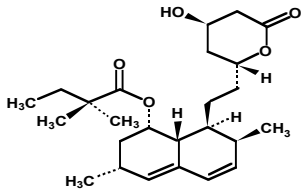
Simvoget™

(Simvastatin Tablets USP)

10mg, 20mg and 40mg Tablets
Lipid Regulating Agent

DESCRIPTION
SIMVOGET (Simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. Chemically simvastatin is (1S, 3R, 7S, 8s,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate. Its molecular formula is $C_{25}H_{38}O_5$ and structural formula is:



Simvastatin

QUALITATIVE & QUANTITATIVE COMPOSITION
SIMVOGET (Simvastatin) is available for oral administration as:

1. SIMVOGET (Simvastatin) Tablets 10mg
   Each film-coated tablet contains:
   Simvastatin USP…. 10mg

2. SIMVOGET (Simvastatin) Tablets 20mg
   Each film-coated tablet contains:
   Simvastatin USP….20mg

3. SIMVOGET (Simvastatin) Tablets 40mg
   Each film-coated tablet contains:
   Simvastatin USP….40mg

CLINICAL PHARMACOLOGY
Mechanism of Action
After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Pharmacokinetics
Simvastatin is absorbed from the gastrointestinal tract and is hydrolysed to its active β-hydroxyacid form. Other active metabolites have been detected and a number of inactive metabolites are also formed. Simvastatin undergoes extensive first pass metabolism in the liver, its primary site of action. Less than 5% of the oral dose has been reported to reach the circulation as active metabolites. Both simvastatin and its β-hydroxyacid metabolite are about 95% bound to plasma proteins. It is mainly excreted in the faeces via the bile as metabolites. About 10 to 15% is recovered in the urine, mainly in inactive forms. The half-life of active metabolite is 1.9 hours.

THERAPEUTIC INDICATIONS
Reductions in Risk of CHD Mortality and Cardiovascular Events
In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, SIMVOGET (Simvastatin) is indicated to:
- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

Patients with Hypercholesterolemia requiring Modifications of Lipid Profiles
SIMVOGET (Simvastatin) is indicated to:
- Reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb4).
- Treat patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- Treat patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)
SIMVOGET (Simvastatin) is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are present:
1. LDL cholesterol remains ≥ 190mg/dL; or
2. LDL cholesterol remains ≥ 160mg/dL and
- There is a positive family history of premature cardiovascular disease (CVD) or
- Two or more other CVD risk factors are present in the adolescent patient.

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130mg/dL.

DOSAGE AND ADMINISTRATION
The patient should be placed on a standard cholesterol-lowering diet before receiving SIMVOGET (Simvastatin) and should continue on this diet during treatment with SIMVOGET (Simvastatin). In patients with CHD or at high risk of CHD, SIMVOGET (Simvastatin) can be started simultaneously with diet. Lipid determination should be performed at intervals of no less than 4 weeks and the dosage should be individualized according to the goals of therapy and the patient's response. (For the treatment of adult dyslipidemia, see below NCEP Treatment Guidelines). The dosage range is 5-80mg/day. The recommended usual starting dose is 20 to 40mg once a day in the evening.

Reductions in Risk of CHD Mortality and Cardiovascular Events
For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter.

Patients with Homozygous Familial Hypercholesterolemia
The recommended dosage for patients with homozygous familial hypercholesterolemia is SIMVOGET (Simvastatin) 40mg/day in the evening or 80mg/day in 3 divided doses of 20mg, 20mg, and an evening dose of 40mg. SIMVOGET (Simvastatin) should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia
The recommended usual starting dose is 10mg once a day in the evening. The recommended dosing range is 10-40mg/day; the maximum recommended dose is 40mg/day. Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more. Doses greater than 40mg have not been studied in this population.

Concomitant Lipid-Lowering Therapy
SIMVOGET (Simvastatin) is effective alone or when used concomitantly with bile-acid sequestrants. If SIMVOGET (Simvastatin) is used in combination with gemfibrozil, the dose of SIMVOGET (Simvastatin) should not exceed 10mg/day.

Patients taking Cyclosporine or Danazol
In patients taking cyclosporine or danazol concomitantly with SIMVOGET (Simvastatin), therapy should begin with 5mg/day and should not exceed 10mg/day.

Patients taking Amiodarone or Verapamil
In patients taking amiodarone or verapamil concomitantly with SIMVOGET (Simvastatin), the dose should not exceed 20mg/day.

Renal Insufficient Patients
Because SIMVOGET (Simvastatin) does not undergo significant renal

excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when SIMVOGET (Simvastatin) is administered to patients with severe renal insufficiency; such patients should be started at 5mg/day and be closely monitored.

The following guidelines may be used to establish treatment goals:

NCEP Treatment Guidelines
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD* or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129:drug optional)**
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor #	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease
** Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
# Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

ADVERSE REACTIONS
Simvastatin is generally well-tolerated and side effects are rare. Minor side effects include, constipation, diarrhea, fatigue, gas, heartburn, and headache. Major side effects include abdominal pain or cramps, blurred vision, dizziness, easy bruising or bleeding, itching, muscle pain or cramps, rash, and yellowing of the skin or eyes.

CONTRAINDICATIONS
Simvastatin is contraindicated in patients
- With hypersensitivity to any component of this medication.
- With active liver disease or unexplained persistent elevations of serum transaminases.
- During pregnancy and lactation.

Simvastatin is also contraindicated in combination with potent inhibitor of cytochrome P450 3A4 including itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone.

PRECAUTIONS
Myopathy/Rhabdomyolysis
All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis.
If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 5 x ULN), treatment should be stopped.
If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Hepatic effect
It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80mg dose should receive an additional test prior to titration, 3 months after titration to the 80mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued.

General
The product should be used with caution in patients who consume substantial quantities of alcohol.

Pediatric Use
Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Drug Interactions
Diltiazem
The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Grapefruit juice
Intake of 240mL of grapefruit juice in the morning and simvastatin in the evening resulted in a 1.9-fold increase of simvastatin concentration. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

Oral anticoagulants
In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants.

STORAGE
Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
SIMVOGET (Simvastatin) tablets 10mg are available in blister pack of 10's.

SIMVOGET (Simvastatin) tablets 20mg are available in blister pack of 10's.

SIMVOGET (Simvastatin) tablets 40mg are available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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