

MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE AND THE COMPANY

Material Lovastatin Tablets USP
10 mg, 20 mg & 40 mg

Manufacturer Lupin Limited
Mumbai 400 098 INDIA

Distributor Lupin Pharmaceuticals, Inc.
Harborplace Tower, 21st Floor
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2. COMPOSITION / INFORMATION ON INGREDIENTS

Ingredients	CAS	Quantity
Lovastatin	75330-75-5	10mg /Tablet; 20mg/Tablet; 40mg/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***CYP3A4 Interactions***

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of lovastatin.

Itraconazole**Ketoconazole****Erythromycin****Clarithromycin****Telithromycin****HIV protease inhibitors****Nefazodone****Large quantities of grapefruit juice (>1 quart daily)****Interactions with lipid-lowering drugs that can cause myopathy when given alone**

The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent CYP3A4 inhibitors, but which can cause myopathy when given alone.

Gemfibrozil**Other fibrates****Niacin (nicotinic acid) (≥1 g/day)*****Other drug interactions***

Cyclosporine or Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of lovastatin.

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class.

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents: In pharmacokinetic studies of lovastatin in hypercholesterolemic noninsulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide.

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]. Lovastatin tablets must be protected from light and stored in a well-closed, light-resistant container.

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: Light green, oval shaped tablets.

20 mg: Light green, circular tablets.

40 mg: Light green, circular, 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	<p>In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of lovastatin.)</p> <p>There was an increase in incidence of papilloma in the non-glandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.</p> <p>In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males at drug exposures between 2-7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).</p> <p>An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.</p>

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high dose females and mid- and high dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy- Pregnancy Category X

Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations in offspring of pregnant mice and rats dosed during gestation at 80 mg/kg/day (affected mouse fetuses/total: 8/307 compared to 4/289 in the control group; affected rat fetuses/total: 6/324 compared to 2/308 in the control group). Female rats dosed before mating through gestation at 80 mg/kg/day also had fetuses with skeletal malformations (affected fetuses/total: 1/152 compared to 0/171 in the control group). The 80 mg/kg/day dose in mice is 7 times the human dose based on body surface area and in rats results in 5 times the human exposure based on AUC. In pregnant rats given doses of 2, 20, or 200 mg/kg/day and treated through lactation, the following effects were observed: neonatal mortality (4.1%, 3.5%, and 46%, respectively, compared to 0.6% in the control group), decreased pup body weights throughout lactation (up to 5%, 8%, and 38%,

respectively, below control), supernumerary ribs in dead pups (affected fetuses/total: 0/7, 1/17, and 11/79, respectively, compared to 0/5 in the control group), delays in ossification in dead pups (affected fetuses/total: 0/7, 0/17, and 1/79, respectively, compared to 0/5 in the control group) and delays in pup development (delays in the appearance of an auditory startle response at 200 mg/kg/day and free-fall righting reflexes at 20 and 200 mg/kg/day).

Direct dosing of neonatal rats by subcutaneous injection with 10 mg/kg/day of the open hydroxyacid form of lovastatin resulted in delayed passive avoidance learning in female rats (mean of 8.3 trials to criterion, compared to 7.3 and 6.4 in untreated and vehicle-treated controls; no effects on retention 1 week later) at exposures 4 times the human systemic exposure at 80 mg/day based on AUC. No effect was seen in male rats. No evidence of malformations was observed when pregnant rabbits were given 5 mg/kg/day (doses equivalent to a human dose of 80 mg/day based on body surface area) or a maternally toxic dose of 15 mg/kg/day (3 times the human dose of 80 mg/day based on body surface area).

Rare clinical reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis[†] of greater than 200 prospectively followed pregnancies exposed during the first trimester to lovastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was sufficient to exclude a 3-fold or greater increase in congenital anomalies over the background incidence. Maternal treatment with lovastatin may reduce the fetal levels of mevalonate, which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia. For these reasons, lovastatin should not be used in women who are pregnant, or can become pregnant. Lovastatin 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. Treatment should be immediately discontinued as soon as pregnancy is recognized.

Nursing Mothers

It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking lovastatin should not nurse their infants.

Overdose

To date, there has been limited experience with overdosage of lovastatin. 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.