SUMMARY OF PRODUCT CHARACTERISTICS
KARDAK
Simvastatin Tablets 5 mg, 10 mg, 20 mg, 40 mg and 80 mg
Rx Only

NAME OF DRUG PRODUCT: Simvastatin Tablets 5 mg.
Simvastatin Tablets 10 mg.
Simvastatin Tablets 20 mg.
Simvastatin Tablets 40 mg.
Simvastatin Tablets 80 mg.

(TRADE) NAME OF PRODUCT: KARDAK 5.
KARDAK 10.
KARDAK 20.
KARDAK 40.
KARDAK 80.

STRENGTH: 5 mg, 10 mg, 20 mg, 40 mg and 80 mg

PHARMACEUTICAL DOSAGE FORM: Tablet.

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

PHARMACEUTICAL FORM:

Simvastatin Tablets 5 mg: Yellow coloured, round shaped, biconvex, film coated tablets, debossed with 'SI' on one side and '5' on the other side.

Simvastatin Tablets 10 mg: Light pink coloured, round shaped, biconvex, coated tablets, debossed with 'SI' on one side and '10' on the other side.

Simvastatin Tablets 20 mg: Light pink coloured, round shaped, biconvex, coated tablets, debossed with 'SI' on one side and '20' on the other side.

Simvastatin Tablets 40 mg: Pink coloured, round shaped, biconvex, coated tablets, debossed with 'SI' on one side and '40' on the other side.

Simvastatin Tablets 80 mg: Pink coloured, capsule shaped, biconvex, film coated tablets, debossed with 'SI' on one side and '80' on the other side.

'Not all presentations may be available locally'

CLINICAL PARTICULARS:

Therapeutic indications

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, Simvastatin Tablets 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, Simvastatin Tablets slows the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

PATIENTS WITH HYPERLIPIDEMIA

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

Posology and method of administration

The dosage range is 5-80 mg/day given orally 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. 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.

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

Homozygous familial hypercholesterolaemia
The recommended dosage is Simvastatin 40 mg/day in the evening or 80 mg/day in 3 divided doses of 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.

Cardiovascular prevention
Patients with coronary heart disease can be treated with a starting dose of 20mg/day given as a single dose in the evening. Patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease have been shown to benefit from 40mg/day and can be started at this dose.

Concomitant therapy
Simvastatin is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or >4 hours after administration of a bile acid sequestrant. In patients taking Simvastatin concomitantly with fibrates other than gemfibrozil (see CONTRAINDICATIONS) or fenofibrate the dose of Simvastatin should not exceed 10mg/day. In patients taking amiodarone, verapamil, diltiazem, or products containing elbasvir or grazoprevir concomitantly with Simvastatin, the dose of Simvastatin should not exceed 20mg/day. In patients taking amlodipine concomitantly with Simvastatin, the dose of Simvastatin should not exceed 40mg/day.

Dosage in renal insufficiency
No modification of dosage should 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.

Use in the 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 ≥ 65 years of age had an increased risk of myopathy compared to patients <65 years of age.

Use in children and adolescents
Simvastatin is not recommended for paediatric use.

Contraindications
Hypersensitivity to Simvastatin or to any of the excipients.
Active liver disease or unexplained persistent elevation of serum transaminase values.
Porphyria. Myopathy.
Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and drugs containing cobicistat), gemfibrozil, cyclosporine, danazol, delaviridine and amiodarone.
Pregnancy and lactation.
Women of child-bearing potential, unless adequate contraception is used.

Special warnings and precautions for use

Creatine Kinase measurement:

Creatine Kinase (CK) should not be measured following strenous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline > 5xULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment:
Clinicians should prescribe statins with caution in patients with pre-disposing factors for rhabdomyolysis. A Creatine Kinase (CK) level should be measured before starting statin treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdo-myolysis.

In such situations the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended.

If CK levels are significantly elevated (> 5xULN) at baseline, treatment should not be started.

Whilst on treatment:
If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found to be significantly elevated (>5xULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are elevated to 5xULN, treatment discontinuation should be considered.
If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

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, occur rarely. The muscular effects are dose-dependent and the monitoring of muscular enzyme should be intensified when Simvastatin is prescribed at the highest dosages.
Myopathy caused by medicinal product interactions: The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with medicinal products that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (1 g/day) of niacin (nicotinicacid).
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 metabolised 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 cyclosporin, the azole antifungals itraconazole and ketoconazole, the macrolide antibiotics, telithromycin, erythromycin and clarithromycin, HIV-protease inhibitors, delavirdine, amiodarone, calcium channel blocker verapamil 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 have pre- existing renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution.
Also, as there are no known 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.
With regard to the risk of adverse events on the muscle being linked to the dosage, a careful benefit/risk assessment should be made before switching to high dosages e.g. 80 mg.
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.

2. Measures to reduce the risk of myopathy caused by medicinal product interactions. Physicians contemplating combined therapy with Simvastatin and any of the interacting medicinal products 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 medicinal product. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.
Concomitant administration of Simvastatin with gemfibrozil should be avoided due to the pharmacokinetics interaction. In patients taking concomitant cyclosporine, fibrates other than gemfibrozil or fenofibrate, the dose of Simvastatin should generally not exceed 10 mg/day, as the risk of myopathy increases substantially at higher doses. Addition of fibrates to Simvastatin typically provides little additional reduction in LDL-cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. Concomitant use of Simvastatin with potent CYP3A4 inhibitors (e.g. itraconazole , ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, or drugs containing cobicistat), gemfibrozil, cyclosporine, danazol, delaviridine and amiodarone is contraindicated. Concomitant use of simvastatin with verapamil is not recommended. If no alternative to a short course of treatment with itracona-zole, ketoconazole, erythromycin, clarithromycin or telithromycin 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 CYP3A4 at therapeutic doses is contraindicated. Concomitant use with moderate inhibitors of CYP3A4, particularly with higher Simvastatin doses, may have an increased risk of myopathy. When coadministering Simvastatin with a moderate inhibitor of CYP3A4, a dose adjustment of Simvastatin may be necessary.

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/laropripant 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. Concomitant intake of grapefruit juice and simvastatin is not recommended due to the grapefruit juice induced extensive increase in Simvastatin AUC.

Hepatic effects: Minor asymptomatic transient rises in serum transaminase may occur soon after initiation of therapy with simvastatin, which do not require the drug to be discontinued. There is no evidence that these 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 80 mg dose should receive an additional test at three months. 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 three times the upper limit of normal and are persistent, the drug should be discontinued. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins,

A/s: 210 x 360 mm ■ Black

AUROBINDO Packaging Development		Product Name	Component	Item Code	Date & Time
		KARDAK	Leaflet	P1530309	19.03.2022 & 05.00 pm
		Country	Version No.	Reason of Issue	Reviewed / Approved by
		Singapore_U15	01	Submission	
Team Leader	Kiran K	Dimensions (mm)	Colours: 01		
Initiator	Shirisha N	A/s: 210 x 360 mm			
Artist	Sree Designers	Pharmacode: 30309			
Additional Information: PK					

30309

including Simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Simvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart Simvastatin.
Simvastatin 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.
There is a risk for increased effect of vitamin K antagonists.

Impaired renal function:
Simvastatin should be used with caution in severe renal impairment (creatinine clearance<30 ml/min).

Secondary hypercholesterolemia:
In case of secondary hypercholesterolemia caused by hypothyroidism or nephrotic syndrome, first treat the underlying disease.

Excipient:
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction
Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/ rhabdomyolysis. Co-administration with fusidic acid is not recommended. 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 coadministration of simvastatin and fusidic acid should only be considered on a caseby-case basis under close medical supervision.
The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine. The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide. The dose of simvastatin should not exceed 40 mg daily in patients with homozygous familial hypercholesterolaemia receiving concomitant medication with lomitapide. Simvastatin is a substrate of the transport protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy. Simvastatin is a substrate of the efflux transporter breast cancer resistant protein (BCRP). Concomitant administration of products that are inhibitors of BCRP (e.g. elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of simvastatin may be necessary. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir.

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. Gemfibrozil and other fibrates, plasma lipid-lowering doses of niacin (nicotinic acid) (1g/day). When these medicinal products are used concomitantly with simvastatin, the risk of myopathy is increased and concurrent use should be avoided. The concurrent use of fibrates is not recommended. Interaction with cytochrome P450 3A4. Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 may increase the risk of myopathy by increasing the activity of HMG-CoA reductase inhibitor in plasma during simvastatin therapy. Such inhibitors include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, verapamil, HIV-protease inhibitors, delaviridine and nefazodone.
Grapefruit juice contains one or more ingredients inhibiting cytochrome P450 3A4 and may therefore increase the plasma concentrations of drugs metabolised via the cytochrome P450 3A4. Concomitant intake of grapefruit juice and simvastatin should be avoided.

Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of drugs metabolised via cytochrome P450 3A4.
Other medicinal products. The risk of myopathy or rhabdomyolysis is increased when simvastatin is given concomitantly with amiodarone.

Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, or drugs containing cobicistat), gemfibrozil, cyclosporine, danazol, delaviridine and amiodarone is contraindicated. Caution should be exercised when combining simvastatin and verapamil.
Coumarin derivatives: In patients treated with coumarin derivatives, prothrombin time should be determined before starting therapy with simvastatin and frequently at the beginning of treatment to ensure that no significant alteration of prothrombin time occurs.

Once a stable prothrombin time occurs, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin. If the dose of simvastatin is changed, the same procedures should be repeated. No haemorrhages or prothrombin time changes have occurred in connection with simvastatin treatment in patients not taking anticoagulants.

Pregnancy and lactation
Pregnancy: Simvastatin is contraindicated in pregnancy.
Atherosclerosis develops slowly and therefore discontinuation of antihyperlipidaemic medication during pregnancy should have little impact on long-term treatment results of primary hypercholesterolaemia. Moreover, cholesterol and other products of cholesterol synthesis chain are important for foetal development, e.g. synthesis of steroids and cell membranes.
Because Simvastatin and other HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly other products of the cholesterol synthesis chain, simvastatin is contraindicated for use in pregnancy and should only be used in women of childbearing potential, if adequate contraceptive methods are used. An interval of one month should elapse between end of therapy with Simvastatin and planned conception.
If the patient becomes pregnant while taking simvastatin, the treatment should be discontinued and the patient to be informed of the potential adverse reactions of the medicinal product to the foetus.
Lactation: Simvastatin may have serious adverse reactions on infants, treatment with simvastatin is not recommended during breast feeding.

Effects on ability to drive and use machines
Simvastatin has no or negligible influence on the ability to drive and use machines.

Undesirable effects
Blood and lymphatic system disorders
Rare (>1/10000, <1/1000): Anaemia.
Nervous system disorders
Uncommon (>1/1000, <1/100): Headache.
Rare (>1/10000, <1/1000): Paresthesias, peripheral neuropathy, dizziness.
Gastrointestinal disorders
Common (>1/100): Constipation, abdominal pain, flatulence, nausea.
Uncommon (>1/1000, <1/100): Dyspepsia, diarrhoea.
Rare (>1/10000, <1/1000): Vomiting.
Hepatic disorders
Rare (> 1 /10000, < 1 /1000): Icterus, hepatitis, pancreatitis.
Skin and subcutaneous tissue disorders
Uncommon (>1/1000, <1/100): Exanthema, skin rash, pruritus.
Rare (> 1 /10000, < 1 /1000): Alopecia.
Musculoskeletal, connective tissue and bone disorders
Rare (>1/10000, <1/1000): Myopathy, myalgia, muscular cramp, rhabdomyolysis.
General disorders and administration site conditions
Uncommon (>1/1000, <1/100): Asthenia.

An apparent hypersensitivity syndrome occurs rarely. It is associated with some of the following symptoms: angioedema, lupus-like syndrome, polymyalgia rheumatic, vasculitis, thrombocytopenia, eosinophilia, elevation of ESR, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise. 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. 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).

Overdosage
In cases of overdose, general therapeutic measures should be adopted and liver function should be monitored.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Simvastatin is a synthetic blood lipid-lowering agent deriving from a fermentation product of Aspergillus terreus.
After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed to the corresponding beta-hydroxyacid. This main metabolite of simvastatin inhibits 3-hydroxy- 3- methyl-glutaryl-coenzyme A (HMG-CoA) reductase which catalyses an early step in the biosynthesis of cholesterol limiting the rate of the total reaction. At daily doses of 10 to 80 mg, simvastatin reduced total plasma cholesterol, LDL and VLDL cholesterol.
Simvastatin also slightly increased HDL cholesterol thus reducing the LDL/HDL ratio and total cholesterol/ HDL ratio.
Patients with hypertriglyceridaemia (TG concentration exceeding 2.25 mmol/l), simvastatin reduces the plasma triglyceride concentration by Upto 30%.
Treatment with simvastatin also results in a substantial reduction of Apo-B.
The active form of simvastatin specifically inhibits HMG-CoA reductase which catalyses the conversion of HMG-CoA to mevalonate. As the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol, treatment with simvastatin is not expected to cause accumulation of potentially toxic sterols. In addition, HMG-CoA is easily converted back into acetyl-CoA which is a common precursor for many biosynthetic reactions.
Simvastatin is very effective in reducing total and LDL cholesterol in plasma in heterozygous familial and non-familial hypercholesterolaemia and in mixed hyperlipidaemia where particularly the cholesterol level is elevated. A clear effect was seen within two weeks and the maximum therapeutic response was achieved within 4 to 6 weeks. The response is maintained on continued treatment. Total cholesterol is found to return to pre-treatment levels when simvastatin treatment is discontinued. Simvastatin does not cause increase in biliary lithogenicity and therefore, would not be expected to increase the incidence of cholelithiasis.
Furthermore, Simvastatin reduced the risk of coronary revascularization procedures (coronary bypass grafts or percutaneous transluminal coronary angioplasty) by 37%.
Simvastatin reduces the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels.

Pharmacokinetic properties
Simvastatin is a pro-drug (inactive lactone) and is hydrolysed to its -hydroxy acid, which is a potent inhibitor of HMG-CoA reductase. The pharmacokinetics is linear within the therapeutic dose range.

Absorption
Simvastatin is well absorbed, but undergoes extensive first-pass extraction. The bioavailability of active inhibitors is less than 5%. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration. Concomitant food intake does not affect absorption.

Distribution
The protein binding of simvastatin and its active metabolite is >95%.

Elimination
The major metabolites of simvastatin in human plasma are Simvastatin hydroxy acid and four other less active metabolites. After oral administration of radioactive simvastatin 13% was excreted in the urine and 60% in the faeces within 96 hours after administration.
The radioactivity detected in the faeces consisted of biliary excreted metabolites and unchanged drug as well as unabsorbed drug. The elimination half-live of active HMGCoA reductase inhibitors is about 2 hours.

PHARMACEUTICAL PARTICULARS

List of excipients
Simvastatin Tablets 5 mg: Ascorbic Acid, Lactose Monohydrate, Microcrystalline cellulose (Avicel PH 101), Microcrystalline cellulose (Avicel PH 112), Pregelatinised Starch, Citric Acid Monohydrate, Butyl Hydroxy Anisole, Isopropyl alcohol, Magnesium Stearate, Opadry Yellow '20A52229' (Hydroxypropyl cellulose, Hypromellose 6cP, Iron oxide yellow, Talc and Titanium dioxide) and Purified Water.
Simvastatin Tablets 10 mg and 20 mg: Ascorbic Acid, Lactose Monohydrate, Microcrystalline cellulose (Avicel PH 101), Microcrystalline cellulose (Avicel PH 112), Pregelatinised Starch, Citric Acid Monohydrate, Butyl hydroxy anisole, Isopropyl alcohol, Magnesium Stearate, Opadry Pink '20A54239' (Hydroxypropyl cellulose, Hypromellose 6cP, Iron oxide red, Iron oxide yellow, Talc and Titanium dioxide) and Purified Water

Simvastatin Tablets 40 mg and 80 mg: Ascorbic acid, Lactose Monohydrate, Microcrystalline cellulose (Avicel PH 101), Microcrystalline cellulose (Avicel PH 112), Pregelatinised Starch, Citric Acid Monohydrate, Isopropyl alcohol, Butyl hydroxy anisole, Magnesium Stearate, Opadry Pink '20A54211' (Hydroxypropyl cellulose, Hypromellose 6cP, Iron oxide red, Talc and Titanium dioxide) and Purified Water.

Incompatibilities
Not applicable

Shelf life
Please refer outer package for expiry date.

Special precautions for storage
Do not store above 30°C.

Nature and contents of container:
KARDAK 5, KARDAK 10, KARDAK 20, KARDAK 40 and KARDAK 80: Blister pack of 10 X 10's tablets.

Product Owner
AUROBINDO
Aurobindo Pharma Ltd.,
Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad-500038,
Telangana State, India.

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