

## PACKAGE INSERT TEMPLATE FOR SIMVASTATIN TABLET

### Brand or Product Name

[Product name] Tablet 10mg

[Product name] Tablet 20mg

[Product name] Tablet 40mg

[Product name] Tablet 80mg

### Name and Strength of Active Substance(s)

Simvastatin 10mg

Simvastatin 20mg

Simvastatin 40mg

Simvastatin 80mg

### Product Description

[Visual description of the appearance of the product (eg colour, markings etc)]

eg White, circular flat beveled edge tablets marked '10' on one side]

### Pharmacodynamics

Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. However, at therapeutic doses, the enzyme is not completely blocked, thereby allowing biologically necessary amounts of mevalonate to be available. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway of cholesterol, therapy with simvastatin would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is metabolized readily back to acetyl-CoA, that participates in many biosynthetic processes in the body. Although cholesterol is the precursor of all steroid hormones, simvastatin has not been shown to have any clinical effect on steroidogenesis. Simvastatin caused no increase in biliary lithogenicity and, therefore, would not be expected to increase the incidence of gallstones.

### Pharmacokinetics

Simvastatin is an inactive lactone which is readily hydrolyzed *in vivo* to the corresponding  $\beta$ -hydroxyacid, L-654,969, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the  $\beta$ -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors). Both are measured in plasma following administration of simvastatin.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post dose.

Simvastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and 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  $\beta$ -hydroxyacid metabolite are about 95% bound to plasma proteins. Simvastatin 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 the active  $\beta$ -hydroxyacid metabolite is 1.9 hours.

### Indication

*Reductions in risk of coronary heart disease (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, 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.

### *Hyperlipidemia*

Simvastatin is indicated as an adjunct to diet to reduce elevated total plasma cholesterol (total-C), low-density lipoprotein (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia, heterozygous familial hypercholesterolemia or combined (mixed) hyperlipidemia when response to diet and other nonpharmacological measures is inadequate. Simvastatin therefore, lowers the LDL-C/HDL-C and the total-C/HDL-C ratios.

### *Pediatric patients with heterozygous familial hypercholesterolemia*

Simvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, TG, 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 (HeFH).

### **Recommended Dosage**

Prior to initiating therapy with simvastatin, secondary causes of hypercholesterolemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

The dosage range for simvastatin is 5-80 mg/day, given as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose of simvastatin is only recommended in patients at high risk for cardiovascular complications who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. The recommended usual starting dose is 20-40 mg once a day in the evening.

### *Patients at high risk of coronary heart disease (CHD) or with existing CHD*

The usual starting dose of simvastatin is 40 mg/day given as a single dose in the evening in patients at high risk of CHD (with or without hyperlipidemia), ie., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD. Drug therapy can be initiated simultaneously with a standard cholesterol-lowering diet and exercise.

### *Patients with hyperlipidemia (who are not in the risk categories above)*

The patient should be placed on a standard cholesterol-lowering diet before receiving simvastatin and should continue on this diet during treatment with simvastatin. The usual starting dose is 20 mg/day given as a single dose a day in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40mg/day given as single dose in the evening. Patients with mild to moderate hypercholesterolemia can be treated with a starting dose of 10mg of simvastatin. Adjustments of dosage, if required, should be made as specified above.

### *Homozygous familial hypercholesterolemia*

The recommended dosage for patients with homozygous familial hypercholesterolemia is simvastatin 40 mg/day in the evening. The 80-mg dose is only recommended when the benefits are expected to outweigh the potential risks. 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.

### *Concomitant therapy*

Simvastatin is effective alone or in combination with bile acid sequestrants. In patients taking simvastatin concomitantly with fibrates (other than gemfibrozil or fenofibrate), the dose of simvastatin should not exceed 10 mg/day. In patients taking amiodarone, verapamil or diltiazem concomitantly with simvastatin,

the dose of simvastatin should not exceed 20mg/day. In patients taking amlodipine or lipid-lowering dose of niacin ( $\geq 1$  g/day) concomitantly with simvastatin, the dose of simvastatin should not exceed 40 mg/day.

#### *Dosage in renal insufficiency*

Because simvastatin does not undergo significant renal excretion, modification of dosage should not be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance  $< 30$  mL/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

#### *Dosage in pediatric patients (10-17 years of age) with heterozygous familial hypercholesterolemia*

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy

### **Mode of Administration**

Oral

### **Contraindications**

Hypersensitivity to any component of this preparation.

Active liver disease or unexplained persistent elevations of serum transaminases.

Pregnancy and nursing

Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)

Concomitant administration of gemfibrozil, cyclosporine, or danazol

### **Warnings and Precautions**

#### *Myopathy/rhabdomyolysis*

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Predisposing factors for myopathy include advanced age ( $\geq 65$  years), female gender, uncontrolled hypothyroidism, and renal impairment.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related.

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. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and a CK level  $> 10$  times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 80 mg dose. There is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer 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.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following:

#### *Contraindicated Drugs*

Potent inhibitors of CYP3A4: e.g.: itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or nefazodone. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment.

Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with simvastatin is contraindicated.

#### Other drugs

- **Fusidic acid:** In patients where the use of systemic fusidic acid is considered essential, simvastatin should be discontinued throughout the duration of fusidic acid treatment. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of simvastatin and fusidic acid should only be considered on a case-by-case basis under close medical supervision.
- **Other fibrates:** The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil or fenofibrate. When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small short-term clinical studies with careful monitoring.
- **Amiodarone:** The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.
- **Calcium channel blockers**
  - **Verapamil or diltiazem:** The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem.
  - **Amlodipine:** The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine.
- **Moderate inhibitors of CYP3A4:** When coadministering simvastatin with a moderate inhibitor of CYP3A4, a dose adjustment of simvastatin may be necessary.
- **Niacin ( $\geq 1$  g/day):** The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with niacin (nicotinic acid)  $\geq 1$  g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses ( $\geq 1$  g/day) of niacin.

#### *Hepatic effects*

Persistent increases (to more than 3X ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Some of these patients had abnormal liver function tests (LFTs) prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

It is recommended that LFTs be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g., semiannually) 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 3X ULN and are persistent, the drug should be discontinued. past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

#### *Ophthalmic evaluations*

In the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging. Current long-term data from clinical studies do not indicate an adverse effect of simvastatin on the human lens.

#### *Pediatric use*

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least one year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. Doses greater than 40 mg have not been studied in this population. In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy. Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

#### *Elderly*

For patients over the age of 65 years who received simvastatin in controlled clinical studies, efficacy, as assessed by reduction in total-C and LDL-C, appeared similar to that seen in the population as a whole, and there was no apparent increase in the overall frequency of clinical or laboratory adverse findings. However, in a clinical trial of patients treated with simvastatin 80 mg/day, patients  $\geq 65$  years of age had an increased risk of myopathy compared to patients  $< 65$  years of age.

#### *Effects on Ability to Drive and Use Machines*

Simvastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

### **Interactions with Other Medicaments**

#### *Contraindicated drugs*

Concomitant use of the following drugs with simvastatin is contraindicated:

#### Potent Inhibitors of CYP3A4:

Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of simvastatin.

Gemfibrozil, Cyclosporine or Danazol: See CONTRAINDICATIONS

*[Specific package insert requirement for statins]*

Concurrent use of fibrates may cause severe myositis and myoglobinuria.

#### *Other drug interactions*

**Other Fibrates:** The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil or fenofibrate. When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small short-term clinical studies with careful monitoring.

**Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy.

**Amiodarone:** In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.

#### **Calcium channel blockers:**

- **Verapamil or diltiazem:** In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem.

- **Amlodipine:** In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine.

**Moderate Inhibitors of CYP3A4:** Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy.

**Niacin (nicotinic acid) ( $\geq 1$  g/day):** The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with niacin (nicotinic acid)  $\geq 1$  g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses ( $\geq 1$  g/day) of niacin.

**Colchicine:** There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Close clinical monitoring of such patients taking this combination is advised.

#### *Other interactions*

**Grapefruit juice** contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drug metabolized by CYP3A4. The effect of typical consumption (one 250-ml glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, very large-quantities (over 1 liter daily) significantly increase plasma level of HMG-CoA reductase inhibitory activity during simvastatin therapy and should be avoided.

### **Statement on Usage During Pregnancy and Lactation**

Simvastatin is contraindicated during pregnancy. Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia. For these reasons, simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with simvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions, women taking simvastatin should not breast-feed their infants.

### **Adverse Effects / Undesirable Effects**

Simvastatin is generally well-tolerated; for the most part side effects have been mild and transient in nature. Possibly, probably or definitely drug-related adverse effects were abdominal pain, constipation and flatulence. Other side effects were asthenia and headache. Myopathy has been reported rarely.

The following additional side effects were reported :

Nausea, diarrhea, rash, dyspepsia, pruritus, alopecia, dizziness, muscle cramps, myalgia, pancreatitis, paresthesia, peripheral neuropathy, memory impairment, insomnia, depression, vomiting, anemia, erectile dysfunction, and interstitial lung disease. There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Rarely rhabdomyolysis and hepatitis/jaundice, and very rarely fatal and non-fatal hepatic failure have occurred. An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnea, and malaise.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

### *Laboratory test findings*

Marked and persistent increases of serum transaminases have been reported infrequently. Elevated alkaline phosphatase and  $\gamma$ -glutamyl transpeptidase have been reported. Liver function test abnormalities generally have been mild and transient. Increases in serum CK levels, derived from skeletal muscle, have been reported.

Increases in HbA1c and fasting serum glucose levels have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

*Pediatric patients (ages 10-17 years)*

The safety and tolerability profile of the group treated with simvastatin was generally similar to that of the group treated with placebo.

**Overdose and Treatment**

A few cases of overdose have been reported. The maximum dose taken was 3.6 g. All patients recovered without sequelae. General measures should be adopted.

**Storage Conditions**

Store below ....°C

**Dosage Forms and Packaging Available**

*[ Packaging type & pack size ]*

**Name and Address of Manufacturer**

*[ Name & full address of manufacturer ]*

**Name and Address of Marketing Authorization Holder**

*[ Name & full address of marketing authorization holder ]*

**Date of Revision of Package Insert**

*[ day/month/year ]*