LIPOSTAT ®

PRAVASTATIN SODIUM

TABLETS

NAME OF THE MEDICINAL PRODUCT

Pravastatin sodium, 20 mg, tablet

Pravastatin sodium, 40 mg, tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION

LIPOSTAT*, 20 mg, tablet* .Each tablet contains 20 mg of pravastatin sodium.

LIPOSTAT*, 40 mg, tablet* .Each tablet contains 40 mg of pravastatin sodium.

Excipients

Microcrystalline cellulose, lactose, magnesium oxide, magnesium stearate, povidone , croscarmellose sodium and ferric oxide yellow .

PHARMACEUTICAL FORM

LIPOSTAT*, 20 mg, tablet* .A yellow colored, capsule-shaped, biconvex tablets with '20' engraved on one side and notched scores on the other side. **LIPOSTAT***, 40 mg, tablet* .A yellow coloured, capsule-shaped, biconvex tablets with 40 engraved on one side and notched scores on the other side.

CLINICAL INFORMATION

Indications

For:

Hypercholesterolaemia

As an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate in:

- primary hypercholesterolaemia,
- mixed dyslipidaemia,

- heterozygous familial hypercholesterolaemia in children and adolescent patients **(**8-18 years of age).

Primary prevention

Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolaemia and at high risk of a first cardiovascular event, as an adjunct to diet.

Secondary prevention

Reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors.

In hypercholesterolaemic patients with atherosclerotic cardiovascular disease, pravastatin sodium is indicated as an adjunct to diet to slow the progressive course of atherosclerosis and reduce the incidence of clinical cardiovascular events.

Post transplantation hyperlipidaemia

Reduction of post transplantation hyperlipidaemia in patients receiving immunosuppressive therapy following solid organ transplantation.

Dosage and Administration

Prior to initiating **LIPOSTAT** , secondary causes of hypercholesterolaemia should be excluded and the patient should be placed on a standard lipid-lowering diet which should be continued during treatment. **LIPOSTAT** is administered orally once daily preferably in the evening with or without food.

Route of Administration

For oral administration.

Adults

Hypercholesterolaemia

The recommended dose range is 10-40 mg once daily. The therapeutic response is seen within a week and the full effect of a given dose occurs within four weeks, therefore periodic lipid determinations should be performed and the dosage adjusted accordingly. The maximum daily dose is 40 mg.

Cardiovascular prevention

In all preventive morbidity and mortality trials, the only studied starting and maintenance dose was 40 mg daily.

Dosage after transplantation

Following organ transplantation a starting dose of 20 mg per day is recommended in patients receiving immunosuppressive therapy. Depending on the response of the lipid parameters, the dose may be adjusted up to 40 mg under close medical supervision.

Children

Children and adolescents (8-18 years of age) with heterozygous familial hypercholesterolaemia

The recommended dose range is 10-20 mg once daily between 8 and 13 years of age as doses greater than 20 mg have not been studied in this population and 10-40 mg daily between 14 and 18 years of age.

Elderly

There is no dose adjustment necessary in these patients unless there are predisposing risk factors.

Renal or hepatic impairment

A starting dose of 10 mg a day is recommended in patients with moderate or severe renal impairment or significant hepatic impairment. The dosage should be adjusted according to the response of lipid parameters and under medical supervision.

Caution should be exercised when pravastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see Sections: Warnings and Precautions; Adverse Reactions)*.

Concomitant therapy

The lipid lowering effects of pravastatin sodium on total cholesterol and LDL-cholesterol are enhanced when combined with a bile acid-binding resin (e.g. colestyramine, colestipol). Pravastatin sodium should be given either one hour before or at least four hours after the resin *(see Section Interactions)*. For patients taking ciclosporin with or without other immunosuppressive medicinal products, treatment should begin with 20 mg of pravastatin sodium once daily and titration to 40 mg should be performed with caution (*see Section Interactions*).

Contraindications

Pravastatin sodium is contraindicated in:

- hypersensitivity to the active substance or to any of the excipients,
- active liver disease including unexplained persistent elevations of serum transaminase elevation exceeding 3 x the upper limit of normal (ULN),
- pregnancy and lactation *(see Section Pregnancy and Lactation)*.

Warnings and Precautions

Muscle disorders (myalgia, myopathy, rhabdomyolysis)
As with other HMG-CoA reductase inhibitors (statins), pravastatin has been associated with the onset of myalgia, myopathy and very rarely, rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness, or muscle cramps.

In such cases creatine kinase (CK) levels should be measured. Statin therapy should be temporarily interrupted when CK levels are > 5 x ULN or when there are severe clinical symptoms. Very rarely (in about 1 case over 100,000 patient-years), rhabdomyolysis occurs, with or without secondary renal insufficiency.

Rhabdomyolysis is an acute potentially fatal condition of skeletal muscle which may develop at any time during treatment and is characterised by massive muscle destruction associated with major increase in CK (usually > 30 or 40 x ULN) leading to myoglobinuria.

The risk of myopathy with statins appears to be exposure-dependent and therefore may vary with individual drugs (due to lipophilicity and pharmacokinetic differences), including their dosage and potential for drug interactions. Although there is no muscular contraindication to the prescription of a statin, certain predisposing factors may increase the risk of muscular toxicity and therefore justify a careful evaluation of the benefit/risk and special clinical monitoring. CK measurement is indicated before starting statin therapy in these patients.

The risk and severity of muscular disorders during statin therapy is increased by the co-administration of interacting medicines. The use of fibrates alone is occasionally associated with myopathy. The combined use of a statin and fibrates should generally be avoided (*see Section Interactions*). The co-administration of statins and nicotinic acid should be used with caution.

An increase in the incidence of myopathy has also been described in patients receiving other statins in combination with inhibitors of cytochrome P450 metabolism. This may result from

pharmacokinetic interactions that have not been documented for pravastatin. When associated with statin therapy, muscle symptoms usually resolve following discontinuation of statin therapy.

Monitoring of creatine kinase (CK)

Routine monitoring of creatine kinase (CK) or other muscle enzyme levels is not recommended in asymptomatic patients on statin therapy. However, measurement of CK is recommended before starting statin therapy in patients with special predisposing factors, and in patients developing muscular symptoms during statin therapy, as described below. If CK levels are significantly elevated at baseline (> 5 x ULN), CK levels should be re-measured about 5 to 7 days later to confirm the results. When measured, CK levels should be interpreted in the context of other potential factors that can cause transient muscle damage, such as strenuous exercise or muscle trauma.

Before treatment initiation

Caution should be used in patients with predisposing factors such as renal impairment, hypothyroidism, previous history of muscular toxicity with a statin or fibrate, personal or familial history of hereditary muscular disorders, or alcohol abuse. In these cases, CK levels should be measured prior to initiation of therapy. CK measurement should also be considered before starting treatment in persons over 70 years of age especially in the presence of other predisposing factors in this population. If CK levels are significantly elevated (> 5 x ULN) at baseline, treatment should not be started and the results should be re-measured after 5 - 7 days. The baseline CK levels may also be useful as a reference in the event of a later increase during statin therapy.

During treatment

Patients should be advised to report promptly unexplained muscle pain, tenderness, weakness or cramps. In these cases, CK levels should be measured. If a markedly elevated (> 5 x ULN) CK level is detected, statin therapy must be interrupted. Treatment discontinuation should also be considered if the muscular symptoms are severe and cause daily discomfort, even if the CK increase remains ≤ 5 x ULN. If symptoms resolve and CK levels return to normal, then reintroduction of statin therapy may be considered at the lowest dose and with close monitoring. If a hereditary muscular disease is suspected in such patients, restarting statin therapy is not recommended.

Hepatic disorders

As with other lipid-lowering agents, moderate increases in liver transaminase levels have been observed. In the majority of cases, liver transaminase levels have returned to their baseline value without the need for treatment discontinuation. Special attention should be given to patients who develop increased transaminase levels and therapy should be discontinued if increases in alanine

aminotransferase (ALT) and aspartate aminotransferase (AST) exceed three times the upper limit of normal and persist *(see Sections: Dosage and Administration; Adverse Reactions)*.

Caution should be exercised when pravastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion.

Severe respiratory failure

Pravastatin should be used with caution in patients with severe respiratory failure. Breathing problems including persistent cough and/or shortness of breath or fever may occur.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Homozygous familial hypercholesterolaemia

Pravastatin has not been evaluated in patients with homozygous familial hypercholesterolaemia. Therapy is not suitable when hypercholesterolaemia is due to elevated HDL-Cholesterol.

Paediatric patients

In children before puberty, the benefit/risk of treatment should be carefully evaluated by physicians before treatment initiation.

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines *(see Section Adverse Reactions)*.

Lactose

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interactions

Fibrates

The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, have been reported when fibrates are co-administered with other statins. These adverse events with pravastatin cannot be excluded; therefore the combined use of pravastatin and fibrates
(e.g. gemfibrozil, fenofibrate) should generally be avoided. If this combination is considered necessary, careful clinical and CK monitoring of patients on such regimen is required (*see Section Warnings and Precautions*).

Colestyramine/ Colestipol

Concomitant administration resulted in approximately 40 to 50% decrease in the bioavailability of pravastatin. There was no clinically significant decrease in bioavailability or therapeutic effect when pravastatin was administered one hour before or four hours after colestyramine or one hour before colestipol *(see Section Dosage and Administration)*.

Ciclosporin

Concomitant administration of pravastatin and ciclosporin leads to an approximately
4-fold increase in pravastatin systemic exposure. In some patients, however, the increase in pravastatin exposure may be larger. Clinical and biochemical monitoring of patients receiving this combination is recommended (*see Section Dosage and Administration*).

Warfarin and other oral anticoagulants

Bioavailability parameters at steady state for pravastatin were not altered following administration with warfarin. Chronic dosing of the two products did not produce any changes in the anticoagulant action of warfarin.

Products metabolised by cytochrome P450

Pravastatin is not metabolised to a clinically significant extent by the cytochrome P450 system. This is why products that are metabolised by, or inhibitors of, the cytochrome P450 system can be added to a stable regimen of pravastatin without causing significant changes in the plasma levels of pravastatin, as have been seen with other statins.

The absence of a significant pharmacokinetic interaction with pravastatin has been specifically demonstrated for several products, particularly those that are substrates /inhibitors of CYP3A4 e.g. diltiazem, verapamil, itraconazole, ketoconazole, protease inhibitors, grapefruit juice and CYP2C9

inhibitors (e.g. fluconazole). In one of two interaction studies with pravastatin and erythromycin a statistically significant increase in pravastatin AUC (70%) and C_{max} (121%) was observed. In a similar study with clarithromycin a statistically significant increase in AUC (110%) and C_{max} (127%) was observed. Although these changes were minor, caution should be exercised when associating pravastatin with erythromycin or clarithromycin.

Other products
In interaction studies, no statistically significant differences in bioavailability were observed when pravastatin was administered with acetylsalicylic acid, antacids (when given one hour prior to pravastatin), nicotinic acid or probucol.

Pregnancy and Lactation

Fertility

There are no relevant data available.

Pregnancy

Pravastatin is contraindicated during pregnancy and should be administered to women of childbearing potential only when such patients are unlikely to conceive and have been informed of the potential risk.

Special caution is recommended in adolescent females of childbearing potential to ensure proper understanding of the potential risk associated with pravastatin therapy during pregnancy. If a patient plans to become pregnant or becomes pregnant, the doctor has to be informed immediately and pravastatin should be discontinued because of the potential risk to the foetus *(see Section Contraindications).*

Lactation

A small amount of pravastatin is excreted in human breast milk, therefore pravastatin is contraindicated during breastfeeding *(see Section Contraindications).*

Ability to perform tasks that require judgement, motor or cognitive skills

Pravastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness and visual disturbances may occur during treatment.

Adverse Reactions

Clinical Trial Data

Adverse reactions are ranked under headings of frequency using the following convention:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).

Pravastatin has been studied at 40 mg in seven randomised double-blind placebo-controlled trials involving over 21,000 patients treated with pravastatin (n = 10764) or placebo (n = 10719), representing over 47,000 patients years of exposure to pravastatin. Over 19,000 patients were followed for a median of 4.8 - 5.9 years.

The following adverse drug reactions were reported; none of them occurred at a rate in excess of 0.3% in the pravastatin group compared to the placebo group.

Nervous system disorders
Uncommon: dizziness, headache, sleep disturbance, insomnia

Eye disorders
Uncommon: vision disturbance (including blurred vision and diplopia)

Gastrointestinal disorders
Uncommon: dyspepsia/heartburn, abdominal pain, nausea/vomiting, constipation, diarrhoea, flatulence

Hepatobiliary disorders
Not known: elevations of serum transaminases *(see Section Warnings and Precautions)*

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash, urticaria, scalp/hair abnormality (including alopecia)

Musculoskeletal and connective tissue disorders

Not known: musculoskeletal pain, arthralgia, muscle cramps, myalgia, muscle weakness, elevated CK levels

Renal and urinary disorders
Uncommon: abnormal urination (including dysuria, frequency, nocturia)

Reproductive system and breast disorders
Uncommon: sexual dysfunction

General disorders
Uncommon: fatigue

Post Marketing Data

In addition to the above the following adverse events have been reported during post marketing experience of pravastatin:

Nervous system disorders
Very rare: peripheral polyneuropathy (in particular if used for long period of time, paraesthesia)

Immune system disorders
Very rare: hypersensitivity reactions: anaphylaxis, angioedema, lupus erythematous-like syndrome

Respiratory, thoracic and mediastinal disorders
Not known: breathing problems, persistent cough, shortness of breath

Gastrointestinal disorders
Very rare: pancreatitis

Hepatobiliary disorders
Very rare: jaundice, hepatitis, fulminant hepatic necrosis *(see Section Warnings and Precautions)*

Musculoskeletal and connective tissue disorders
Very rare: rhabdomyolysis, which can be associated with acute renal failure secondary to myoglobinuria, myopathy, myositis, polymyositis
Not known: tendon disorders (sometimes complicated by rupture)

The following adverse events have been reported with some statins:

- nightmares,
- memory loss,
- depression,
- exceptional cases of interstitial lung disease, especially with long term therapy (*see Section Warnings and Precautions*),
- diabetes mellitus: frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30kg/m^2, raised triglycerides, history of hypertension) *(see Section Warnings and Precautions)*.

Overdosage

Symptoms, signs, and treatment

To date there has been limited experience with overdosage of pravastatin. There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required.

Clinical Pharmacology

Pharmacodynamics

Pharmacotherapeutic group

HMG-CoA reductase inhibitors

ATC Code

C10AA03

Mechanism of Action

Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalysing the early rate-limiting step in cholesterol biosynthesis, and produces its lipid-lowering effect in two ways.

Firstly, with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and

clearance of circulating LDL-cholesterol. Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL-cholesterol, the LDLcholesterol precursor.

In both healthy subjects and patients with hypercholesterolaemia, pravastatin sodium lowers the following lipid values: total cholesterol, LDL-cholesterol, apolipoprotein B, VLDL-cholesterol and triglycerides; while HDL-cholesterol and apolipoprotein A are elevated.

Pharmacokinetics

Absorption

Pravastatin is administered orally in the active form. It is rapidly absorbed; peak serum levels are achieved 1 to 1.5 hours after ingestion. On average, 34% of the orally administered dose is absorbed, with an absolute bioavailability of 17%.

The presence of food in the gastrointestinal tract leads to a reduction in the bioavailability, but the cholesterol-lowering effect of pravastatin is identical whether taken with or without food. After absorption, 66% of pravastatin undergoes a first-pass extraction through the liver, which is the primary site of its action and the primary site of cholesterol synthesis and clearance of LDL-cholesterol. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes and with substantially less intake in other cells.

In view of this substantial first pass through the liver, plasma concentrations of pravastatin have only a limited value in predicting the lipid-lowering effect. The plasma concentrations are proportional to the doses administered.

Distribution

About 50% of circulating pravastatin is bound to plasma proteins. The volume of distribution is about 0.5 l/kg. A small quantity of pravastatin passes into the human breast milk.

Metabolism and Elimination

Pravastatin is not significantly metabolised by cytochrome P450 nor does it appear to be a substrate or an inhibitor of P-glycoprotein but rather a substrate of other transport proteins. Following oral administration, 20% of the initial dose is eliminated in the urine and 70% in the faeces. Plasma elimination half-life of oral pravastatin is 1.5 to 2 hours.

After intravenous administration, 47% of the dose is eliminated by the renal excretion and 53% by biliary excretion and biotransformation. The major degradation product of pravastatin is the 3-α-

hydroxy isomeric metabolite. This metabolite has one-tenth to one-fortieth the HMG-CoA reductase inhibitor activity of the parent compound.

The systemic clearance of pravastatin is 0.81 l/h/kg and the renal clearance is 0.38 l/h/kg indicating tubular secretion.

Accumulation of drug and/or metabolites may occur in patients with renal or hepatic insufficiency, although, as there are dual routes of elimination, the potential exists for compensatory excretion by the alternate route.

Special patient populations

Children

Mean pravastatin C_{max} and AUC values for paediatric subjects pooled across age and gender were similar to those values observed in adults after a 20 mg oral dose.

Hepatic impairment

Systemic exposure to pravastatin and metabolites in patients with alcoholic cirrhosis is enhanced by about 50% comparatively to patients with normal liver function.

Renal impairment

No significant modifications were observed in patients with mild renal impairment. However severe and moderate renal insufficiency may lead to a two-fold increase of the systemic exposure to pravastatin and metabolites.

Elderly

There are no relevant data available.

Clinical Studies

Not relevant for this product.

NON-CLINICAL INFORMATION

Based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity on reproduction, there are no other risks for the patient than those expected due to the pharmacological mechanism of action.

Repeated dose studies indicate that pravastatin may induce varying degrees of hepatotoxicity and myopathy; in general, substantive effects on these tissues were only evident at doses 50 or more times the maximum human mg/kg dose.

In vitro and *in vivo* genetic toxicology studies have shown no evidence of mutagenic potential.

In mice, a 2-year carcinogenicity study with pravastatin demonstrates at doses of 250 and 500 mg/kg/day (≥ 310 times the maximum human mg/kg dose) produces statistically significant increases in the incidence of hepatocellular carcinomas in males and females, and lung adenomas in females only.

In rats, a 2-year carcinogenicity study demonstrates at a dose of 100 mg/kg/day (125 times the maximum human mg/kg/dose) produces a statistically significant increase in the incidence of hepatocellular carcinomas in males only.

When administered to juvenile rats (postnatal days [PND] 4 through 80), 5 to 45 mg/kg/day, thinning of the corpus callosum was observed at serum pravastatin levels approximately ≥1 times (AUC) the maximum paediatric and adolescent dose of 40 mg. At pravastatin levels approximately ≥2 times (AUC) the 40 mg human dose, neurobehavioural changes were observed (enhanced startle response and increased errors in watermaze learning). No thinning of the corpus callosum was observed in rats dosed with pravastatin (≥ 250 mg/kg/day) beginning PND 35 for 3 months suggesting increased sensitivity in younger rats. The cause and significance of the corpus callosum thinning and neurobehavioural effects in juvenile rats are unknown.

Altered sperm endpoints and reduced fertility were observed in males at 335 times (AUC) the human dose. The no-observed effect-levels for reproductive endpoints were 1 (male) and 2 (female) times (AUC) the 40 mg human dose.

Presentation

LIPOSTAT tablets for oral administration providing 20 mg and 40mg pravastatin sodium.

Storage

Do not store above 25°C. Keep it tightly closed (protect from moisture). Protect from light.

NCDS version No: 2
Date: 26-Sep-2012