is excreted in breast milk, Siprolip should not be used during breastfeeding.

Driving and using machines

Siprolip has no or negligible influence on the ability to drive and use machines.
When driving vehicles or operating machines, you should consider, however, that after taking simvastatin, dizziness was rarely reported.

Important information about some of the excipients of Siprolip

This medicinal product contains lactose.

Please take Siprolip only after consulting your doctor if you know that you have an intolerance to some sugars.

The film-coating of Siprolip tablets, Opadry II pink, contains AZO colouring agents, respectively Ponceau 4R (E 124) and Sunset Yellow FCF (E 110) which may cause allergic reactions.

3. HOW TO TAKE SIPROLIP?

Take Siprolip exactly as your doctor has told you. Please check with your doctor or pharmacist if you are not sure.

Unless otherwise prescribed by your doctor, the usual dose is:

The dosage range of simvastatin is from 5 mg per day to 80 mg per day.

The usual recommended dose for children (10-17 years) in the beginning of treatment is 10 mg simvastatin daily as a single dose in the evening. The maximum recommended dose is 40 mg per day.

The dose of 80 mg is recommended for adult patients with severely elevated blood lipid levels and high risk for complications associated with heart disease.

If necessary, your doctor may adjust the dose based on the blood cholesterol levels at intervals of 4 weeks or more.

To facilitate an individual dosage, Siprolip film-coated tablets are available in strengths of 10 mg, 20 mg, 40 mg.

Special instructions:

To reduce blood lipid levels:

Patients with hypercholesterolemia (primary or mixed hyperlipidemia)

Before starting treatment with Siprolip, appropriate cholesterol-lowering diet should be started, which should be continued during treatment.

Unless otherwise prescribed by your doctor, the recommended starting dose is 10 mg to 20 mg simvastatin, as a single dose once daily in the evening.

If your blood fat levels need to be markedly reduced, a starting dose of 20 mg to 40 mg simvastatin daily should be prescribed.

Dose adjustments, if necessary, should be conducted as described above.

Patients with homozygous familial hypercholesterolemia
Unless otherwise prescribed by the doctor, the recommended starting dose is: 40 mg simvastatin per day, once a day as a single dose in the evening or 80 mg simvastatin daily administered divided into 3 doses per day, i.e. two times 20 mg during the day and 40 mg in the evening (the dose of 80 mg is recommended only for patients with severe hypercholesterolaemia and at high risk of cardiovascular complications, who didn't respond to lower doses). In these patients, where possible, Siprolip should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis).

For the prevention of cardiovascular diseases:
Unless otherwise prescribed by the doctor, for patients (with normal or increased cholesterol levels in the blood) at high risk for coronary heart disease, the recommended dose is 20 mg to 40 mg simvastatin once daily in the evening.
Treatment with this drug can be started simultaneously with diet and physical exercise.
Dose adjustments, if necessary, should be conducted as described above.

Combined treatment with other medicines:
If your doctor has prescribed Siprolip with cholestyramine (an anion exchanger) or another anion exchanger, take Siprolip at least 2 hours before or at least 4 hours after the anion exchanger.
If you are taking fibrates (except gemfibrozil which is contraindicated or fenofibrate) or lipid-lowering doses (≥ 1 g / day) of niacin (nicotinic acid), a dose of 10 mg simvastatin daily should not be exceeded.
If you take amiodarone, verapamil, diltiazem, amlodipine or ranolazine (drugs to treat various cardiovascular diseases), a dose of 20 mg simvastatin daily should not be exceeded.
The dose of 20 mg Siprolip daily should not be exceeded in patients that are treated concomitantly with products containing elbasvir or grazoprevir, while in patients that are taking lomitapide or ticagrelor should not be exceeded the dose of 40 mg Siprolip daily.
(See also Section 2 "Before you take Siprolip / Taking Siprolip with other medicines").

Use in elderly patients:
No dose adjustment is required.

Use in renal impairment

If you suffer from moderate renal impairment, usually no dose adjustment is required. If you have severe renal impairment, doses above 10 mg simvastatin daily should be carefully considered and, if necessary, should be carefully, prescribed by your doctor.

Method of administration

Please take the film-coated tablets with plenty of fluid (a glass of water) in the evening.
You can take Siprolip with or without food.
In certain cases, when administered orally at 80 mg, you can divide the dose into 3 doses per day; take twice 20 mg simvastatin during the day and 40 mg simvastatin in the evening.

Duration of treatment

Taking Siprolip is typically a long-term treatment. The duration of treatment is determined by your physician.
Please talk to your doctor or pharmacist if you have the impression that the effect of Siprolip is too strong or too weak.

If you take more Siprolip than you should

If you take more film-coated tablets than prescribed, please contact your doctor immediately.

If you forget to take Siprolip

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

If you stop taking Siprolip

Take Siprolip as long as prescribed by the doctor. If you stop the treatment, your cholesterol levels may rise again.
If you have any questions about taking this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines Siprolip can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below are defined as:

Very common	Affect more than 1 in 10 patients
Common	Affect 1 to 10 patients out of 100
Uncommon	Affect 1 to 10 patients out of 1,000
Rare	Affect 1 to 10 patients out of 10,000
Very rare	Affect less than 1 in 10,000 patients
Not known	Frequency can not be estimated from the available data

Blood and lymphatic system disorders:

Rare: anemia.

Psychiatric disorders:

Very rare: insomnia.

Not known: depression.

Immune system disorders

Very rare: a serious allergic reaction which causes difficulty in breathing or dizziness (anaphylaxis).

Nervous system disorders:

Rare: headache, paresthesia, dizziness, disease of the nerves (peripheral neuropathy).

Very rare: memory impairment.

Not known: Myasthenia gravis (a disease causing general muscle weakness including in some cases muscles used when breathing). Talk to your doctor if you experience weakness in your arms or legs that worsens after periods of activity, difficulty swallowing, or shortness of breath; sleep disorders, e.g. nightmares.

Gastrointestinal tract disorders:

Rare: constipation, abdominal pain, bloating, indigestion, diarrhea, nausea, vomiting, inflammation of the pancreas (pancreatitis).

Hepatobiliary disorders:
Rare: hepatitis / jaundice.
Very rare: fatal or non-fatal hepatic failure.

Metabolism and nutrition disorders:
Not known: diabetes. The risk of developing a blood sugar disease is greater if you have elevated blood sugar and blood fat, are overweight and have high blood pressure. Your doctor will monitor you during treatment with Siprolip.

Reproductive system and breast disorders:
Not known: sexual dysfunction.

Skin and subcutaneous tissue disorders:
Rare: skin rash, itching, hair loss.

Eye disorders
Not known: Ocular myasthenia (a disease causing eye muscle weakness).
Talk to your doctor if you experience double vision or drooping of your eyelids.

Respiratory, thoracic and mediastinal disorders:
In exceptional cases: breathing problems including persistent cough and / or shortness of breath or fever.

Musculoskeletal and connective tissue disorders:
Rare: muscle disorder (myopathy) (including myositis), disintegration of skeletal muscle cells (rhabdomyolysis) with or without acute renal failure, (see Section 2 „Before you take Siprolip / Take special care with Siprolip, Musculoskeletal disorders“), muscle pain, muscle cramps.
Not known: tendinopathy, sometimes complicated with rupture; immune-mediated necrotizing myopathy which is characterized by persistent muscle weakness and increased serum level of creatine kinase.

General disorders and administration site conditions:
Rare: fatigue (asthenia)
Rarely, signs that were obviously related with hypersensitivity (hypersensitivity syndrome) have occurred: vascular swelling (angioedema), lupus-like syndrome, rheumatic disease of

the muscles (polymyalgia rheumatica), autoimmune disease involving the skin and muscles (dermatomyositis), blood vessel inflammation (vasculitis), changes in blood count (thrombocytopenia, eosinophilia, and acceleration of erythrocyte sedimentation rate), arthritis and joint pain (arthralgia), itchy rash (urticaria), photosensitivity reaction, fever, flushing, shortness of breath (dyspnea), general malaise.

Investigations:
Rare: increases of various liver function tests (serum transaminase [ALT, AST, g-GT], alkaline phosphatase) (see Section 2 “Before you take Siprolip / Take special care with Siprolip, Liver dysfunction) and a muscle enzyme (CK levels in serum) (see “Take special care with Siprolip, Musculoskeletal disorders”).

Significant side effects or signs for which you should take care and measures to be taken, if you are affected.
If during treatment with Siprolip you notice unexplained muscle pain, tenderness or weakness, please contact your doctor immediately, because muscle disorders can be severe in rare cases (see Section 2 “Before you take Siprolip / Take special care with Siprolip, Musculoskeletal disorders”).
Please tell your doctor or pharmacist if any of the side effects gets serious, or if you notice any side effects not listed in this leaflet.

5. HOW TO STORE SIPROLIP
Keep out of the reach and sight of children.
Do not use this medicine after the expiry date, which is stated on the packaging.

6. OTHER INFORMATION
What Siprolip 10 mg, 20 mg, or 40 mg film-coated tablets contain
The **active substance** is simvastatin.
1 film-coated tablet contains 10 mg, 20 mg or 40 mg simvastatin.

The **excipients** are:
tablet core: lactose monohydrate, pregelatinized starch (maize), microcrystalline cellulose, talc, magnesium stearate, butylhydroxyanisole (E 320);
film-coating: Opadry II pink (polyvinyl alcohol, titanium dioxide, polyethylene glycol / macrogol, talc, Ponceau 4R lake [E 124], Sunset yellow FCF aluminum lake [E 110]).

Contents of the pack

Siprolip is available in packs of 30 film-coated tablets.

Marketing Authorisation Holder (MAH) and Manufacturer:

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