SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE FINISHED PRODUCT

Stavid Tablet 20mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIVE INGREDIENTS	PER TABLET (MG)
Simvastatin	20 mg

Kindly refer to Section 6.1 for excipient.

3. PHARMACEUTICAL FORM

Oval, peach film-coated tablet, shallow convex with "HD" and break bar embossed on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Coronary Heart Disease

In patients with coronary heart disease with plasma cholesterol level of 5.5 mmol/L or greater, simvastatin is indicated to:

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

Hyperlipidaemia

Simvastatin is indicated as an adjunct to diet to reduce elevated total cholesterol, LDL-chloresterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combine (mixed) hyperlipidaemia when response to diet and other non-pharmacological measures is inadequate. Simvastatin also increases HDL-cholesterol and therefore lowers the LDL-cholesterol / HDL-cholesterol and the total cholesterol / HDL-cholesterol ratios.

As with any cholesterol-lowering therapy, other modifiable risk factors should be also be considered when treatment is started.

Homozygous Familial Hypercholesterolaemia

Simvastatin is indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol and apolipoprotein B in patients with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

4.2 Posology and Method of administration

Route of administration is oral. 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 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.

Coronary Heart Disease:
Patients with coronary heart disease can be treated with a starting dose of 20mg/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, depending on the patient's individual response.
If LDL-cholesterol levels fall below 75mg/dL (1.94 mmol/L) or total serum cholesterol levels fall below 140 mg/dL (3.6 mmol/L), consideration should be given to reducing the dose of simvastatin.

Hyperlipidaemia:
The usual starting dose is 20 mg/day given as a single dose a day in the evening. Patients who require only a moderate reduction of LDL-cholesterol may be started at 10mg. Adjustments of dosage, if required, should be made as specified in dosage and administration for Coronary Heart Disease.

Homozygous Familial Hypercholesterolaemia:
Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolemia is simvastatin 40mg/day in the evening or 80mg/day in 3 divided doses of 20 mg, 20 mg and an evening dose of 40 mg. 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 cyclosporine, fibrates or niacin concomitantly with simvastatin, the maximum recommended dosage is 10mg/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<30mL/min), dosages above 10mg/day should be carefully considered and if deemed necessary, implemented cautiously.

Use in the Elderly:
Although experience in elderly patients is limited, efficacy using standard doses appears similar to that seen in the population as a whole. There is no apparent increase in the frequency of clinical or laboratory adverse findings.

Use in Children:
Safety and efficacy in children have not been established.

4.3 Contraindication

- Contraindicated in patients with hypersensitivity for this product; active liver disease or unexplained persistent elevations of serum transaminases; porphyria; pregnancy and breast-feeding; women of childbearing potential unless adequately protected by non-hormonal methods.
- 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.

4.4 Warnings and precautions

MUSCLE EFFECTS
Simvastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine phosphokinase (CPK) (>10X the upper limit of normal [ULN]). Rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, has been reported rarely.

Myopathy Caused By Drug Interactions:
The incidence and severity of myopathy are increased by concomitant administration of HMG CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates and lipid lowering doses (≥1g/day) of niacin (nicotinic acid). In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Simvastatin and other HMG-CoA reductase inhibitors are metabolized by the cytochrome P450 isoform 3A4(CYP3A4). Certain drugs that have a significant inhibitory effect at therapeutic doses on this metabolic pathway can substantially raise the plasma levels of HMG-CoA reductase inhibitors and thus increase the risk of myopathy. These include cyclosporine, the azole antifungals itraconazole and ketoconazole, the macrolide antibiotics, erythromycin and clarithromycin, HIV protease inhibitors and the antidepressant nefazodone.

Reducing the risk of myopathy:

1. General measures

Patients starting therapy with simvastatin should be advised of the risk of myopathy and told to report promptly unexplained muscle pain, tenderness or weakness. A CPK level above 10x ULN in a patient with unexplained muscle symptoms indicates myopathy. Simvastatin therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CPK increases resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. Caution in dose escalation is required in such patients. Also, as there are no know adverse consequences of brief interruption of therapy, treatment with simvastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions

Physicians contemplating combined therapy with simvastatin and any of the interacting drugs should weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of simvastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels / concentrations is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of simvastatin have been used without myopathy in small, short-term clinical studies with careful monitoring. Addition of these drugs to HMG-CoA reductase inhibitors typically provides little additional reduction in LDL-cholesterol, but further reductions of triglycerides and further increases in HDL-cholesterol may be obtained. If one these drugs must be used with simvastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of Simvastatin should generally not exceed 10 mg/day, as the risk of myopathy increases substantially at higher doses. Concomitant use of simvastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, or nefazodone is not recommended. If no alternative to a short course of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is available, a brief suspension of simvastatin therapy can be considered as there are no known adverse consequences to brief interruption of long-term cholesterol-lowering therapy. Concomitant use with other medicines labeled as having a potent inhibitory effect on cytochrome CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

HEPATIC EFFECTS

Minor asymptomatic transient rises in serum transaminases may occur soon after initiation of therapy with simvastatin which do not require the drug to be discontinued. There is no evidence that the changes are due to hypersensitivity to simvastatin.

It is recommended that liver-function tests be performed before treatment begins and periodically thereafter (e.g. twice a year) for the first year of treatment or until one year after the last elevation in dose in all patients. Patients titrated to the 80mg dose should receive an additional test at 3 months. Special attention should be paid to patients who develop elevated serum transaminase levels, 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 times 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 elevations are contraindications to the use of simvastatin.

OPHTHALMIC EVALUATION / EXAMINATION

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.

4.5 Drug Interactions

Contraindicated Drugs

Potent inhibitors of CYP3A4: Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g.: itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir or 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. Concurrent use of fibrates may cause severe myositis and myoglobinuria.

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 two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. 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.

4.6 Pregnancy and lactation

PREGNANCY:
Simvastatin is contraindicated in pregnancy.
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 hypercholesterolaemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as simvastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, simvastatin is contraindicated in pregnancy and women of

childbearing potential unless such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, simvastatin should be discontinued immediately and patient apprised of the potential hazard to the fetus.

A few reports have been received of congenital anomalies in infants whose mother were treated during pregnancy with HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal death/stillbirths did not exceed what would be expected in the general population. As safety in pregnant women has not been established and there is no apparent benefit to therapy with simvastatin during pregnancy, treatment should be immediately discontinued as soon as pregnancy is recognized.

LACTATION:
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.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Main Side/ Adverse Effects

Simvastatin is generally well-tolerated; for the most part side effects have been mild and transient in nature. Less than 2% of patients were discontinued from controlled clinical studies due to side effects attributable to simvastatin.

In the pre-marketing controlled clinical studies, adverse effects occurring with a frequency of 1% or more and considered by the investigator as possibly, probably or definitely drug-related were: abdominal pain, constipation and flatulence. Other side effects occurring in 0.5-0.9% of patients were asthenia and headache. Myopathy has been reported rarely.

The following additional side effects were reported either in long-term extension studies or in marketed use: nausea, diarrhea, rash, dyspepsia, pruritus, alopecia, dizziness, muscle cramps, myalgia, pancreatitis, paraesthesia, peripheral neuropathy, vomiting and anaemia. Rarely rhabdomyolysis and hepatitis/jaundice occurred.

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

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 symptom onset (1 day to years) and symptom 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.

Laboratory Test Findings:
Marked and persistent increases of serum transaminases have been reported infrequently. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have reported. Liver function test abnormalities generally have been mild and transient. Increases in serum creatine phosphokinase (CPK) levels derived from skeletal muscle have been reported.

4.9 Overdose

A few cases of overdose have been reported; no patient had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 450mg. General measures should be adopted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hydrolyzed form of simvastatin, beta-hydroxy acid inhibits enzyme HMG-CoA reductase. Inhibition of HMG-CoA reductase prevents conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Inhibition of cholesterol synthesis in the liver leads to upregulation of LDL receptors and an increase in catabolism of LDL-cholesterol. Simvastatin reduces LDL-cholesterol, VLDL-cholesterol, and to a lesser extent, plasma triglyceride concentrations, and slightly increase high-density lipoprotein (HDL) concentrations.

5.2 Pharmacokinetic properties

Simvastatin is absorbed from the gastrointestinal tract and is hydrolysed to its active beta-hydroxy acid 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. The half-life of the active metabolite is 1.9 hours. Both simvastatin and its beta-hydroxy acid metabolite are about 95% bound to plasma proteins. The maximum plasma concentration of inhibitors occurred within 1.3 to 2.4 hours of administration. 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.

5.3 Preclinical Safety Data

NOT APPLICABLE

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxyanisole
Ascorbic acid
Colloidal silicon dioxide
Citric acid anhydrous
Magnesium stearate
Lactose monohydrate
Microcrystalline cellulose pH102
Partially Pregelatinised starch
Hydroxypropyl methylcellulose E-5
Hydroxypropyl methylcellulose E-15
Titanium dioxide
Talc
Propylene glycol
Iron oxide red
Iron oxide yellow
Isopropyl alcohol
Purified water

6.2 Incompatibilities

NOT APPLICABLE

6.3 Shelf life

3 years from date of manufacture

6.4 Special precaution for storage

Store below 30°C. Protect from heat and moisture.

6.5 Nature and contents of container

Blister Pack

Type:
Push-through blister pack; the package consists of a transparent themoformable plastic material and a heat-sealable lacquered backing material.

Material:
Thermoformable plastic material : PVC film-coated with PVDC
Backing Material : Aluminium Foil

6.6 Instructions for use and handling <and disposal>

NOT APPLICABLE

7. MARKETING AUTHORISATION HOLDER

Name	:	HOVID Bhd. Address : 121, Jalan Tunku Abdul Rahman, (Jalan Kuala Kangsar) 30010 Ipoh, Perak, Malaysia
Manufacturer Name :		
Name	:	HOVID Bhd.
Address	:	Lot 56442, 7 ½ Miles, Jalan Ipoh / Chemor, 31200 Chemor, Perak., Malaysia.

8. NUMBER (S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

HOV/MAL/022

9. DATE OF FIRST AUTHORISATION\

2016

10. DATE OF REVISION OF THE TEXT

January 2018