VASCOR TABLET 20MG F/C

DESCRIPTION: VASCOR TABLET 20MG F/C: 11mm, oval, scored and marked '20' on one side, and marked 'VAS' on the other side, orange film-coated tablet.

COMPOSITION: Each tablet contains 20mg of Simvastatin.

PHARMACODYNAMICS: The active form of Simvastatin is a specific inhibitor of 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 amount 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 billiary 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 ß-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 ß-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors). Both are measured in plasma following administration of simvastatin.
In a disposition study with ^{14}C-labeled simvastatin, 100 mg (20 µCi) of drug was administered as capsules (5 X 20 mg), and blood, urine, and feces collected. Thirteen percent of the radioactivity was recovered in the urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Less than 0.5% of the dose was recovered in urine as HMG-CoA reductase inhibitors. In plasma, the inhibitors account for 14 percent and 28 percent (active and total inhibitors) of the AUC of total radioactivity, indicating that the majority of chemical species present were inactive or weak inhibitors. Both simvastatin and L-654,969 are bound to human plasma protein (95%). The major metabolites of simvastatin present in human plasma L-654,969 and four additional active metabolites. The availability of L-654,969 to the systemic circulation following an oral dose of simvastatin was estimated using an i.v. reference dose of L-654,969, the value was found to be less than 5% of the dose. By analogy to the dog model, simvastatin is well absorbed and undergoes extensive first-pass extraction in the liver, the primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the general circulation is low. In dose-proportionality studies utilizing doses of simvastatin of 5, 10, 20, 60, 90 and 120 mg there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before a test meal. 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. In a study of patients with severe renal insufficiency (creatinine clearance < 30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two- fold higher than those in healthy volunteers. In a study of 12 healthy volunteers, simvastatin at the maximal 80-mg dose had no effect on the metabolism of the probe CYP3A4 substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4. Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see PRECAUTIONS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).

INDICATION: Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate.

Patients at High Risk of Coronary Heart Disease (CHD) or With Existing CHD:
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. Vascor 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.

In hypercholesterolemic patients with coronary heart disease, Vascor slows the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

Patients with Hyperlipidemia:
Vascor is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia, heterozygous familial hypercholesterolemia or combined (mixed) hyperlipidemia (Fredrickson type IIb), when response to diet and other nonpharmacological measures is inadequate. Vascor therefore, lowers the LDL-C/HDL-C and the total-C/HDL-C ratios.
Vascor is also indicated as an adjust to diet and other non-dietary measures for the treatment of patients with homozygous familial hypercholesterolemia to reduce evelated total-C, LDL-C and apo B.

RECOMMENDED DOSAGE: The dosage range for Vascor Tablet is 5-80mg/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 80mg/day given as a single dose in the evening. The 80mg dose 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.

Patients at High Risk of Coronary Heart Disease (CHD) or With Existing CHD:
The usual starting dose of Vascor is 40mg 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 celebrovascular disease, peripheral vessel disease, or with existing CHD, Drug therapy can 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 Vascor Tablet and should continue on this diet during treatment with Vascor Tablet.
The usual starting dose is 20 mg/day given as a single dose a day in the evening. Patients who require a large a 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 treated with a starting dose 10mg of Vascor Tablet**.** Adjustments of dosage, if required, should be made as specified above.

Patients with Homozygous Familial Hypercholesterolemia:
The recommended dosage for patients with homozygous familial hypercholesterolemia is Vascor 40mg/day in the evening. The 80mg dose is recommended when benefits are expected to outweigh the potential risks (see below; CONTRAINDICATION; PRECAUTIONS, Myopathy/Rhabdomyolsis). Vascor should be used as an adjunct to the 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 fibrates (other than gemfibrozil and fenofibrate) concomitantly with Vascor Tablet, the dose of Vascor Tablet should not exceed 10mg/day. In patients taking amiodarone, verapamil or diltiazem concomitantly with Vascor Tablet, the dose of Vascor Tablet should not exceed 20mg/day. In patients taking amlodipine or lipid-lowering dose of niacin (≥1g/day) concomitantly with Vascor Tablet, the dose of Vascor Tablet should not exceed 40mg/day. (See PRECAUTIONS, Myopathy/ Rhabdomyolysis and DRUG INTERACTIONS).

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Dosage in Renal Insufficiency:
Because Vascor Tablet 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), dosage above 10mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

ROUTE OF ADMINISTRATION: Oral

CONTRAINDICATIONS:
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone). (See DRUG INTERACTIONS).
- Concomitant administration of gemfibrozil, cyclosporine, or danazol. (See DRUG INTERACTIONS).
- Hypersensitivity to any components of this preparation.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (See PRECAUTIONS, PREGNANCY AND NURSING MOTHER/ LACTATION).

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

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related.
The risk of myopathy is greater in patients on simvastatin 80mg compared with other statin based therapies with similar LDL-C lower efficacy. Therefore, the 80mg dose Vascor Tablet should only be used in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking simvastatin 80mg for whom an interacting agent is needed, a lower of simvastatin or an alternative statin based regimen with less potential for drug-drug interactions should be used (see RECOMMENDED DOSE).

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/ or a CK level > 10 times the upper limit of normal indicated 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 does is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have 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.

Hepatic Effects:
It is recommended that LFTs 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., 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 transminase levels show evidence of progression, particularly if they rise to 3x ULN and are persistent, the drug should be discontinued.
The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase evelations 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.

Use in Children:
Vascor Tablet is not recommended for paediatric use. Safety and effectiveness in paediatric patients have not been established.

Use in 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 frequency of clinical or laboratory adverse findings.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by:
- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatments;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents

INTERACTION WITH OTHER MEDICAMENTS:
Contraindicated Drugs:
Potent inhibitors or CYP3A4: Concomitant use with medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g.: itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) is contraindicated. If 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:
Other fibrates: The dose of simvastatin should not exceed 10mg 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: In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80mg and amiodarone. The dose of simvastatin should not exceed 20mg 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 80mg had an increased risk of myopathy. The dose of simvastatin should not exceed 20mg daily in patients receiving concomitant medication with verapamil or diltiazem.
- Amlodipine: in a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with amlodipine.

- Niacin (≥1g/day): the dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥1g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin co- administered with lipid modifying doses (≥1g/day) of niacin.

Coumarin derivatives:
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. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin 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 drug metabolized by CYP3A4. The effect of typical consumption (one 250-ml glass daily) is minimal 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 (see PRECAUTIONS, Myopathy/ Rhabdomyolysis.)
Concurrent use of fibrates may cause severe myositis and myoglobinuria.

USE IN PREGNANCY & LACTATION: Vascor Tablet 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. Vascor Tablet 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, Vascor Tablet should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus.
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 Vascor Tablet should not breastfeed their infants (See CONTRAINDICATIONS).

SIDE EFFECTS: The commonest adverse effects of therapy with simvastatin and other HMG-CoA reductase inhibitors are gastrointestinal disturbances like abdominal pain, constipation, and flatulence. Other adverse effects reported include headache, skin rashes, dizziness, blurred vision, and dyspepsia. 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.
The following-effects have been reported with drugs in this class. Not all the effects listed below have necessarily associated with simvastatin therapy.
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 nerve palsy, psychic disturbances, anxiety, insomnia, depression.
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, vasculis, purpura, thrombocytopenia, leucopenia, 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 Steven-Johnson syndrome.
Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in the 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), opthalmoplegia.
There have been rare post-marketing 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 non-serious and reversible upon statin discontinuation, with variable times to symptoms onset (1 day to years) and symptoms resolution (median 3 weeks).
Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.
Musculoskeletal disorders: Frequency not known: Immune-mediated necrotizing myopathy.

SYMPTOMS AND TREATMENT OF OVERDOSE: There are few reports on patients with maximum dose of 450mg, none had typical symptoms and all recovered. Should adopt general measures.

STORAGE CONDITIONS: Store in a dry place below 30º C. Protect from light. Keep medicines out of reach of children. *Jauhkan daripada kanak-kanak.*

SHELF LIFE: Please refer to outer package.

PACK SIZE: Pack in blister pack of 3 x 10's tablets, 10 x 10's tablets, 12 x 10's tablets in a box.

PRODUCT REGISTRATION HOLDER & MANUFACTURER:
DUOPHARMA (M) SDN BHD
Lot 2599, Jalan Seruling 59 Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor, MALAYSIA.