LIPONORM PLUS ™

ATORVASTATIN + EZETIMIBE

Tablets
Under prescription only
Made in Argentina

COMPOSITION

Each tablet of **LIPONORM PLUS™** 10/10 contains:

Atorvastatin	10 mg
Ezetimibe	10 mg
Microcrystalline Cellulose	48,44 mg
Povidone K30	2,69 mg
Sodium Lauryl Sulfate	4,31 mg
Magnesium Stearate	1,61 mg
Lactose CD	63,51 mg
Sodium Croscarmellose	8,62 mg

Each tablet of **LIPONORM PLUS™** 20/10 contains:

Atorvastatin	20 mg
Ezetimibe	10 mg
Microcrystalline Cellulose	74,38 mg
Povidone K30	4,13 mg
Sodium Lauryl Sulfate	6,62 mg
Magnesium Stearate	2,47 mg
Lactose CD	97,52 mg
Sodium Croscarmellose	13,24 mg

DESCRIPTION

LIPONORM PLUS™ is a fixed-dose combination of atorvastatin and ezetimibe.

PHARMACOLOGY

Pharmacodynamics

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. **LIPONORM PLUS™** contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. **LIPONORM PLUS™** reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis. The combination of atorvastatin and ezetimibe is effective in improving total cholesterol, LDL, triglycerides and HDL beyond either treatment alone.

Atorvastatin

Atorvastatin is a selective competitive inhibitor of 3-hydroxy-3-methyl-glutarylcoenzyme A (HMG-CoA) reductase enzyme. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the synthesis of cholesterol.

The primary site of action of HMG-CoA reductase inhibitors is the liver. Inhibition of cholesterol synthesis in the liver leads to upregulation of LDL-receptors and an increase in LDL-catabolism. There is also some reduction of LDL-production as a result of inhibition of hepatic synthesis of very low density lipoprotein (VLDL), the precursor of LDL-cholesterol. Atorvastatin reduces total cholesterol, LDLcholesterol and apo B in patients with homozygous and heterozygous familial hypercholesterolemia, non familial forms of hypercholesterolemia and mixed dyslipidemias. Atorvastatin also reduces VLDL-cholesterol and triglycerides and produces variable increases in HDL-cholesterol and apolipoprotein A1.

Atorvastatin reduces total cholesterol, LDL-cholesterol, VLDL-cholesterol, apo B, triglycerides, and non-HDL-cholesterol, and increases HDL-cholesterol in patients with isolated hypertriglyceridemia. Atorvastatin also reduces intermediate density lipoprotein (IDL) cholesterol in patients with dysbetalipoproteinemia.

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. Drug dosage rather than systemic drug concentration correlates better with LDL-cholesterol reduction. Individualization of drug dosage should be based on therapeutic response.

Ezetimibe

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo. Ezetimibe had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E and did not impair adrenocortical steroid hormone production. Ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors.

Pharmacokinetics

Atorvastatin

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.

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. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults.
- *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 Impairment:* 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.
- *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 Impairment:* 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 Childs-Pugh A disease. C max and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease.

Ezetimibe

Absorption: After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibeglucuronide). Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as 10-mg tablets. The C max value of ezetimibe was increased by 38% with consumption of high-fat meals.

Distribution: Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism and Excretion: Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated. In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling. Following oral administration of 14 C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

INDICATIONS

LIPONORM PLUS™ is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

LIPONORM PLUS™is also indicated for the reduction of elevated total cholesterol and LDL in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (eg LDL apheresis) or if such treatments are unavailable

DOSAGE AND ADMINISTRATION

The recommended dosage is one tablet once daily.

Dose Titration Guided by Clinical Effect. A patient whose dyslipidemia is not adequately controlled with atorvastatin (or another statin) alone or with ezetimibe alone may be switched to combination therapy with **LIPONORM PLUS™.**

Replacement Therapy

For convenience, patients receiving atorvastatin and ezetimibe from separate tablets may instead wish to receive tablets of **LIPONORM PLUS™** containing the same component doses.

Dosage in Patients Taking Cyclosporine, Clarithromycin or A Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir

In patients taking cyclosporine, therapy should be limited to atorvastatin 10 mg once daily. In patients taking clarithromycin or in patients with HIV taking a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, for doses of atorvastatin exceeding 20 mg appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

CONTRAINDICATIONS

Hypersensitivity to any component.

Active liver disease or unexplained persistent elevations of serum transaminases.

Pregnancy and lactation

WARNINGS AND PRECAUTIONS

Drug interactions:

Fibric acid derivatives,lipid modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g. cyclosporine, erythromycin, clarithromycin, and azole antifungals): The risk of myopathy during treatment with drugs belonging to the class of HMG-CoA reductase inhibitors is increased with concurrent administration of these agents. The safety and effectiveness of ezetimibe administered with fibrates other than fenofibrate have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gall bladder bile. Coadministration of ezetimibe with fibrates is not recommended until use in patients is studied. If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered.

Inhibitors of cytochrome P450 3A4:

Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of **LIPONORM PLUS™** with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4. Clarithromycin: Concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) resulted in a 4.4-fold increase in atorvastatin AUC.

Erythromycin:

Concurrent administration with erythromycin may result in higher plasma concentrations of atorvastatin.

Combination of Protease Inhibitors:

Concomitant administration of atorvastatin 40 mg with ritonavir plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) resulted in a 5.9-fold increase in atorvastatin AUC.

Itraconazole:

Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with a 2.5-3.3-fold increase in atorvastatin AUC.

Diltiazem hydrochloride:

Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin.

Grapefruit juice:

Contains one or more components that inhibit CYP 3A4 and can increase plasma

concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

Cyclosporine:
Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an 8.7-fold increase in atorvastatin AUC. Caution should be exercised when using ezetimibe and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving ezetimibe and cyclosporine. The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to **LIPONORM PLUS™** from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In cases where coadministration of **LIPONORM PLUS™** with cyclosporine is necessary, the dose should not exceed one tablet once daily.

Inducers of cytochrome P450 3A4:
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of **LIPONORM PLUS™** with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Antacids:
Decreased plasma concentrations of atorvastatin may occur when **LIPONORM PLUS™** is administered along with an oral antacid suspension containing magnesium and aluminium hydroxides; however, LDL-cholesterol reduction is not altered.

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.

Digoxin:
Administration of multiple doses of atorvastatin with digoxin increases the steady state plasma digoxin concentration by approximately 20%; patients taking digoxin and **LIPONORM PLUS™** should be monitored appropriately.

Oral contraceptives:
Administration of atorvastatin with an oral contraceptive containing norethindrone and ethinyl oestradiol produces increased plasma concentrations of norethindrone and ethinyl oestradiol. These increases should be considered when selecting an oral contraceptive for a woman taking **LIPONORM PLUS™.**

Coumarin anticoagulants:
If ezetimibe is added to warfarin, a coumarin anticoagulant, the International Normalized Ratio (INR) should be appropriately monitored.

Liver enzymes:
In controlled clinical combination studies of ezetimibe initiated concurrently with a statin, the incidence of consecutive elevations (≥3 x ULN) in serum transaminases was 1.3% for patients treated with ezetimibe administered with statins and 0.4% for patients treated with statins alone. These elevations in transaminases were generally asymptomatic, not associated with cholelithiasis and returned to baseline after discontinuation of therapy or with continued treatment. HMG-CoA reductase inhibitors, like some other lipid lowering therapies, have been associated with biochemical abnormalities of liver function. 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 three 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 the upper limit of normal persist, withdrawal of **LIPONORM PLUS™** is recommended. **LIPONORM PLUS™** should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

Skeletal muscle:
Uncomplicated myalgia has been reported in atorvastatin-treated patients. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. **LIPONORM PLUS™** 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 (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures). The risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin or azole anti-fungals. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **LIPONORM PLUS™** should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

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 **LIPONORM PLUS™** is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone and cimetidine.

Renal impairment:
Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin or ezetimibe; hence no adjustment of dose is required. Haemodialysis is not expected to significantly enhance the clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic impairment:
In patients with chronic alcoholic liver disease, the therapeutic response to atorvastatin is unaffected but exposure to the drug is greatly increased. C max increases by approximately 16-fold and AUC (0-24) by approximately 11-fold. Therefore caution should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Pregnancy:
Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, **LIPONORM PLUS™** may cause fetal harm when administered to pregnant women. Therefore, **LIPONORM PLUS™** is contraindicated during pregnancy and in nursing mothers. **LIPONORM PLUS™** 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.

Lactation:
Because of the potential for adverse reactions in nursing infants, women taking **LIPONORM PLUS™** should not breast-feed.

Pediatric use:
Safety and effectiveness of atorvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months duration in adolescent boys and postmenarchal girls. Doses greater than 20 mg have not been studied in this patient population. There was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. Atorvastatin has not been studied in controlled clinical trials involving prepubertal patients or patients younger than 10 years of age. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with sitosterolemia and 5 patients (11 to 17 years) with homozygous familial hypercholesterolemia. Treatment with **LIPONORM PLUS™** in children <10 years is not recommended. Adolescent females should be counseled or appropriate contraceptive methods while on **LIPONORM PLUS™** therapy.

UNDESIRABLE EFFECTS
LIPONORM PLUS™ is generally well tolerated. Adverse reactions have usually been mild and transient. Occasional undesirable effects include abdominal pain, asthenia, constipation, diarrhoea, dyspnea, flatulence, nausea, headache and myalgia.

OVERDOSAGE
There is no specific treatment available for atorvastatin overdosage. General supportive measures should be adopted as required. Liver function tests and serum CPK levels should be monitored. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.
No cases of overdosage with ezetimibe have been reported. Administration of ezetimibe 50 mg/day to 15 subjects for up to 14 days was generally well tolerated. In the event of an overdose, symptomatic and supportive measures should be employed.

HOW SUPPLIED
LIPONORM PLUS™ is supplied in 30 tablet pack.

STORAGE
Store between 15 and 30ºC (59 and 86º F).

KEEP AWAY FROM THE REACH OF THE CHILDREN

Medicine Approved by Ministry of Health.
Certificate Nº 55.618.

LAZAR

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Distributed in Lebanon by:
DROGUERIE PHENICIA
Reg. N° in Lebanon:
Liponorm Plus 10/10: 78814/1
Liponorm Plus 20/10: 78914/1

36914/1
P266