ORIGINAL CONTRIBUTION

Congenital Absence of the Cruciate Ligaments

Derek B. Smith,1 BScEng, MScEng MD '00, J. David Amirault,2 MD, FRCS(C) and Lorne Leahey,3 MD, FRCS(C)

1Department of Surgery, Dalhousie University

2Associate professor, Department of Surgery (Division of Orthopaedic Surgery), Dalhousie University and Chief of Surgery, New Halifax Infirmary, QEII Health Sciences Centre

3Associate professor, Department of Surgery (Division of Orthopaedic Surgery), Dalhousie University, Orthopaedic Surgery, IWK-Grace Health Centre.

Congenital absence of one or both cruciate ligaments is a rare event, and little literature exists regarding this abnormality. Patients with this condition often have associated anomalies. This study looked at 6 subjects with congenital abnormalities often associated with absence of the cruciate ligaments. The subjects were followed by a questionnaire and knee examination. This paper presents results of congenital absence of the cruciate ligaments on knee instability and activities of daily living.

INTRODUCTION

Congenital absence of one or both of the cruciate ligaments is an uncommon occurrence, and has been only sporadically reported in the literature. Most reports are in association with a congenitally short femur or other abnormality, such as congenital dislocation of the knee. A study by Giorgi (1956) looking at morphologic variations in the intercondylar eminence of the knee contained the first mention of congenital absence of the cruciates: one case showed total aplasia of the intercondylar eminence, which Giorgi attributed to a congenital lack of the cruciates. A study by Katz et al (1967) reported a relationship between congenital cruciate ligament anomalies and congenital dislocation of the knee. This study was the first to report confirmed congenital absence of the cruciate ligaments. Since then, it has been reported in association with a number of congenital abnormalities, [3-8]. Congenital absence of one or both cruciates is usually detected during examination for a separate abnormality, such as congenital dislocation of knee, [2], or preparation for leg-lengthening procedures, [3]. During clinical analysis for the presenting abnormality, ipsilateral instability of the knee is noted, with follow-up tests revealing cruciate ligament insufficiency. This study is intended to add to the existing base of reported cases of congenital absence of one or both cruciate ligaments.

METHODS

Using resources at the IWK Grace Health Centre Orthopaedics Clinic, a list of patients with possible congenital absence of the cruciate ligaments was compiled. These subjects all had associated abnormalities that are often linked to congenital absence of the cruciate ligaments, such as fibular hemimelia and proximal femoral focal deficiencies. A total of 9 patients were identified as having congenital abnormalities associated with congenital absence of the cruciate ligaments. Two of these patients lived a significant distance away and could not be obtained for examination purposes, and 1 patient could not be reached; this left 6 subjects with possible congenital absence of the cruciate ligaments. The subjects were relatively young, ranging in age from 7 to 24 years old. Each subject was asked a series of questions and had his or her knee examined. This was in an effort to clinically determine the presence or absence of the cruciate ligaments and, if absent, any effects this may have had on the subject. The questions included *The Knee Society* clinical rating system [10] as well as some questions regarding any impact the patient's knee might have had on the subject's life and/or activity levels, associated abnormalities and previous treatments. Each subject signed an informed consent form prior to any investigations.

Address correspondence to:
Derek Smith, Med IV
Box 80, Sir Charle s Tupper Building, Dalhousie University
Halifax, Nova Scotia, Canada. dbsmith@is2.dal.ca. (902)492-7153

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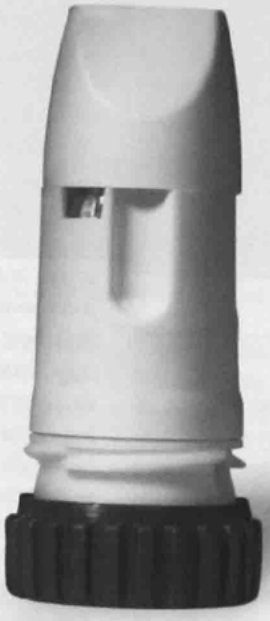

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Table I - Associated Abnormalities As Identified in the Literature

Congenital knee dislocation
Congenital leg length discrepancy
Hypoplastic or absent fibula
Absent 5th ray of foot
Dislocation of patella
Femoral dysplasia
Congenital talipes equinovarus
Osteogenic scoliosis
Bilateral dislocation of hip
Incomplete sagittal septum
Proximal femoral focal deficiencies
Congenital thrombocytopenia
Genu valgum
Genu varum
Absent radius syndrome
Congenital absence of the menisci

RESULTS

The limited amount of literature regarding absence of the cruciate ligaments indicates the relative rarity of this condition. As well, there were only 9 patients who were suspected of congenital absence of one or both cruciate ligaments in a database of approximately 13000 patients spanning 3 years at the IWK Grace Health Centre Orthopaedics Clinic. From the literature, the most commonly associated abnormalities were congenital knee dislocation and congenital leg-length discrepancies, [2-8]. Table I contains specific conditions that have been reported in cases with congenital absence of the cruciate ligaments.

Abnormal laxity of the knee is noted upon clinical examination of a subject with congenital absence of one or both cruciate ligaments, [3-6]. Subjects with absent anterior cruciate ligaments show positive anterior drawer and Lachman tests, [3-5][9], medial lateral translational instability, [4][6][7][9], and possible habitual subluxation of the tibia in extension, [4][6]. In cases where the posterior cruciate ligament is absent, subjects exhibit positive posterior drawer signs, [3][8][9]. Of the 6 subjects examined, four had posterior drawer tests of less than 5 mm deviation, and two had deviations of 5 - 10 mm. There were five subjects with anterior drawer tests of 5-10 mm deviation and one with a deviation of greater than 10 mm. Five subjects also had Lachman tests of 5-10 mm deviation and one had a deviation of less than 5 mm. Five of the six subjects had a positive pivot shift. All six subjects had normal range of motion for the knee in question, and 4 of the 6 had less than 5 degrees of mediolateral laxity (the other 2 had 6-9().

In the majority of cases reported with congenital absence of the cruciate ligaments, subjects had no complaints of instability, and even subjects in whom the knee gives way more than once a week are active. Despite the clinically unstable knee, subjects are frequently involved in sports and other strenuous activities with no difficulties, unless precipitated by an associated abnormality, [3-6]. In agreement with this, none of the 6 subjects investigated claimed to have any problems with regards to knee stability, and 4 subjects were active in athletics, with no limitations. The remaining 2 subjects were active in sports, but found that other factors limited their participation (prosthetic devices and ankle deformity). None of the subjects felt that their knee affected their daily living, nor did any subject find any limitation in walking or stairs. Two subjects mentioned occasional discomfort, although neither would refer to it as pain. One subject mentioned that she thought her knee may have "given way" once, but that it was of no consequence for her. Another mentioned that her knee had locked, but that once again the subject did not feel that it had interfered with her life. A summary of the patients seen during this study is contained in Table II. It is interesting to note that although none of the subjects had intact knees according to objective evaluation, they all had complete function (both values are out of one hundred).

Radiographic findings can be quite useful in differentiating between congenital absence and traumatic effect. Radiographic changes in the subjects missing one or both cruciate ligaments can include: hypoplasia of the intercondylar tubercles (lateral for anterior cruciate; medial for posterior cruciate), [3][4][6]; hypoplasia of the femoral condyles (medial for anterior cruciate; lateral for posterior cruciate), [4-6]; tarsal coalition, [6]; and hypoplasia to aplasia of the intercondylar emi-

Table 2: Patient Characteristics

Gender	Age (yrs)	Cruciate(s)	Knee Society Score	Associated Abnormalities
M	13	ACL	92:100	fibular hemimelia, leg length discrepancy, absent 5th ray of foot
F	21	ACL and PCL	82:100	fibular hemimelia, leg length discrepancy
F	24	ACL	90:100	proximal femoral focal deficiency, leg length discrepancy
F	9	ACL and PCL	80:100	fibular hemimelia, leg length discrepancy
M	6	ACL (R&L)	R - 75:100 L - 89:100	absent 5th ray (upper limb), agenesis of lateral ray (R foot), L fibular hypoplasia, R fibular aplasia, R syndactyly of toes
M	7	ACL	92:100	absent 5th ray of foot, club foot, fibular hemimelia, leg length discrepancy

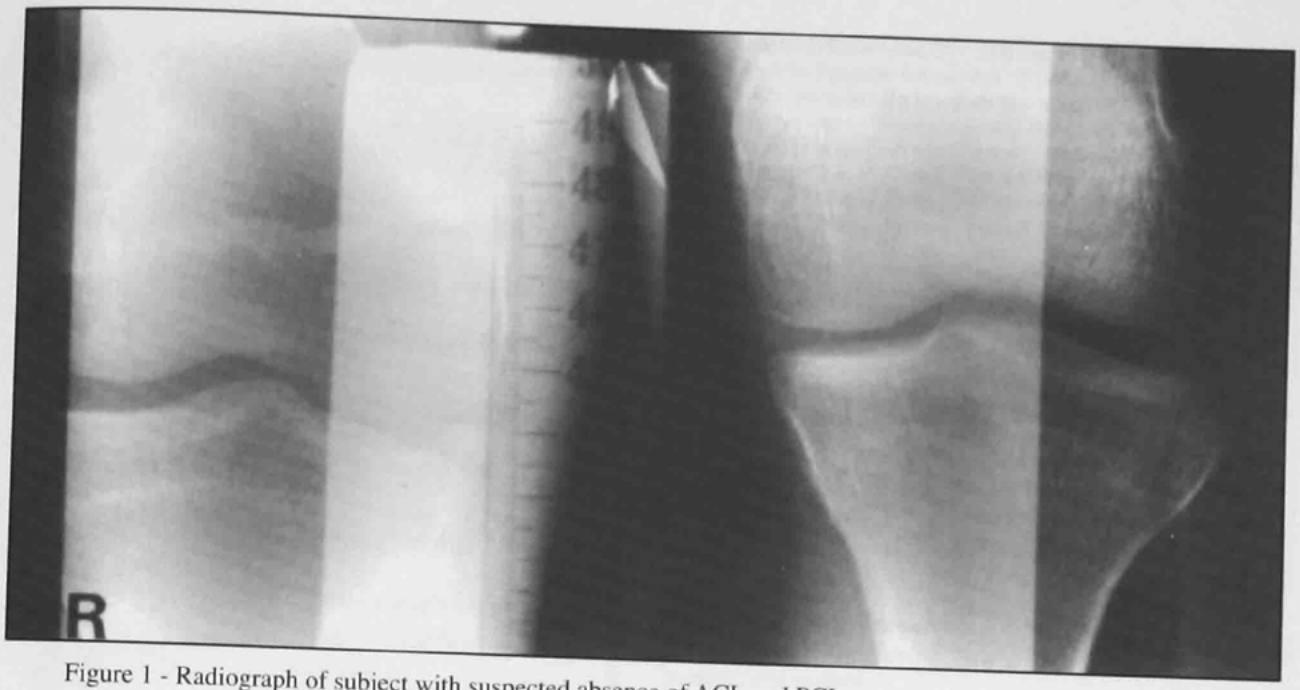

Figure 1 - Radiograph of subject with suspected absence of ACL and PCL.

nence and corresponding adjustment in the shape of the intercondylar fossa, [3][4][6][8]. Hypoplasia of the lateral femoral condyles has also been accompanied by a valgus deformity, [6]. As well, there have been reports of patellar hypoplasia and absent or hypoplastic tibia being associated with absence of the anterior cruciate ligament [3][4]. Note that while any of the above radiographic changes may occur, they may also accompany each other or not be present at all. Figure I presents a sample knee radiograph from this study. In the image, radiographic changes in the affected (right) knee are evident. Note in particular the hypoplasia of the intercondylar eminence and intercondylar groove.

DISCUSSION

The long-term effects on knees of patients with congenital absence of the cruciate ligaments are not completely known [3-5]. The largest concern is whether or not patients will develop the degenerative changes seen in patients who have suffered acute cruciate rupture [3-5]. This is particularly intriguing in that a study by Johansson and Aparisi (1983) contained data on a sixty year old patient with congenital absence of the anterior cruciate ligament who exhibited no significant osteoarthritis. As well, an autopsy performed on an 81 year old male with congenital absence of the cruciate ligaments and a ring meniscus showed no arthritic changes, significant at age 80 [3][5][8]. It has been postulated that the meniscus rather than the anterior cruciate ligament is a better prognosticator of degenerative joint disease, [3][5], and that ring meniscus may be a developmental change attempting to provide more stability [5]. As well, the authors of a study in which 5 patients complained of their knee giving way more than once a week, [4], have suggested that this might lead to the development of degenerative changes similar to those seen in adults who have suffered acute ligamentous disruptions; however, this was only an assumption at the time of their study. Further long term studies are needed to evaluate this area. The current study cannot comment on long term effects because of the young age of the subjects.

Congenital absence of the cruciate ligaments is a relatively rare condition usually associated with other abnormalities. The majority of subjects suffer no ill effects in the short term, and are often active, with no difficulties or restrictions arising from the absence of the cruciate ligament(s). Patients don't have the same demand on the knee because of associated abnormalities, but they do function at a high level. Although these patients are not elite athletes, many engage in competitive sport as associated abnormalities permit. For example, one young male plays in the area hockey league, and the females in their twenties engage in recreational soccer and volleyball. These characteristics are found in both the literature and the results of this study. Finally, due to the dearth of information currently available, further work in determining the long term effects of congenital absence of the cruciate ligaments is indicated.

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LIPITOR*

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ACTIONS AND CLINICAL PHARMACOLOGY

LIPITOR (atorvastatin calcium) is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-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. 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 Co-A 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 diet, at least equivalent to the American Heart Association (AHA) Step 1 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.

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%). Chylomicrons, which characterize Types I and V, have not been measured in clinical studies in patients with high TG levels (>11 mmol/L).

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.

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

<u>**Pharmacokinetic Interactions**</u>

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).

<u>**Hepatic Effects**</u>

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.

<u>Liver function tests should be performed before the initiation of treatment, and periodically thereafter</u>. 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.

[1]Friedewald, WT et al. Clin Chem 1972; 18(6): 499-502.

<u>**Muscle Effects**</u>

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine 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, 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 a pharmacokinetic study with erythromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, 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

<u>**General**</u>

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.

<u>**Effect on the Lens**</u>

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

<u>**Effect on Ubiquinone (CoQ_{10}) Levels**</u>

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).

<u>**Effect on Lipoprotein (a)**</u>

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) levels. Until further experience is obtained, it is suggested, where feasible, that measurements of serum Lp(a) be followed up in patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

<u>**Hypersensitivity**</u>

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.

<u>**Use in Pregnancy**</u>

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.

<u>**Nursing Mothers**</u>

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).

<u>**Pediatric Use**</u>

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.

<u>**Geriatric Use**</u>

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).

<u>**Renal Insufficiency**</u>

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.

<u>**Endocrine Function**</u>

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.

<u>**Drug Interactions**</u>

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 no 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 is increased with concurrent administration (see WARNINGS, Muscle Effects).

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

Digoxin: Coadministration of multiple doses of LIPITOR and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored closely and appropriately.

Oral Contraceptives: Coadministration of LIPITOR with an oral contraceptive, containing 1mg norethindrone and 35µg 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.

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, macrolide antibiotics (including erythromycin and clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), or the antidepressant nefazodone may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). 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 a study with 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.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of LIPITOR and erythromycin, a known inhibitor of CYP 3A4 (see WARNINGS, Muscle Effects).

Other Concomitant Therapy: In clinical studies, LIPITOR was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence to date of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

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 creatine 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 of severe myopathy with or without rhabdomyolysis have been reported (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated cases of thrombocytopenia and allergic reactions (including urticaria, angioneurotic edema and anaphylaxis) that may have no causal relationship to atorvastatin, have also been reported.

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 American Heart Association (AHA) Step 1 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]), 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

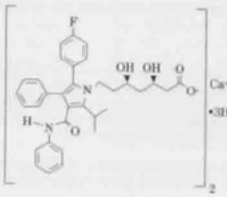
Proper Name: Atorvastatin calcium

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 or 40 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 25°C.

AVAILABILITY OF DOSAGE FORMS

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

References:

1. Koren MJ, Smith DG, Hunninghake DB, *et al*. The cost of reaching National Cholesterol Education Program goals in hypercholesterolemic patients: A comparison of atorvastatin, simvastatin, lovastatin and fluvastatin. *Pharmacoeconomics* 1998;14:59-70. 2. LIPITOR (atorvastatin calcium) Product Monograph, Parke-Davis Div., Warner-Lambert Canada Inc., Dec. 1998. 3. Dart A, *et al*. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol* 1997;80:39-44. 4. Bertolini S, *et al*. Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis* 1997;130:191-7. 5. Data on file. 6. ODB Formulary, Dec. 1998.

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

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Norvasc*

(amlodipine besylate/pfizer)

Brief Prescribing Information
NORVASC
(amlodipine besylate)
Tablets 2.5, 5 and 10 mg
Antihypertensive-Antianginal Agent

ACTION AND CLINICAL PHARMACOLOGY
NORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

INDICATIONS AND CLINICAL USE
Hypertension
NORVASC (amlodipine besylate) is indicated in the treatment of mild-to-moderate essential hypertension.
NORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. NORVASC can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of NORVASC with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.
Chronic Stable Angina
NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. NORVASC may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS
NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

WARNINGS
Increased Angina and/or Myocardial Infarction
Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.
Outflow Obstruction (Aortic Stenosis)
NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).
Use in Patients with Impaired Hepatic Function
There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. NORVASC should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).
Beta-blocker Withdrawal
NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

PRECAUTIONS
Use in Patients with Congestive Heart Failure
Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that NORVASC had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.
Hypotension
NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.
Peripheral Edema
Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.
Use in Pregnancy
Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with NORVASC in pregnant women. NORVASC should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.
Nursing Mothers
It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, NORVASC should not be given to nursing mothers.
Use in Children
The use of NORVASC is not recommended in children since safety and efficacy have not been established in that population.
Use in Elderly
In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. NORVASC should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).
Interaction with Grapefruit Juice
Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice.
Drug Interactions
As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme.
Coadministration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.
Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.
Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.
Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.
Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.
Cimetidine, Warfarin, Cyclosporin, Digoxin: Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:
- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin**.
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

Antacids
Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.
Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with NORVASC, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

ADVERSE REACTIONS
NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity.
Hypertension
In the 805 hypertensive patients treated with NORVASC in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):
Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).
Angina
In the controlled clinical trials in 909 angina patients treated with NORVASC, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%).
The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):
Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** abnormal vision (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).
NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.
The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.
Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension. **Central and Peripheral Nervous System:** hypoesthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapular, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, increased sweating. **Metabolic and Nutritional:** thirst. **Hemopoietic:** purpura.
†These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.
The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia.
Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Symptoms
Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of NORVASC (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.
Treatment
Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION
Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of NORVASC (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.
Use in the Elderly or in Patients with Impaired Renal Function
The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).
Use in Patients with Impaired Hepatic Function
Dosage requirements have not been established in patients with impaired hepatic function. When NORVASC is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS
Availability
NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE
Store at 15-30°C. Protect from light.

REFERENCES: ANGINA

1. Norvasc® Product Monograph, Pfizer Canada Inc., Dec. 19, 1997.
2. Purcell H, Waller DG, Fox K. Therapeutic focus: calcium antagonists in cardiovascular disease. Br J Clin Pract 1989;43(10):369-79.
3. Salerno SM and Zugibe FT. Calcium channel antagonists. What do the second generation agents have to offer? Postgrad Med 1994;95(1):181-90.
4. Deanfield JE et al. Amlodipine reduces transient myocardial ischemia in patients with coronary artery disease: double-blind circadian anti-ischemia program in Europe (CAPE trial). J Am Coll Cardiol 1994;24(6):1460-7.
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REFERENCES: HYPERTENSION

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3. Lüscher TF and Cosentino F. The classification of calcium antagonists and their selection in the treatment of hypertension - a reappraisal. Drugs 1998;55(4):509-17.
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THERAPEUTIC CLASSIFICATION

Glucocorticosteroid for the treatment of bronchial asthma.

INDICATIONS AND CLINICAL USE:

Patients with bronchial asthma: 1. In patients who require inhaled steroids, 2. In patients for whom a reduction of systemic glucocorticoids is desirable.

CONTRAINDICATIONS: 1. Status asthmaticus; not to be used in primary treatment of acute episodes of asthma or in patients with moderate to severe bronchiectasis, 2. Hypersensitivity to budesonide, 3. Active or quiescent pulmonary tuberculosis, 4. Untreated fungal, bacterial or viral infections of the respiratory system.

WARNINGS: 1. PULMICORT is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required. If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for anti-inflammatory therapy, e.g., higher doses of inhaled budesonide or a course of oral corticosteroid. 2. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to inhaled corticosteroids; therefore particular care is needed in patients who are transferred from systemically active corticosteroids to PULMICORT (budesonide). After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis, or other conditions associated with severe electrolyte loss. Although PULMICORT may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid which is necessary for coping with these emergencies. During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large dosages) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level. Patients previously on high doses of systemic steroids may regain earlier symptoms not related to asthma such as rhinitis and eczema when transferred from oral therapy to PULMICORT. These symptoms are a result of the generally lower systemic steroid action which will be experienced. Patients may also suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. Temporary resumption of systemic steroids may be necessary to treat these conditions. 3. The development of pharyngeal and laryngeal candidiasis is cause for concern because the extent of its penetration of the respiratory tract is unknown. If oral pharyngeal candidiasis develops, appropriate anti-fungal therapy should be implemented to eradicate the infection. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouths out with water after each inhalation. (See DOSAGE AND ADMINISTRATION.) 4. Glucocorticosteroids may mask some signs of infection and new infections may appear during their use. 5. There is no evidence that control of asthma can be achieved by administration of PULMICORT in doses higher than those recommended. During such episodes, patients may require therapy with systemic corticosteroids.

PRECAUTIONS: 1. In transferring patients from a systemic steroid to PULMICORT (budesonide), the reduction of the systemic steroid must be very gradual and carefully supervised by the physician since systemic withdrawal symptoms (e.g. joint and/or muscular pain, lassitude, depression) may occur in spite of maintenance or improvement of respiratory functions. (See DOSAGE AND ADMINISTRATION). 2. It is essential that the patient be instructed that PULMICORT is a preventative agent which must be taken at regular intervals and is not to be used to relieve an acute asthmatic attack. 3. The long-term effects of budesonide on developmental or immunologic processes in the mouth, pharynx, trachea, eyes, and lung are unknown. With the recommended therapeutic doses of PULMICORT, there is little risk of adverse systemic effects. 4. In children, treated for 2 to 6 years, with budesonide via TURBUHALER® at daily doses up to 400 µg, no effect was demonstrated on statural growth compared with nonsteroidal therapy. However, to allow for individuals that are excessively sensitive, it is recommended that height is monitored in growing children. 5. Treatment with PULMICORT should not be stopped abruptly, but tapered off gradually. 6. Pulmonary infiltrates with eosinophilia may occur in patients on PULMICORT therapy. Although this is possible in some patients who are administered inhalational steroids, their causative role cannot be ruled out. 7. **Usage During Pregnancy.** Administration of PULMICORT during pregnancy should be avoided unless there are compelling reasons. In experimental animal studies, budesonide was found to cross the placental barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats, and mice. The relevance of these findings to humans has not yet been established. In the absence of further studies in humans, budesonide should be used during pregnancy only if the potential benefits clearly outweigh the risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids, especially oral steroids, during pregnancy should be carefully observed for hypoadrenalism. 8. **Lactation.** Glucocorticoids are secreted in human milk. It is not known whether budesonide would be secreted in human milk, but it is suspected to be likely. The use of PULMICORT in nursing mothers requires that the possible benefits of the drug be weighed against the potential hazards to the mother, or infant. 9. **Children Under 6 Years of Age.** PULMICORT is not presently recommended for children younger than 6 years of age due to limited clinical data in this age group. 10. Corticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. During long-term therapy, pituitary-adrenal function and height (in children) should be periodically assessed. 11. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids. 12. There may be enhanced systemic effects of budesonide in patients with an advanced liver cirrhosis, and in those with hypperthyroidism. Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide however, are similar in cirrhotic patients and in healthy subjects. The pharmacokinetics after oral ingestion of budesonide were affected by compromised liver function as evidenced by increased systemic availability. This is however, of little importance for PULMICORT, as after inhalation the oral contribution to the systemic availability is very small. 13. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. 14. Special care is needed in patients with lung tuberculosis and fungal and viral infections. Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops treatment with antiviral agents may be considered. If, however, a viral upper respiratory infection is present, the patient should adhere to the regular asthma medication. In patients who are known to deteriorate rapidly when they have a viral respiratory infection, a short course of oral corticosteroid therapy should be considered. Clinical studies have shown that viral infections cause significantly fewer problems in patients who are on regular treatment with topical glucocorticosteroids. 15. To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of PULMICORT TURBUHALER®. 16. Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as Candida albicans. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: Budesonide has not been observed to interact with any drug used for the treatment of asthma. Cimetidine: The kinetics of budesonide were investigated in a study of healthy subjects without and with cimetidine 1000 mg daily. After a 4 mg oral dose the values for C_{max} (nmol/L) and systemic availability (%) of budesonide without and with cimetidine (3.3 vs 5.1 nmol/L and 10 vs 12%, respectively) indicated a slight inhibitory effect on hepatic metabolism of budesonide, caused by cimetidine. This should be of little clinical importance. Ketoconazole: Ketoconazole, a potent inhibitor of cytochrome P450 3A, the main metabolic enzyme for corticosteroids, increases plasma levels of orally ingested budesonide. Omeprazole: At recommended doses, omeprazole has no effect on the pharmacokinetics of oral budesonide.

ADVERSE REACTIONS: No major side effects attributable to the use of PULMICORT (budesonide), in all dosage forms, have been reported. During clinical trials, the frequency of subjectively reported side effects was low. The most common side effects were cough, throat irritation, and hoarseness (2-4%). Bad taste, headache, nausea and dryness of the throat were reported less frequently. Other side effects reported on occasion during budesonide treatment were tiredness, thirst, and diarrhea. Skin reactions (urticaria, rash, dermatitis, angioedema, etc.) may, in rare cases, occur in association with local corticosteroid therapy. In rare cases, skin bruising has been reported following treatment with inhaled glucocorticosteroids. Psychiatric symptoms such as nervousness, restlessness and depression, as well as behavioural disturbances in children, have been observed. As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

In rare cases, signs or symptoms of systemic glucocorticosteroid effect including hypofunction of the adrenal gland and oropharyngeal complications may occur, depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity. Candidiasis has been reported by some patients and may occur at therapeutic doses. In patients in whom systemic steroids are reduced or stopped, withdrawal symptoms due to decreased systemic activity occur frequently. (See DOSAGE AND ADMINISTRATION: CLINICAL MANAGEMENT).

DOSAGE AND ADMINISTRATION

Adults and Children over 12 Years of Age. When treatment with inhaled glucocorticosteroids is started, during periods of severe asthma, and while reducing or discontinuing oral glucocorticosteroids the dosage should be 400-2400 µg daily divided into 2-4 administrations. The maintenance dose is usually 200-400 µg twice daily but higher doses may be necessary for longer or shorter periods of time in some patients. The dose of PULMICORT (budesonide) should be individualized to the patient's need and should be the lowest possible dose that fills the therapeutic objective. Once daily dosing may be considered in patients who require a dosage of 400 µg budesonide per day. The dose may then be given in the morning or in the evening. If deterioration of asthma occurs, the frequency of dosing and the daily dose should be increased.

Treatment with PULMICORT should not be stopped abruptly, but tapered off gradually.

Children 6-12 Years. When starting therapy with budesonide in children, during periods of severe asthma and while reducing or discontinuing oral corticosteroids, the dosage should be 200-400 µg daily, given in divided doses twice daily at 100 to 200 micrograms per inhalation. The maintenance dose is individual and should be the lowest dose which keeps the patient symptom-free. Administration twice daily is usually adequate in stable asthmatics.

Children Under 6 Years of Age. Not recommended in children in this age group.

Clinical studies in man have shown an improved efficacy for the same amount of budesonide delivered via TURBUHALER® inhaler as compared with the pressurized aerosol with NEBUHALER® spacer device. It may be possible to reduce the dose of PULMICORT TURBUHALER when the patient is in a stable phase.

Approximately 30% of the metered dose is deposited in the lungs.

In patients where an increased therapeutic effect is desired, an increased dose of PULMICORT TURBUHALER is recommended because of the lower risk of systemic effects as compared with a combined treatment with oral glucocorticosteroids.

TURBUHALER®: TURBUHALER is a breath-activated dry powder inhaler which does not require a coordinated inhalation technique. It contains only the active ingredient budesonide – no propellants or preservatives, and as such, offers those patients sensitive to excipients an alternative dosage form. **NOTE: The patient may not taste or feel any medication when inhaling from TURBUHALER. This lack of feeling does not mean that the patient is not receiving benefit from PULMICORT TURBUHALER. NOTE: The medication from PULMICORT TURBUHALER is delivered to the lungs as the patient inhales and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. When prescribing PULMICORT TURBUHALER to young children it is necessary to ascertain that they can follow the instructions for use. The patient may not taste or feel any medication when using PULMICORT TURBUHALER due to the small amount of drug dispensed. Patients should be instructed to rinse their mouths out with water after each inhalation. This will help prevent the occurrence of candidiasis. Cleansing dentures has the same effect.**

CLINICAL MANAGEMENT

Patients – Non-Steroid Dependent

Treatment with the recommended doses of PULMICORT usually gives a therapeutic effect within 10 days. However, certain patients might have an excessive collection of mucous secretion in the bronchi which reduces the penetration of the active substance in PULMICORT into the bronchial mucosa. In these cases, it is desirable to initially give a short (about 2 weeks) oral corticosteroid regimen in addition to PULMICORT. The oral treatment is started on a rather large dose which is then gradually reduced. Thereafter, treatment with PULMICORT only is sufficient. Exacerbations of the asthma caused by bacterial infections are controlled by adequate antibiotic regimens and also by increasing the PULMICORT dosage.

Patients – Steroid Dependent

Transferal of patients dependent upon oral steroids to treatment with PULMICORT demands special care mainly because of the slow restitution of the disturbed hypothalamic-pituitary-adrenal function caused by extended treatment with oral corticosteroids. When PULMICORT treatment is initiated, the patient should be in a relatively stable phase. PULMICORT is then given in combination with the previously used oral steroid dose for about 10 days. After this period of time, reduction of the oral corticoid dose may be started gradually. The oral dose is thus reduced to the lowest level which, in combination with PULMICORT, gives a stable respiratory capacity.

In adults, the usual rate of withdrawal of the systemic corticosteroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close observation. **If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower,** approximately 2.5 mg of prednisone (or equivalent) every 10 days. A slow rate of withdrawal cannot be overemphasized. If withdrawal symptoms appear, the previous dosage of the systemic drug should be resumed for a week before further decrease is attempted. During withdrawal, some patients may experience symptoms of systemically active steroid withdrawal, eg., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. Such patients should be encouraged to continue with PULMICORT, but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dosage should be boosted temporarily and thereafter further withdrawal should continue more slowly.

In many cases it may be possible to completely replace the oral steroid with PULMICORT treatment. In other patients, a low oral steroid maintenance dosage may be required. The length of time needed for the body to regain its natural production of corticosteroid in sufficient quantity is often extended. **Thus, during severe asthma attacks or physically stressing situations such as severe infections, trauma, and surgical operations, it is necessary to resume systemic steroids (in large dosages) in order to avoid adrenocorticoid insufficiency.** Acute exacerbations, especially in connection with increased viscosity and mucous plugging, may require complementary treatment with a short course of oral corticosteroids which are gradually tapered as symptoms subside.

During transfer from oral therapy to PULMICORT, a lower general steroid action is experienced. The patients might regain earlier symptoms (rhinitis, eczema) or suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. In these cases, further medical support may be required.

AVAILABILITY OF DOSAGE FORMS: PULMICORT TURBUHALER is a dry powder inhaler containing 200 doses of 100 µg, 200 µg, and 400 µg or 100 doses of 200 µg of micronized budesonide. Each inhalation from PULMICORT TURBUHALER will provide either 100 µg, 200 µg or 400 µg of budesonide active substance; no additives or carrier substances are included. PULMICORT TURBUHALER cannot be re-filled and should be discarded when empty.

References:

Turbuhaler® Ad

1. Duncan J, *et al. Drug Invest* 1990;2(2):136-137.
2. van Spiegel PI, *et al. British Journal of Clinical Research* 1997;8:33-45.

Pulmicort® Turbuhaler® Ad

1. Agertoft L and Pedersen S. *Respiratory Medicine* 1994;88:373-381.
2. Pulmicort® Turbuhaler® (budesonide) Product Monograph, Astra Pharma Inc.

Product monograph available on request. 09/99

BAYCOL®

(Cerivastatin Sodium)
0.2 and 0.3 mg Tablets

THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

ACTION AND CLINICAL PHARMACOLOGY

BAYCOL® (cerivastatin sodium) is an entirely synthetic, enantiomerically pure cholesterol-lowering agent and is structurally similar to the fungal derivatives of this therapeutic class.

Cerivastatin is a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. The inhibition of cholesterol biosynthesis by cerivastatin reduces the level of cholesterol in hepatic cells, which stimulates the synthesis of low density lipoprotein (LDL) receptors, thereby increasing the uptake of cellular LDL particles. The end result of these biochemical processes is a reduction of plasma total cholesterol (Total-C) and low density lipoprotein cholesterol (LDL-C).

Cerivastatin is rapidly absorbed following oral dosing. The absolute bioavailability of cerivastatin sodium tablets is 60% compared to oral solution. The pharmacokinetics of cerivastatin are linear over the dose range of 0.05 to 0.4 mg. Cerivastatin is >99% bound to plasma proteins. The elimination half-life is in the range of 2 to 4 hours; consequently no drug accumulation with once daily dosing is observed. The pharmacokinetics of cerivastatin are similar under fed and fasted conditions.

When ^{14}C-cerivastatin was given as an oral solution, the mean urinary excretion of total radioactivity was 24% of dose, while a mean of 70% was excreted in the feces. Thus, biliary secretion is a major pathway of drug (or metabolite) elimination. Only negligible quantities of ^{14}C were associated with unchanged drug, indicating extensive metabolism. Cerivastatin is metabolized via a dual metabolic pathway utilizing at least two cytochrome P-450 isoenzymes, CYP2C8 and CYP3A4. If one of the metabolic pathways (e.g., CYP3A4) is blocked, cerivastatin is metabolized, although not completely in some cases, by the alternate metabolic route. Three metabolites have been identified, and M1 and M23 are present in plasma, urine and feces, whereas M24 is present in urine and feces only. Plasma concentrations of all identified metabolites are substantially lower than those of parent drug, and the elimination half-lives are similar. Therefore, while some metabolites have pharmacologic (i.e., HMG-CoA reductase inhibitory) activity, they do not contribute significantly to the overall efficacy of cerivastatin.

INDICATIONS AND CLINICAL USE

BAYCOL® (cerivastatin sodium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated Total-C and LDL-C levels in patients with primary hypercholesterolemia (types IIa and IIb) when the response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures alone has been inadequate. BAYCOL® is indicated for the reduction of elevated cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia, when the hypercholesterolemia is the abnormality of most concern.

Prior to initiating therapy with BAYCOL®, secondary causes for hyperlipoproteinemia, such as obesity, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy (e.g., some anti-hypertensive agents) or alcoholism, should be excluded. A lipid profile should be performed to measure Total-C, high density lipoprotein cholesterol (HDL-C) and triglycerides. For patients with total triglycerides less than 4.52 mmol/L (400 mg/dL), LDL-C can be estimated using the following equations:

LDL-C (mmol/L) = Total-C – [(0.37 x Trig) + HDL-C]
LDL-C (mg/dL) = Total-C – [(0.16 x Trig) + HDL-C]

When total triglyceride levels exceed 4.52 mmol/L (400 mg/dL), this equation is less accurate and LDL-C concentrations should be directly measured by preparative ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, BAYCOL® is not indicated. Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

BAYCOL® has not been studied in conditions where the major abnormality is elevation of chylomicrons, very low density lipoprotein (VLDL), or intermediate-density lipoprotein (IDL), i.e., hyperlipoproteinemia types I, III, IV or V.

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. Cerivastatin is metabolized via a dual metabolic pathway utilizing at least two cytochrome P-450 isoenzymes, CYP2C8 and CYP3A4. If one of the metabolic pathways (e.g., CYP3A4) is blocked, cerivastatin is metabolized, although not completely in some cases, by the alternate metabolic route (see WARNINGS, Muscle Effects; PRECAUTIONS; DRUG INTERACTIONS, Cytochrome P-450 Inhibitors).

(For more information on the metabolism of cerivastatin in humans, see ACTION AND CLINICAL PHARMACOLOGY.)

Hepatic Effects: In clinical trials, persistent increases of serum transaminase values to more than 3 times the upper limit of normal (ULN) (occurring on two or more, not necessarily sequential, occasions) have been reported in <1.0% of patients treated with cerivastatin sodium. Most of these abnormalities occurred within the first 6 weeks of treatment, resolved after discontinuation of the drug, and were not associated with cholestasis. In most cases, these biochemical abnormalities were asymptomatic.

It is recommended that liver function tests be performed before the initiation of treatment, and within 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter, e.g., semiannually. 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 >3 times the ULN and are persistent, the dosage should be reduced or the drug discontinued.**

The drug should be used with caution in patients with a history of liver disease or heavy alcohol ingestion (>14 drinks/week).

Active liver disease or unexplained transaminase elevations are contraindications to the use of BAYCOL® (cerivastatin sodium); if such conditions develop during therapy, the drug should be discontinued (see CONTRAINDICATIONS).

Muscle Effects: Myopathy, defined as muscle aching or muscle weakness, associated with increases in plasma creatine phosphokinase (CPK) values to greater than 10 times the ULN was rare (<0.2%) in cerivastatin clinical trials. Myopathy 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.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased if therapy with cyclosporine, fibric acid derivatives, erythromycin, niacin (nicotinic acid) in lipid-lowering doses, nefazodone or azole antifungals is administered concurrently. The benefits and risks of combined therapy should be carefully considered (see PRECAUTIONS; DRUG INTERACTIONS).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria have been reported with other HMG-CoA reductase inhibitors. This has not been reported with cerivastatin sodium to date. BAYCOL® therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. BAYCOL® should be temporarily withheld in any patient experiencing an acute or serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine or electrolyte disorders; or uncontrolled epilepsy.

PRECAUTIONS

General: The effects of cerivastatin-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 BAYCOL® (cerivastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of BAYCOL® or any other lipid-lowering agent.

Effect on Lens: Current data from clinical trials do not indicate an adverse effect of BAYCOL® on the human lens.

Use in Homozygous Familial Hypercholesterolemia: Cerivastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. Most HMG-CoA reductase inhibitors are less or not effective in this subgroup of hypercholesterolemic patients.

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 the Lipoprotein (a) [Lp(a)] levels. Therefore, until further experience is obtained from controlled clinical trials, it is suggested that measurements of serum Lp(a) be followed up in patients placed on BAYCOL® therapy.

Effect on CoQ_{10} Levels (Ubiquinone): Significant decreases in circulating ubiquinone levels in patients treated with other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not yet 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.

Hypersensitivity: An apparent hypersensitivity syndrome has been reported rarely with other HMG-CoA reductase inhibitors. This has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus–like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocyte sedimentation rate (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, BAYCOL® should be discontinued if hypersensitivity is suspected.

Use in Pregnancy: BAYCOL® is contraindicated during pregnancy (see CONTRAINDICATIONS).

Safety in pregnant women has not been established. Atherosclerosis is a chronic process and discontinuation of lipid metabolism regulators 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. Cerivastatin sodium should be administered to women of child-bearing 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, cerivastatin sodium should be discontinued and the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers: Based on preclinical data, cerivastatin sodium is present in breast milk in a 1.3:1 ratio (milk: plasma). It is not known whether cerivastatin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, women taking BAYCOL® should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Limited experience with the use of other HMG-CoA reductase inhibitors is available in children. Safety and effectiveness of BAYCOL® in children have not been established.

Geriatric Use and Gender: The effect of age on the pharmacokinetics of BAYCOL® was evaluated. Results indicate that for the general patient population, plasma concentrations of BAYCOL® do not vary as a function of age. A slight increase in plasma cerivastatin levels was observed in females (approximately 12% higher for C_{max} and 16% higher for AUC).

Use in Patients with Impaired Renal Function: No dose adjustment is necessary for patients with mild renal dysfunction (creatinine clearance 61–90 mL/min/1.73 m²). In patients with significant renal impairment (creatinine clearance <60 mL/min/1.73 m²), the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects).

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Cerivastatin sodium demonstrated no effect upon non-stimulated cortisol levels and no effect on thyroid metabolism as assessed by TSH. Clinical studies with other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce plasma testosterone concentration. In rare cases, however, impotence may occur following their administration. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with cerivastatin sodium 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 also receiving other drugs, e.g., ketoconazole, spironolactone, or cimetidine, that may decrease the levels of endogenous steroid hormones. (See DRUG INTERACTIONS, Cytochrome P-450 Inhibitors).

DRUG INTERACTIONS

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: Co-administration of cerivastatin sodium and cholestyramine resulted in a 22% decrease in cerivastatin plasma concentration (AUC). Administration of cholestyramine 1 hour before the evening meal and cerivastatin sodium 4 hours after the same evening meal resulted in a decrease in the cerivastatin plasma concentration of less than 8%. Therefore, it would be expected that a dosing schedule of cerivastatin sodium given at bedtime and cholestyramine administered before the evening meal would not result in a significant decrease in the clinical effect of cerivastatin sodium.

Gemfibrozil, Fenofibrate and Niacin: Myopathy, including rhabdomyolysis, has occurred in patients receiving HMG-CoA reductase inhibitors with fibric acid derivatives and niacin (in lipid-lowering doses), particularly in subjects with pre-existing renal insufficiency (see WARNINGS, Muscle Effects).

Erythromycin: Co-administration of erythromycin 500 mg bid, a known inhibitor of cytochrome P-450 3A4, with cerivastatin sodium 0.3 mg qd during 10 days in hypercholesterolemic patients resulted in a 50% increase in cerivastatin AUC and in a 24% increase in C_{max} (see WARNINGS, Pharmacokinetic Interactions and Muscle Effects; PRECAUTIONS, P-450 Inhibitors).

Azole Antifungals: Co-administration with the antifungal agent itraconazole 200 mg qpm, another potent CYP3A4 inhibitor, and cerivastatin 0.3 mg qpm during 10 days in hypercholesterolemic patients resulted in a 40% increase in cerivastatin steady-state plasma concentrations (see WARNINGS, Pharmacokinetic Interactions and Muscle Effects; PRECAUTIONS, P-450 Inhibitors).

Calcium Channel Blockers: Co-administration of a single dose of 60 mg nifedipine extended release and cerivastatin sodium 0.3 mg to hypercholesterolemic patients did not show any effect on either nifedipine or cerivastatin plasma concentrations.

Coumarin Anticoagulants: Co-administration of warfarin and cerivastatin sodium had no effect on the plasma concentration of either agent.

Digoxin: Co-administration of cerivastatin sodium and digoxin resulted in a <10% increase in plasma digoxin levels. Patients taking digoxin should be monitored appropriately when cerivastatin sodium therapy is initiated. Digoxin did not alter the pharmacokinetics of cerivastatin.

Antacid (Magnesium-Aluminum Hydroxide): Co-administration of antacid with cerivastatin resulted in an approximate 10% decrease in the cerivastatin plasma concentration.

Cimetidine: Co-administration of cerivastatin sodium (0.2 mg) with cimetidine (400 mg) resulted in an 11% decrease in the cerivastatin plasma concentration.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies cerivastatin sodium was used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, diuretics, estrogen replacement therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence to date of clinically significant adverse interactions.

Cytochrome P-450 Inhibitors: Cerivastatin is metabolized via a dual metabolic pathway utilizing at least two cytochrome P-450 isoenzymes, CYP2C8 and CYP3A4. Although not complete in some cases, a compensatory effect is observed when one pathway is inhibited. When co-administered with erythromycin, a known inhibitor of cytochrome P-450 isoform 3A4, cerivastatin plasma concentrations increased by 50%. Drugs or common agents such as grapefruit juice that inhibit this enzyme may represent a potential for drug interactions when combined with cerivastatin. Caution should thus be exercised with concomitant use of drugs such as immunosuppressants, antifungal agents (e.g., itraconazole, ketoconazole), macrolide antibiotics including erythromycin, antidepressants (e.g., nefazodone) or grapefruit juice (see WARNINGS, Muscle Effects and PRECAUTIONS, Endocrine Function).

Patients with Severe Hypercholesterolemia: Higher drug dosages (0.3 mg/day) required for some patients with severe hypercholesterolemia are associated with increased plasma level of cerivastatin. **Caution should be exercised in such patients who are also significantly renally impaired, elderly, or are concomitantly being administered digoxin, erythromycin or other cytochrome P-450 inhibitors (see WARNINGS, Muscle Effects; PRECAUTIONS; DRUG INTERACTIONS).**

Drug/Lab Interactions: HMG-CoA reductase inhibitors may elevate CPK and transaminase levels (see ADVERSE REACTIONS, Laboratory Tests). In the differential diagnosis of chest pain in a patient on therapy with BAYCOL®, cardiac and non-cardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

BAYCOL® (cerivastatin sodium) is generally well tolerated. Adverse events have usually been mild and transient. In 1394 patients treated in placebo-controlled clinical studies investigating doses of 0.2 mg and 0.3 mg, less than 2% of patients were discontinued due to adverse reactions attributable to BAYCOL®, compared to 2.5% for placebo. Of these 1394 patients, 855 were treated for ≥1 year.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of BAYCOL® 0.2 or 0.3 mg/day and reported to be possibly, probably, or definitely drug-related are shown in the following table.

Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials of 0.2 and 0.3 mg BAYCOL®

	Placebo % (n = 641)	BAYCOL® % (n = 1394)
GASTROINTESTINAL		
Dyspepsia	2	2
Flatulence	1	1
Abdominal pain	2	1
Diarrhea	2	1
Constipation	1	<1
NERVOUS SYSTEM		
Headache	2	2

Ophthalmological Observations: See PRECAUTIONS, Effect on Lens.

Laboratory Tests: Increases of serum transaminases and CPK have been noted in clinical trials (see WARNINGS).

The following effects have been reported with drugs in this class. Not all of the effects listed have necessarily been associated with cerivastatin therapy: myopathy, muscle cramps, rhabdomyolysis, arthralgias, dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, vertigo, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression, pancreatitis, hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis (rare), fulminant hepatic necrosis (rare), hepatoma (rare), anorexia, vomiting, alopecia, pruritus, gynaecomastia, loss of libido, erectile dysfunction, progression of cataracts (lens opacities), ophthalmoplegia.

Hypersensitivity: anaphylaxis, angioedema, lupus erythematosus–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.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The maximum single oral dose of cerivastatin sodium received by healthy volunteers and patients is 0.8 mg. No specific recommendations concerning the treatment of an overdosage can be made. Should an overdose occur, it should be treated symptomatically and supportive measures should be undertaken as required.

The ability of cerivastatin and its metabolites to be dialyzed in humans is not known.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet (at least equivalent to the American Heart Association [AHA] Step 1) diet before receiving BAYCOL® (cerivastatin sodium) and should continue on this diet during treatment with BAYCOL®. If appropriate, a program of weight control and physical exercise should be implemented.

The recommended starting dose is 0.2 mg once daily in the evening. The recommended dosing range is 0.2–0.3 mg as a single dose in the evening. BAYCOL® may be taken with or without food since there are no apparent differences in the lipid-lowering effects of BAYCOL® administered with the evening meal or at bedtime. Dosages should be individualized according to the recommended goal of therapy and the patient's response. Since the maximal effect of a given dose of BAYCOL® is seen within 4 weeks, periodic lipid determinations should be performed at this time and the dosage adjusted to the patient's response to therapy and established treatment guidelines.

Consideration should be given to reducing the dosage of BAYCOL® if cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP) and/or the Canadian Consensus Conference Guidelines.

Severe Hypercholesterolemia: In patients with severe hypercholesterolemia, higher dosages (0.3 mg/day) may be required (see WARNINGS, Muscle Effects; PRECAUTIONS; DRUG INTERACTIONS).

Concomitant Therapy: See PRECAUTIONS; DRUG INTERACTIONS.

Dosage in Patients with Renal Insufficiency: See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance: Cerivastatin sodium

Chemical Name: (+)-[3R,5S,(E)]-sodium-7-[4-(4-fluorophenyl)-2,6-diisopropyl-5 methoxymethylpyrid-3-yl]-3,5-dihydroxyhept-6-enoate

Molecular Formula: $C_{26}H_{33}FNO_5Na$

Molecular Weight: 481.5

Description: Cerivastatin sodium is a white to almost-white amorphous powder (lyophilisate). It is soluble in water, methanol and ethanol. The pka_1 is 5.8 and pka_2 is 4.4 determined using a 0.01g/L solution. The partition coefficient of cerivastatin was determined in octanol/phosphate buffer pH = 7 (log P = 3.0) and octanol/phosphate buffer pH = 5 (log P = 2.0) at room temperature. Cerivastatin remains solid up to 200°C. At higher temperatures, the active ingredient decomposes without melting.

Composition: BAYCOL® (cerivastatin sodium) tablets contain 0.2 or 0.3 mg of cerivastatin sodium.

Nonmedicinal ingredients: crospovidone, magnesium stearate, mannitol, povidone 25, sodium hydroxide, hydroxypropyl methylcellulose, polyethylene glycol 4000, titanium dioxide and ferric oxide.

Stability and Storage Recommendations: The tablets should be stored between 15° and 25°C. Dispense in tight containers.

AVAILABILITY OF DOSAGE FORMS

BAYCOL® (cerivastatin sodium) is supplied as 0.2 mg and 0.3 mg tablets. The different tablet strengths can be identified as follows.

Strength	Colour	Markings
0.2 mg	light yellow-brown	283 on one side, 200 MCG on the other
0.3 mg	yellow brown	284 on one side, 300 MCG on the other

Nonmedicinal ingredients: crospovidone, magnesium stearate, mannitol, povidone 25, sodium hydroxide, hydroxypropyl methylcellulose, polyethylene glycol 4000, titanium dioxide, and ferric oxide.

BAYCOL® is supplied in bottles of 100 tablets.

The tablets should be stored at room temperature (15° to 25°C).

Product monograph available on request.

References:

1. Stein et al. Cerivastatin, a new potent synthetic HMG-CoA reductase inhibitor: Effect of 0.2 mg daily in subjects with primary hypercholesterolemia. J Cardiovasc Pharmacol Therapeut 1997;2(1):7–16. 2. Angerbauer et al. BAY W6228: Rivastatin: Hypolipidemic HMG-CoA reductase inhibitor. Drugs Fut 1994;19(6):537–541. 3. Angerbauer et al. BAY W6228: Synthesis and biological activity of a new generation HMG-CoA reductase inhibitor. 12th Int Symposium Med Chem 1992: Abstract OC-05 1. 4. Corsini et al. Effect of the new HMG-CoA reductase inhibitor cerivastatin (BAY W6228) on migration, proliferation and cholesterol synthesis in arterial myocytes. Pharmacol Res 1996;33(1):55–61. 5. Steinke et al. Cerivastatin, a new inhibitor of HMG-CoA reductase: Pharmacokinetics in rats and dogs. Japan Pharmacol Therapeut 1996;24(suppl 9): 1217–1237. 6. Bischoff et al. Cerivastatin: Pharmacology of a novel synthetic and highly active HMG-CoA reductase inhibitor. Atherosclerosis 1997;135:119–130. 7. Mück et al. Absolute and relative bioavailability of the HMG-CoA reductase inhibitor cerivastatin. Int J Clin Pharmacol Therapeut 1997;35(6):255–260. 8. Data on file. Pooled from cerivastatin studies nos. 120, 124, 132 and 149. 9. BAYCOL® product monograph. 10. Data on file. Pooled from cerivastatin studies nos. 109, 110, 111, 120, 123, 124, 132, 139 and 149. 11. Data on file. Cerivastatin Study No. 132.

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2. Hahn JF, Mason L. Low back pain in children. In: Hardy Rw Jr, ed. *Lumbar disc disease*. New York: Raven Press, 1982:217-28. (Seminars in neurological surgery).

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3. Katz J. *Common orthopedic problems in pediatric practice*. New York: Raven Press, 1981:125-7.

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