KARDAK 10 (Simvastatin Tablets 10mg)
KARDAK 20 (Simvastatin Tablets 20mg)
KARDAK 40 (Simvastatin Tablets 40mg)
KARDAK 80 (Simvastatin Tablets 80mg)

Description and Composition:

KARDAK 10 (Simvastatin Tablets 10 mg)

Light pink coloured, round shaped, biconvex, film coated tablets, debossed with' A' on one side and '01'on the other side. Each film coated tablet contains: Simvastatin Ph.Eur. 10mg

KARDAK 20 (Simvastatin Tablets 20 mg)

Light pink coloured, round shaped, biconvex, film coated tablets, debossed with 'A' on one side and '02' on the other side. Each film coated tablet contains: Simvastatin Ph Eur. 20mg

KARDAK 40 (Simvastatin Tablets 40 mg)

Pink coloured, round shaped, biconvex, film coated tablets, debossed with 'A' on one side and '03'on the other side. Each film coated tablet contains: Simvastatin Ph.Eur. 40mg

KARDAK 80 (Simvastatin Tablets 80 mg)

Pink coloured, capsule shaped, biconvex, film coated tablets, debossed with 'A' on one side and '04' on the other side. Each film coated tablet contains: Simvastatin Ph.Eur. 80mg

Pharmacodynamics
Simvastatin is a synthetic blood lipid-lowering agent deriving from fermentation product of Aspergillus terreus.

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed to the corresponding betahydroxyacid. 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 up to 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 HMGCoA 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.

Pharmacokinetics

Simvastatin is a prodrug (inactive lactone) and is hydrolyses to its β-hydroxy acid, which is a potent inhibitor of HMG-CoA reductase. The pharmacokinetics is linear within the therapeutics 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 HMG-CoA reductase inhibitors is about 2 hours.

Indications

1) REDUCTIONS IN RISK OF CORONARY HEART DISEASE (CHD) MORTALITY AND CARDIOVASCULAR EVENTS In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, KARDAK 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.

2) HYPERLIPIDEMIA KARDAK 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 hypercholes terolemia or combined (mixed) hyperlipidemia when response to diet and other nonpharmaco-logical measures is inadequate. KARDAK therefore, lowers theLDL-C/HDL-C and the total-C/HDL-C ratios.

Recommended dose

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.

The 80 mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

The 80 mg dose is only recommended in patients at high risk for cardiovascular compilations who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the potential risks.

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 10-20 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:
The usual dose of Simvastatin is 20 to 40 mg/day given as a single dose in the evening in patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia). Drug therapy can be initiated simultaneously with diet and exercise.

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 Fibrates (other than gemfibrozil and fenofibrate) concomitantly with Kardak, the dose of Kardak should not exceed 10mg/day.

In patients taking amiodarone, verapamil or diltiazem concomitantly with Kardak, the dose of Kardak should not exceed 20mg/day.

In patients taking amlodipine or lipid-lowering dose of niacin (≥1g/day) concomitantly with Kardak, the dose of Kardak 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:
No dosage adjustment is necessary.

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

Recommended Dosage Schedule:
The patient should be placed on a conventional cholesterol-lowering diet before initiating simvastatin treatment and should continue on this diet during treatment with simvastatin.
Simvastatin film-coated tablets should be taken with water. The tablets can be taken either on an empty stomach or after a meal.

Mode of administration
Oral route of administration.
Recommended Dosage Schedule:
The patient should be placed on a conventional cholesterol-lowering diet before initiating simvastatin treatment and should continue on this diet during treatment with simvastatin.
Simvastatin film-coated tablets should be taken with water. The tablets can be taken either on an empty stomach or after a meal.

Contraindication
Contraindicated in patients with hypersensitivity 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.

Warning and precautions
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 rhabdomyolysis.
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 HMGCoA 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 (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 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:
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 bene t/risk assessment should be made before switching to high dosages e.g. 80 mg.

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.

The combined use of simvastatin with fibrates or niacin is not recommended unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination.

The combination of simvastatin with other fibrates or niacin should explicitly be restricted to patients with severe combined hyperlipidaemia and a high cardiovascular risk. Addition of these drugs to simvastatin typically provides little additional reduction in LDL-cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with simvastatin, the risk of myopathy is less with niacin than with the fibrates. Concomitant administration of simvastatin with gemfibrozil should be avoided due to the Pharmacokinetics interaction.

In patients taking concomitant cyclosporin, 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, HIV-protease inhibitors, delavirdine and amiodarone is contraindicated. Concomitant use of simvastatin with erythromycin, clarithromycin, telithromycin, verapamil or nefazodone is not recommended. If no alternative to a short course of treatment with itraconazole, 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 should be avoided unless the benefits of combined therapy outweigh the increased risk.

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.

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 glucosegalactose malabsorption should not take this medicine.

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 treatment;
• Muscle biopsy showing necrotizing myopathy without significant inflammation;
• Improvement with immunosuppressive agents.

Interactions with other medicaments

Contraindicated Drugs
Concurrent use of fibrates may cause severe myositis and myoglobinuria.
Gemfibrozil and other fibrates, plasma lipid-lowering doses of niacin (nicotinic acid) (1 g/day). When these medicinal products are used concomitantly with simvastatin, the risk of myopathy is increased and concurrent use should be avoided. Concurrent use of fibrates may cause severe myositis and myoglobinuria.
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.
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.
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.

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

Amiodarone:
The risk of myopathy or rhabdomyolysis is increased when simvastatin is given concomitantly with amiodarone. In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.
Combination with ketoconazole, itraconazole, HIV-protease inhibitors, delavirdine and amiodarone is contra-indicated.

Calcium channel blockers:
Caution should be exercised when combining simvastatin and nefazodone, verapamil, erythromycin, clarithromycin or telithromycin.
Verapamil or diltiazem: In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem.
Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine.

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.

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 (≥ 1 g/day) of niacin.

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.

Side effects

Blood and lymphatic system disorders

Rare: Anaemia.

Nervous system disorders

Uncommon: Headache. Rare: Paresthesias, peripheral neuropathy, dizziness. *Gastrointestinal disorders*

Common: Constipation, abdominal pain, flatulence, nausea. Uncommon: Dyspepsia, diarrhoea.

Rare: Vomiting. *Hepatic disorders*

Rare: Icterus, hepatitis, pancreatitis.

Skin and subcutaneous tissue disorders

Uncommon: Exanthema, skin rash, pruritus.

Rare: Alopecia.

Musculoskeletal, connective tissue and bone disorders

Rare: Myopathy, myalgia, muscular cramp, rhabdomyolysis.

Frequency not known: Immune-mediated necrotizing myopathy

General disorders and administration site conditions

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

Post Marketing Reports

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.

Symptoms and Treatment of over dose
In cases of overdose, general therapeutic measures should be adopted and liver function should be monitored.

Storage condition
Do not store above 30°C.

Shelf life
36 months.

Presentation
For Kardak 10 mg:
10 Blisters of 10 tablets each are packed in a printed carton along with a pack insert.

For Kardak 20 mg:
3 blisters of 10 tablets each are packed in a printed carton along with a package insert.
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For Kardak 40 mg:
3 Blisters of 10 tablets each are packed in a printed carton along with a package insert.
10 Blisters of 10 tablets each are packed in a printed carton along with a pack insert.

For Kardak 80 mg:
10 Blisters of 10 tablets each are packed in a printed carton along with a pack insert.

Manufactured by
Unit III, Survey No. 313 and 314, Bachupally, Bachupally Mandal, Medchal-Malkajgiri District, Telangana State, INDIA.

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