What are Decision Aids; can they help your patients with their health care choices?

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Medicine is striving to achieve greater patient involvement in their health care choices. With such endeavors come tools that attempt to make this process easier. Two such tools are discussed briefly in this review, Patient Decision Aids (PDAs) being the main focus, contrasted with Health Education Material (HEM). This paper will try to give you a brief background on each and their usefulness in your medical practice.

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Patient decision aids (DAs) are growing in number and new DAs are cropping up all the time. The purpose of this review is to clarify how DAs differ from health education material and to help determine their usefulness in a health care setting - do they really help your patients make a decision when they are presented with more than one option?

A literature search performed on Pubmed using the terms patient decision aids, randomized control trial, with the limits of English language and human trials, yielded 55 hits. A more refined list of searches using the above qualifiers plus, in successive order, atrial fibrillation yielded 6 hits, prostate cancer 7 hits and lastly breast cancer 10 hits. During the literature search it was found that the Cochrane database has a site that is dedicated to the evaluation of patient decision aids, and is updated on a regular basis (www.cochranelibrary.net). An additional source of information on available DA's is the Ottawa Health Research Institute (OHRI) where DA's are listed alphabetically (www.ohri.ca/home.asp).

Patient decision aids are tools that help patients make *specific* and *deliberative* choices among treatment options. They are designed as adjuncts to, not replacement of, physician counseling. They give information on the available options and outcomes that are relevant to the patient's illness, *based on their category of risk*. Patient DAs may include some or all of the following: background information on the disease or illness, costs of the treatment options, category of risk stratification and probability of an outcome based on risk category. They also often include worksheets that aid a patient in assessing their values, and a sampling of different opinions from other patients (i.e. what they would chose in the same situation)[1].

Decision aids are being used predominantly in North America and Europe. The driving force behind their development is the desire to have patients more involved in the health care process and enable them to give their physicians their informed *choice* instead of their informed *consent*[1]. The ethical issues around this topic are many. The patient cannot give informed choice unless they are fully aware of what is being presented to them, they can give informed consent simply by agreeing with what the doctor has offered them. Patient decision aids are also an attempt to reduce geographic variations in practice and to reduce costs by not having patients undergo treatments that they do not really want and would not choose for themselves if they had more information.

Patient DAs differ from health education material (HEMs) in that they are more specific and they have a more personalized focus on the patient. HEMs are broader in perspective, giving information on the disease process itself. HEMs are not intended to help the patient make a specific decision with regards to their preference for treatment[1]. Do PDAs work; are they effective? It was found that DAs improve patient knowledge, which is of significant importancebecause many patients, when given the usual care and tested for their level of knowledge, were not even at the level of being able to give informed consent[2]. DAs also give the patient better insight into what to expect based on the treatment option they choose[2,3], they reduce patient conflict in that the patient feels better informed and more confident with the decision they make, and lastly they increase patient participation[2]. Consequently, PDAs are not the method of choice for all patients; not all patients want to be active participants[1].

These three points seem to make a good argument for the use of DAs, but some other issues identified give some reason to further evaluate DA's before widespread implementation. DAs do not, at this point, increase patient satisfaction[2], nor is there an improvement in the emotional state of patients, in their general or condition-specific health outcomes, or in their persistence with their chosen decision[1]. There was also no difference found when factors of agreement between the decisions made and the patient's values (or the patient's regret over their decision) were studied[4].

It has been suggested that we need to delineate inclusion criteria as to what makes up a successful DA, and we need stringent factors that are to be used when a decision aid is being evaluated. Patient decision aids are not currently sophisticated enough to be used widely. More research needs to be done with regards to the areas of medicine that would benefit most from the development of DAs. Also current gaps in the DA library, some areas being over represented while others are not represented at all, need to be remedied. Research also needs to be done regarding physician opinions on this subject, the costs of developing these aids, and their cost effectiveness[1].

Conclusion

In conclusion, with more decision aids being developed every year it would seem as though DAs are here to stay. Stay abreast with the new developments on the Cochrane web site: www.cochranelibrary.com.

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About the Author

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LIPITOR
atorvastatin calcium
tablets

EFFICACY TO REACH TARGETS

LIPITOR
(atorvastatin calcium)
10 mg, 20 mg, 40 mg and 80 mg tablets

THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

LIPITOR (atorvastatin calcium) is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).

LIPITOR reduces LDL-Cholesterol (LDL-C) and the number of LDL particles. Lipitor also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Low serum concentration of HDL-C is also an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥98% bound to plasma proteins. Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. 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 longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to lifestyle changes, including diet, [at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet], for the reduction of elevated total cholesterol, (total-C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa);
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
- Dysbetalipoproteinemia (Type III);
- Hypertriglyceridemia (Type IV);
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

LIPITOR also raises HDL-cholesterol and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia (Fredrickson Type IIa and IIb dyslipidemia). In pooled data from 24 controlled clinical trials, LIPITOR raised HDL-C levels 5%-7% in primary hypercholesterolemic (type IIa) patients and 10%-15% in mixed (type IIb) dyslipidemic patients. These changes in HDL-C with HMG-CoA reductase inhibitors should be considered as modest when compared to those observed in LDL-C and do not play a primary role in the lowering of LDL-C/HDL-C and total-C/HDL-C ratios.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25-56%) and LDL-C levels (23-40%). LIPITOR has not been studied in conditions where the major abnormality is elevation of chylomicrons (TG levels > 11 mmol/L), i.e. types I and V.

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open label study in patients with homozygous familial hypercholesterolemia (FH) LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

$$\text{LDL-C (mmol/L)} = \text{total-C} - [(0.37 \times \text{TG}) + \text{HDL-C}]$$

$$\text{LDL-C (mg/dL)} = \text{total-C} - [(0.2 \times \text{TG}) + \text{HDL-C}]^{1}$$

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

Patients with high or very high triglyceride levels, i.e. >2.2 mmol/L (200 mg/dL) or >5.6 mmol/L (500 mg/dL), respectively, may require triglyceride-lowering therapy (fenofibrate, bezafibrate or nicotinic acid) alone or in combination with LIPITOR.

In general, combination therapy with fibrates must be undertaken cautiously and only after risk-benefit analysis (see WARNINGS, Muscle Effects, PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions).

Elevated serum triglycerides are most often observed in patients with the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, small dense LDL particles and low HDL-cholesterol), insulin resistance with or without glucose intolerance, raised blood pressure and prothrombic and proinflammatory states).

(For the treatment of specific dyslipidemias refer to the Report of the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias or to the US NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III], under SELECTED BIBLIOGRAPHY in product monograph).

When drugs are prescribed attention to therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, weight reduction, increased physical activity, ingestion of soluble fibres) should always be maintained and reinforced.

The Atorvastatin Versus Revascularization Treatments (AVERT) study examined the effect of intensive lipid-lowering in patients with stable coronary artery disease and LDL-C at least 3.0 mmol/L in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Patients were randomized for 18 months to LIPITOR 80 mg daily or to PTCA with usual medical care which could include lipid metabolism regulators. The results of the AVERT study should be considered as exploratory since several limitations may affect its design and conduct. In the medical-treated group with LIPITOR there was a trend for a reduced incidence of ischemic events and a delayed time to first ischemic event. The results also suggest that intensive treatment to target LDL-C levels with LIPITOR is **additive and complementary** to angioplasty and would benefit patients referred for this procedure (see SELECTED BIBLIOGRAPHY in product monograph).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme. (See WARNINGS, Muscle Effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated Interactions).

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Hepatic Effects

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatinine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, 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. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic studies conducted in healthy subjects with erythromycin and clarithromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions).

Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors. LIPITOR 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 (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity or mortality or total mortality have not been established.

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY in product monograph).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY in product monograph).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

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 harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR 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 LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; SELECTED BIBLIOGRAPHY in product monograph).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)], the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions).

Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, 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.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution

should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Pharmacokinetic Interaction Studies and Potential Drug Interactions

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also Geriatric Use; Renal Insufficiency; Patients with Severe Hypercholesterolemia).

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is limited experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class, including atorvastatin, is increased with concurrent administration (see WARNINGS, Muscle Effects and SELECTED BIBLIOGRAPHY in product monograph).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY in product monograph).

Digoxin: In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily (see Human Pharmacokinetics). Patients taking digoxin should be monitored appropriately.

Antihypertensive agents (amlodipine): In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state (see Human Pharmacokinetics).

(quinapril): In a randomized, open-label study in healthy subjects, steady-state quinapril dosing (80 mg QD) did not significantly affect the pharmacokinetic profile of atorvastatin tablets (10 mg QD) (see Human Pharmacokinetics).

Oral Contraceptives and Hormone Replacement Therapy: Coadministration of LIPITOR with an oral contraceptive, containing 1mg norethindrone and 35 µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e. erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), protease inhibitors, or the antidepressant, nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY in product monograph). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; SELECTED BIBLIOGRAPHY in product monograph).

In healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. preexisting prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin): In healthy adults, coadministration of LIPITOR (10 mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg QD) with erythromycin (500 mg QID) or clarithromycin (500 mg BID), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin approximately 40% and 80%, respectively (see WARNINGS, Muscle Effects; Human Pharmacokinetics).

Protease Inhibitors (nelfinavir mesylate): In healthy adults, coadministration of nelfinavir mesylate (1250 mg BID), a known CYP 3A4 inhibitor, and atorvastatin (10 mg QD) resulted in increased plasma concentrations of atorvastatin. AUC and C_{max} of atorvastatin were increased by 74% and 122% respectively.

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions; DOSAGE AND ADMINISTRATION).**

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and creatinine phosphokinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

TABLE 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials

	Placebo % (n=270)	LIPITOR % (n=1122)
GASTROINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVOUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports: severe myopathy with or without rhabdomyolysis (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated reports: thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis). These may have no causal relationship to atorvastatin.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, 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

Patients should be placed on a standard cholesterol-lowering diet (at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet) before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia, Including Familial Combined Hyperlipidemia: The recommended dose of LIPITOR is 10 mg once a day. The majority of patients achieve and maintain target cholesterol levels with LIPITOR 10 mg/day. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy. Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. Doses should be individualized according to baseline LDL-C and/or TG levels, the desired LDL-C and/or TG target (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Dyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP Adult Treatment Panel III]), the goal of therapy and the patient's response. Adjustments of dosage, if necessary, should be made at intervals of 4 weeks or more. The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients (see section below).

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

The following reductions in total cholesterol and LDL-C levels have been observed in 2 dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia
(Mean Percent Change from Baseline)[a]

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L[b] (273 mg/dL)[b]	-29	-33	-37	-45
LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b]	-39	-43	-50	-60

a. Results are pooled from 2 dose-response studies.
b. Mean baseline values.

Severe Dyslipidemias

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions).

Concomitant Therapy

See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency

See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance

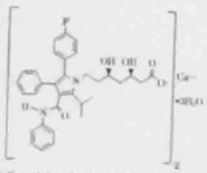
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$

Molecular Weight: 1209.42

Structural Formula:



Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition:

Each tablet contains either 10 mg, 20 mg, 40 mg or 80 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations:

Store at controlled room temperature 15 to 30°C.

AVAILABILITY OF DOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg atorvastatin per tablet.

10 mg: White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

20 mg: White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other. Available in bottles of 90 tablets.

40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PD 157" on the other. Available in bottles of 90 tablets.

80 mg: White, elliptical, film-coated tablet, coded "80" on one side and "PD 158" on the other. Blisters of 30 tablets (3 strips x 10).

References:

1. LIPITOR (atorvastatin calcium) Product Monograph, Pfizer Canada Inc., February 2002. **2.** IMS Health MIDAS; Quarter 3 1997 – Quarter 3 2002. **3.** Pitt B, Waters D, Brown WV *et al.* Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med* 1999;341:70-76. **4.** Data on File, Pfizer Canada Inc. **5.** Simon Day. Dictionary for Clinical Trials, 1999, John Wiley & Sons Ltd. Pages 137-138.

For a copy of the Product Monograph or full Prescribing Information, please contact:

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