

MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE AND THE COMPANY

Material	Pravastatin Sodium Tablets USP 10 mg, 20 mg, 40 mg & 80 mg
Manufacturer	Lupin Limited Mumbai 400 098 INDIA
Distributor	Lupin Pharmaceuticals, Inc. Harborplace Tower, 21 st Floor 111, South Calvert Street Baltimore, MD 21202 United States Tel. 001-410-576-2000 Fax. 001-410-576-2221

2. COMPOSITION / INFORMATION ON INGREDIENTS

Ingredients	CAS	Quantity
Pravastatin Sodium	81093-37-0	10mg /Tablet; 20mg/Tablet; 40mg/Tablet & 80mg/Tablet
Non-hazardous ingredients	-----	q.s.

3. HAZARDOUS IDENTIFICATION

Fire and Explosion	Assume that this product is capable of sustaining combustion.
Health	Exposure might occur via skin; eyes; ingestion; inhalation. May cause sensitization by inhalation or skin contact.
Environment	No information is available about the potential of this product to produce adverse environmental effects.

4. FIRST AID MEASURES

Inhalation	Move individual to fresh air. Obtain medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance.
-------------------	---

Skin Contact

Remove contaminated clothing and flush exposed area with large amounts of water. Wash all exposed areas of skin with plenty of soap and water. Obtain medical attention if skin reaction occurs.

Eye Contact

Flush eyes with plenty of water. Get medical attention.

NOTES TO HEALTH PROFESSIONALS**Medical Treatment**

Treat according to locally accepted protocols. For additional guidance, refer to the current prescribing information or to the local poison control information center.

Drug Interactions**Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:**

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in three reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to two years concurrently with pravastatin 10-40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus one of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy.

Cytochrome P450 3A4 Inhibitors:

In vitro and *in vivo* data indicate that pravastatin is not metabolized by cytochrome P450 3A4 to a clinically significant extent. This has been shown in studies with known cytochrome P450 3A4 inhibitors. Other examples of cytochrome P450 3A4 inhibitors include ketoconazole, mibefradil, and erythromycin.

Diltiazem:

Steady-state levels of diltiazem (a known, weak inhibitor of P450 3A4) had no effect on the pharmacokinetics of pravastatin. In this study, the AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 3.6 and 4.3, respectively.

Itraconazole:

The mean AUC and C_{max} for pravastatin were increased by factors of 1.7 and 2.5, respectively, when given with itraconazole (a potent P450 3A4 inhibitor which also inhibits p-glycoprotein transport) as compared to placebo. The mean $t_{1/2}$ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

Antipyrine:

Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected.

Cholestyramine/Colestipol:

Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect.

Warfarin:

Concomitant administration of 40 mg pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.

Cimetidine:

The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin:

In a crossover trial involving 18 healthy male subjects given 20 mg pravastatin and 0.2 mg digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Cyclosporine:

Some investigators have measured cyclosporine levels in patients on pravastatin (up to 20 mg), and to date, these results indicate no clinically meaningful elevations in cyclosporine levels. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine.

Gemfibrozil:

In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max} , and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids (1 hour prior to pravastatin), cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when pravastatin sodium was administered.

Antidotes

No specific antidote exists.

5. FIRE-FIGHTING MEASURES**Fire and Explosion Hazards**

Assume that this product is capable of sustaining combustion.

Extinguishing Media

Water spray, carbon dioxide, dry chemical powder or appropriate foam.

Special Firefighting Procedures

For single units (packages): No special requirements needed. For larger amounts (multiple packages/pallets) of product: Since toxic, corrosive or flammable vapors might be evolved from fires involving this product and associated packaging, self contained breathing apparatus and full protective equipment are recommended for firefighters.

Hazardous Combustion Products

Hazardous combustion or decomposition products are expected when the product is exposed to fire.

6. ACCIDENTAL RELEASE MEASURES

Personal Precautions

Wear protective clothing and equipment consistent with the degree of hazard.

Environmental Precautions

For large spills, take precautions to prevent entry into waterways, sewers, or surface drainage systems.

Clean-up Methods

Collect and place it in a suitable, properly labeled container for recovery or disposal.

7. HANDLING AND STORAGE

Handling

No special precautions are necessary when handling packed product. In case of accident, avoid breathing dust from crushed tablets. Avoid contact with skin and eyes. Wash hands after use.

Storage

Store at 25°C (77° F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. Keep tightly closed (protect from moisture). Protect from light.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Wear appropriate clothing to avoid skin contact. Wash hands and arms thoroughly after handling.

9. PHYSICAL & CHEMICAL PROPERTIES

Physical Form

Tablets.

Appearance

10 mg: Yellow, capsule shaped, biconvex tablets.

20 mg: Yellow, capsule shaped, biconvex Tablets.

40 mg: Yellow, capsule shaped, biconvex Tablets.

80 mg: Yellow, oval shaped, biconvex Tablets.

10. STABILITY AND REACTIVITY

Stable under recommended storage conditions.

11. TOXICOLOGICAL INFORMATION

Oral Toxicity	Not expected to be toxic following ingestion of recommended maximum daily dose.
Inhalation Toxicity	Can produce respiratory irritation. Adverse effects might occur following inhalation.
Skin Effects	Irritation might occur following direct contact.
Eye Effects	Irritation might occur following direct contact with eyes.
Gastrointestinal	Decreased appetite.
Carcinogenesis, Mutagenesis, Impairment or of Fertility	<p>In a 2-year study in rats fed pravastatin at doses of 10, 30, 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). These effects in rats were observed at approximately 12 times the human dose (HD) of 80 mg based on body surface area mg/m^2 and at approximately 4 times the human dose, based on AUC.</p> <p>In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p < 0.0001$). At these doses, lung adenomas in females were increased ($p = 0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the human dose of 80 mg, based on AUC. In another 2-year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the human dose of 80 mg, based on AUC), there were no drug-induced tumors.</p> <p>No evidence of mutagenicity was observed <i>in vitro</i>, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of <i>Salmonella typhimurium</i> or <i>Escherichia coli</i>; a forward mutation assay in L5178Y TK +/- mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using <i>Saccharomyces cerevisiae</i>. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.</p>

Pregnancy- Pregnancy Category X

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 10X (rabbit) or 120X (rat) the human exposure based on surface area (mg/meter²). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review⁷ of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with pravastatin during pregnancy, treatment should be immediately discontinued as soon as pregnancy is recognized. Pravastatin (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking pravastatin should not nurse

Overdose

To date, there has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required.

12. ECOLOGICAL INFORMATION

No information available

13. DISPOSAL CONSIDERATION**Waste Disposal Method**

Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

14. TRANSPORT INFORMATION

The Material Safety Data Sheet (MSDS) should accompany all shipments for reference in the event of spillage or accidental release. Transportation and shipping of this product is not restricted. It has no known, significant hazards requiring special packaging or labeling for air, maritime, or ground transport purposes.

15. REGULATORY INFORMATION

No information available.

16. OTHER INFORMATION

The above information is believed to be correct but does not purport to be all-inclusive and shall be used only as a guide. Nothing herein shall be deemed to create any warranty, express or implied. It is the responsibility of the user to determine the applicability of this information and the suitability of the material or product for any particular purpose.

Lupin shall not be held liable for any damage resulting from handling or from contact with the above product. Lupin reserves the right to revise this MSDS.