LIPONORM™

ATORVASTATIN

Coated Tablets
Made in Argentina
Only With Prescription

Formula qualitative-quantitative:

Each coated tablet of **10 mg** contains

Atorvastatin calcium trihydrate	10,85 mg
Avicel pH102 Vivapur (Microcrystalline cellulose)	80,00 mg
Lactose monohydrate	46,15 mg
Ac-Di-Sol (Sodium croscarmellose)	4,00 mg
Magnesium stearate.	3,00 mg
Aerosil (Silycic dioxide)	6,00 mg
Opadry IS-7003	6,00 mg
Carbowax 6000	0,12 mg
Polyethylene glycol	0,24 mg
Iron oxide yellow	0,01 mg

Each tablet of **20 mg** contains:

Atorvastatin calcium trihydrate	21,70 mg
Avicel pH102 Vivapur (Microcrystalline cellulose)	160,00 mg
Lactose monohydrate	92,30 mg
Ac-Di-Sol (Sodium croscarmellose)	8,00 mg
Magnesium stearate	6,00 mg
Aerosil (Silycic dioxide)	12,00 mg
Opadry IS-7003	8,00 mg
Carbowax 6000	0,16 mg
Polyethylene glycol	0,32 mg
Iron oxide yellow	0,01 mg

Each tablet of **40 mg** contains:

Atorvastatin calcium trihydrate	43,40 mg
Avicel pH102 Vivapur (Microcrystalline cellulose)	320,00 mg
Lactose monohydrate	184,60 mg
Ac-Di-Sol (Sodium croscarmellose)	16,00 mg
Magnesium stearate	12,00 mg
Aerosil (Silycic dioxide)	24,00 mg
Opadry IS-7003	24,00 mg
Carbowax 6000	0,48 mg
Polyethylene glycol	0,96 mg
Iron oxide yellow	0,04 mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

PHARMACOKINETICS AND DRUG METABOLISM

◆ **Absorption**: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to Atorvastatin dose. The absolute bioavailability of Atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether Atorvastatin is given with or without food. Plasma Atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

◆ **Distribution**: Mean volume of distribution of Atorvastatin is approximately 381 liters. Atorvastatin is >/=98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, Atorvastatin is likely to be secreted in human milk.

◆ **Metabolism**: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of Atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of Atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of Atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

◆ **Excretion**: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of Atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of Atorvastatin is recovered in urine following oral administration.

◆ **Special Populations**

- **Geriatric**: Plasma concentrations of Atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age >/=65 years) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of Atorvastatin.
- **Pediatric**: Pharmacokinetic data in the pediatric population are not available.
- **Gender**: Plasma concentrations of Atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with Atorvastatin between men and women.

◆ **Renal Insufficiency**: Renal disease has no influence on the plasma concentrations or LDL-C reduction of Atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

◆ **Hemodialysis**: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of Atorvastatin since the drug is extensively bound to plasma proteins.

◆ **Hepatic Insufficiency**: In patients with chronic alcoholic liver disease, plasma concentrations of Atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Child-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Child-Pugh B disease (see CONTRAINDICATIONS).

INDICATIONS AND USAGE

Atorvastatin is indicated:

I. as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);

II. as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);

III. for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;

IV. to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable.

CONTRAINDICATIONS

Active liver disease or unexplained persistent elevations of serum transaminases.
Hypersensitivity to any component of this medication.

PRECAUTIONS

◆ **General:** Before instituting therapy with Atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

◆ **Information for Patients:** Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

◆ **Drug Interactions:** The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).

- **Antacid:** When Atorvastatin and Maalox™ TC suspension were coadministered, plasma concentrations of Atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.
- **Antipyrine**: Because Atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.
- **Colestipol**: Plasma concentrations of Atorvastatin decreased approximately 25% when colestipol and Atorvastatin were coadministered. However, LDL-C reduction was greater when Atorvastatin and colestipol were coadministered than when either drug was given alone.
- **Cimetidine**: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.
- **Digoxin**: When multiple doses of Atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.
- **Erythromycin**: In healthy individuals, plasma concentrations of Atorvastatin increased approximately 40% with coadministration of Atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS , Skeletal Muscle).
- **Oral Contraceptives**: Coadministration of Atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking Atorvastatin.
- **Warfarin**: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

◆ **Endocrine Function**

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that Atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

◆ **CNS Toxicity:** Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

◆ **Carcinogenesis, Mutagenesis, Impairment of Fertility**: In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, Atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of Atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

◆ **Pregnancy**

◆ **Pregnancy Category X:** See **CONTRAINDICATIONS.**

Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times

(rat) or 20 times (rabbit) the human exposure based on surface area (mg/m2).
In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.
Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Atorvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Atorvastatin, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

◆ **Nursing Mothers:** Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking Atorvastatin should not breast-feed (see CONTRAINDICATIONS).

◆ **Pediatric Use**: Treatment experience in a pediatric population is limited to doses of Atorvastatin up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age.

◆ **Geriatric Use:** Treatment experience in adults age >/=70 years with doses of Atorvastatin up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of Atorvastatin in this population were similar to those of patients <70 years of age.

ADVERSE REACTIONS

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to Atorvastatin. The most frequent adverse events thought to be related to Atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain.

◆ **Clinical Adverse Experiences:** Adverse experiences reported in >/=2% of patients in placebo-controlled clinical studies of Atorvastatin, regardless of causality assessment, are shown in **Table 1.**

◆ **Pregnancy and Lactation**: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

TABLE 1. Adverse Events in Placebo-Controlled studies. (% of patients)

BODY SYSTEM Adverse Event	Placebo N=270	Atorvastatin 10 mg N=863	Atorvastatin 20 mg N=36	Atorvastatin 40 mg N=79	Atorvastatin 80 mg N=94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.3	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	5.6	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	2.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

WARNINGS

◆ **Liver Dysfunction:** HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received Atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**
One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of Atorvastatin.
It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with Atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of Atorvastatin is recommended.
Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of Atorvastatin (see CONTRAINDICATIONS).

◆ **Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with Atorvastatin and with other drugs in this class**.
Uncomplicated myalgia has been reported in Atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.
The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with Atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.
Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

The following adverse events were reported, regardless of causality assessment in patients treated with Atorvastatin in clinical trials. The events in *italics* occurred in >/=2% of patients and the events in plain type occurred in <2% of patients.

◆ **Body as a Whole:** *Chest pain*, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

◆ **Digestive System**: *Nausea*, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

◆ **Respiratory System:** *Bronchitis, rhinitis*, pneumonia, dyspnea, asthma, epistaxis.

◆ **Nervous System**: *Insomnia, dizziness*, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

◆ **Musculoskeletal System**: *Arthritis*, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

◆ **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

◆ **Urogenital System**: *Urinary tract infection*, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

◆ **Special Senses**: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

◆ **Cardiovascular System**: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

◆ **Metabolic and Nutritional Disorders**: *Peripheral edema*, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

◆ **Hemic and Lymphatic System**: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

◆ **Postintroduction Reports:** Adverse events associated with Atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis.

OVERDOSAGE: There is no specific treatment for Atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance Atorvastatin clearance.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin and should continue on this diet during treatment with Atorvastatin.

◆ **Hypercholesterolemia** (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb).
The recommended starting dose of Atorvastatin is 10 mg once daily. The dosage range is 10 to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. Therapy should be individualized according to goal of therapy and response. After initiation and/or upon titration of Atorvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.
Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

◆ **Homozygous Familial Hypercholesterolemia:** The dosage of Atorvastatin in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) in these patients or if such treatments are unavailable.

◆ **Concomitant Therapy:** Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle, and PRECAUTIONS, Drug Interactions for other drug-drug interactions).

◆ **Dosage in Patients With Renal Insufficiency:** Renal disease does not affect the plasma concentrations nor LDL-C reduction of Atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY , Pharmacokinetics).

HOW SUPPLIED

LIPONORM™ (Atorvastatin) 10 mg, 20 mg and 40 mg x 30 coated tablets.

STORAGE

Store at controlled room temperature 15°-30°C (59°F - 86°F)

KEEP OUT THE REACH OF CHILDREN

Medicinal Product Authorised by the Ministry of Health.
Certificate N°: 48.128

Technical Director: Daniela A. Casas, Pharmacist

LAZAR

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