XEPA COVASTIN®

Simvastatin

COMPOSITION
Xepa Covastin Film-Coated **Tablets 10mg:**
Each tablet contains Simvastatin 10 mg
Xepa Covastin Film-Coated Tablets 20mg:
Each tablet contains Simvastatin 20 mg

MODE OF ACTION
Simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form after oral ingestion. 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.

PHARMACOLOGY
Covastin reduces both normal and elevated low-density lipoprotein cholesterol (LDL-C) concentrations in plasma. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high-affinity LDL receptor on hepatocyte membranes. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL cholesterol (VLDL-C) concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. In addition, **Covastin** also reduces VLDL-C and triglycerides (TG) and increases high-density lipoprotein cholesterol (HDL-C) concentrations.

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, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin, the availability of active metabolites of an oral dose to the general circulation is low, reported to be less than 5%. Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Peak plasma concentration of β-hydroxyacid metabolites was attained within 1.3 to 2.4 hours postdose. Simvastatin is mainly excreted in the feces via the bile as metabolites. About 10 to 15% is recovered in the urine, mainly in inactive forms.

INDICATION
Therapy with lipid-altering agents should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence of congestive heart failure, or other risk factors. **Covastin** is used when the response to a saturated fat and cholesterol-restricted diet and other non-pharmacological measures alone has been inadequate.

Coronary Heart Disease
In patients with coronary heart disease and hypercholesterolemia, **Covastin** is indicated to:

- Reduce the risk of total mortality by reducing coronary death.
- Reduce the risk of non-fatal myocardial infarction.
- Reduce the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty).
- Slow the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

Hyperlipidemia
Covastin is indicated as an adjunct to diet for reduction of elevated total-cholesterol, LDL-C, apolipoprotein B (Apo B), and TG in patients with primary hypercholesterolemia, heterozygous familial hypercholesterolemia or combined (mixed) hyperlipidemia when response to diet and other nonpharmacological measures is inadequate. **Covastin** also raises HDL-C and therefore lowers the LDL/HDL and total cholesterol/HDL ratios.

DOSAGE AND ADMINISTRATION
Before receiving **Covastin**, patient should be placed on a standard cholesterol-lowering diet and should continue on this diet during treatment with **Covastin**.

Coronary Heart Disease
The recommended usual starting dose is 20 mg once a day in the evening. Adjustments of dosage, if required, should be made at intervals of 4 weeks or more, to a maximum of 80mg/day given as a single dose in the evening.
Cholesterol levels should be monitored periodically and dosage reduction should be considered if cholesterol falls significantly below the targeted range, i.e. LDL-C levels fall below 75 mg/dL (1.94 mmol/L) or total-C levels fall below 140 mg/dL (3.6 mmol/L).

Hyperlipidemia
The usual starting dose is 20 mg once a day in the evening. Patients who require only a moderate reduction of LDL-C may be started at 10mg. Adjustment of dosage, if required, should be made as directed above (see DOSAGE AND ADMINISTRATION, *Coronary Heart Disease*).

Homozygous Familial Hypercholesterolemia
In patients with homozygous form of familial hypercholesterolemia, in whom there is a complete absence of LDL receptors, therapy with **Covastin** is unlikely to result in clinical benefit.

Dosage in Elderly
In the elderly, maximum reductions in LDL-C may be achieved with daily doses of 20 mg of **Covastin** or less.

Concomitant Lipid-Lowering Therapy
Use of **Covastin** with fibrates or niacin should generally be avoided. However, if **Covastin** is used in combination with fibrates (except gemfibrozil which is contraindicated), the dose of **Covastin** should not exceed 10 mg. In patients taking concomitant fibrates (except gemfibrozil which is contraindicated) , the dose of **Covastin** should not exceed 10 mg, as the risk of myopathy increases substantially at higher doses.

Dosage in Patients with Renal Insufficiency
Because simvastatin does not undergo significant renal excretion, modification of dosage is not necessary in patients with mild to moderate renal insufficiency.
However, caution should be exercised when **Covastin** administered to patients with severe renal insufficiency (creatinine clearance <30 ml/min); such patients should be started at 5 mg/day and be closely monitored.

Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of simvastatin should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. Patients unable to achieve their LDL-C goal utilizing the 40-mg dose of simvastatin should not be titrated to the 80-mg dose, but should be placed on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering.

CONTRAINDICATIONS
Covastin is contraindicated in patients with hypersensitivity to any component of this product. It should not be given to patients with acute liver disease or unexplained persistent raised serum-aminotransferase concentrations.

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.

Pregnancy and Lactation
Covastin is contraindicated during pregnancy and in nursing mothers since there is a possibility that it could interfere with fetal sterol synthesis. Cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Moreover, atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. **Covastin** should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, **Covastin** should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS
General
Covastin may cause elevation of creatinine kinase and transaminase concentrations. This should be considered in the differential diagnosis of chest pain in a patient on therapy with **Covastin**.
Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness.

Skeletal Muscle
It has been noted that myositis and myopathy are well known to occur with lipid lowering drugs such as fibrates and statins. Rhabdomyolysis, presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure, has also been reported but appears to be rare.

Simvastatin 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 (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

As with other statins, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with simvastatin, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded. In a clinical trial in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%. The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C-lowering efficacy. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of simvastatin should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. Patients unable to achieve their LDL-C goal utilizing the 40- mg dose of simvastatin should not be titrated to the 80-mg dose, but should be placed on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering. In patients taking simvastatin 80 mg for whom an interacting agent is needed, a lower dose of simvastatin or an alternative statin-based regimen with less potential for drug-drug interactions should be used.

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.

Prescribing recommendations for interacting agents are summarized in the table below:

Drug Interactions Associated with Increased Risk of Myopathy/ Rhabdomyolysis

Interacting Agent	Prescribing Recommendations
Potent CYP3A4 inhibitors, e.g.: Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Cylosporine Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10mg simvastatin daily
Fusidic acid	It is not recommended with simvastatin
Amiodarone Verapamil Diltiazem	Do not exceed 20mg simvastatin daily
Amlodipine	Do not exceed 40mg simvastatin daily
Grapefruit juice	Avoid grapefruit juice

In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05% for non-Chinese patients (n=7367) compared with 0.24% for Chinese patients (n=5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing simvastatin to Asian patients and the lowest dose necessary should be employed.

Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid modifying doses (>1 g/day) of niacin. In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥ 1 g/day) of niacin. Therefore, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. In addition, in this trial, the incidence of myopathy was approximately 0.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24% for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with extended-release niacin/laropiprant 2 g/40 mg. While the only Asian population assessed in this clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in non-Chinese patients, coadministration of simvastatin with lipid modifying doses (>1 g/day) of niacin is not recommended in Asian patients.

Liver Dysfunction
It is recommended that liver function tests be performed before the initiation of treatment with **Covastin**, and periodically thereafter (*e.g.*, semiannually) for the first year of treatment or until one year after the last elevation in dose or when clinically indicated. Patients titrated to the 80mg dose should receive an additional test at 3 months. Patients who develop increased transaminase levels should be monitored with a second liver function test to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 times the ULN or greater persist, withdrawal of therapy is recommended.
Covastin should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.
As with other lipid-lowering agents, moderate (less than 3 times the 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 and not accompanied by any symptoms and did not require interruption of treatment.

Pregnancy
See CONTRAINDICATIONS.

Nursing Mothers
It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants.

Paediatric Use
Covastin is not recommended for paediatric use. Safety and effectiveness in paediatric patients have not been established.

DRUG INTERACTIONS
Contraindicated drugs
Concomitant use of the following drugs 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.
Concomitant use of drugs labeled as having a potent inhibitory effect on CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone) is contraindicated.

Other drug interactions:
Other Fibrates: The risk of myopathy is increased by gemfibrozil and other fibrates (except fenofibrate); these lipid-lowering drugs can cause myopathy when given alone. 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.
Fusidic Acid: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid. Temporary suspension of simvastatin treatment may be considered.
Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin.
Calcium channel blockers: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or 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) (≥ 1g/day): Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1g/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.
Antipyrine: Simvastatin had no effect on the pharmacokinetics of antipyrine. However, since simvastatin is metabolized by the cytochrome P450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform.
Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin had been reported to result in slight elevation (less than 0.3 ng/ml) in digoxin plasma concentrations compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when **Covastin** is initiated.
Warfarin: It was reported that simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulant. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting **Covastin** and frequently enough during early therapy to insure 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. If the dose of **Covastin** is changed or discontinued, the same procedure should be repeated. **Covastin** therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other interactions: Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs 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, because large quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided during simvastatin therapy.

SIDE EFFECTS / ADVERSE REACTIONS
The commonest adverse effects of therapy with simvasatin and other HMG-CoA reductase inhibitors are gastrointestinal disturbances. Other adverse effects reported include headache, skin rashes, dizziness, blurred vision, and dysgeusia. Reversible increases in serum aminotransferase concentrations may occur and liver function should be monitored. Myopathy, characterised by myalgia and muscle weakness and associated with increased creatinine phosphokinase concentrations, has been reported, especially in patients taking simvastatin concurrently with immunosuppressive drugs, fibric acid derivatives, or nicotinic acid. Rarely, rhabdomyolysis with acute renal failure may develop.

Nervous system: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

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).

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA (antinuclear antibody), ESR (erythrocyte sedimentation rate) increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: Alopecia, pruritus. A variety of skin changes (*e.g.*, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Metabolic Disorders : Increases in HbA1c and fasting serum glucose levels.

SYMPTOMS AND TREATMENT FOR OVERDOSAGE
A few cases of overdosage with simvastatin have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 450 mg. Until further experience is obtained, no specific treatment of overdosage with simvastatin can be recommended. General measures should be adopted. The dialyzability of simvastatin and its metabolites in man is not known at present.

SHELF-LIFE
The expiry date is indicated on the packaging.

STORAGE
Store in a cool dry place below 30°C.
KEEP ALL MEDICINES OUT OF REACH OF CHILDREN / JAUHI DARI KANAK-KANAK

DESCRIPTION
Xepa Covastin Film-Coated Tablets 10mg:
Peach coloured round shape film coated tablet, with breakline and marking "XS" on one side and plain on reverse.

Xepa Covastin Film-Coated Tablets 20mg:
Brown coloured pentagon shape film coated tablet, with "XS" marking and breakline on one side and plain on reverse.

PACKING / PACK SIZES
30's in blister pack of 1 0's

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Xepa SP

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