

# Benefits of Insulin Therapy Sequence Confirmed

BY KATE JOHNSON

MONTREAL — Insulin added to oral therapy in patients with longstanding type 2 diabetes is best initiated as a basal formulation and then intensified with prandial doses, according to the 3-year results of the Treat to Target in Type 2 Diabetes (4-T) trial.

“The results of our trial support current guidelines, which suggest that basal

and prandial insulin regimens should be considered if adequate glycemic control is not achieved with initial regimens,” reported lead author Rory Holman, MB, ChB, of the diabetes trials unit at Oxford (England) University.

The findings were announced at the World Diabetes Congress, with simultaneous publication in the New England Journal of Medicine (2009;361:1736-47).

“I think we now have very clear evi-

dence that the sequence of basal with added prandial gives you less weight gain and less hypoglycemia,” said Dr. Holman in an interview immediately following his presentation. “It’s a no-brainer that that is the way we should now initiate treatment for these patients.”

“The 4-T study supports the initiation of treatment with basal insulin, which is consistent with the concept that fasting hyperglycemia contributes more than

postprandial hyperglycemia to glycated hemoglobin levels during periods of poor glycemic control,” commented Dr. Michael Roden from the German Diabetes Center and the Heinrich Heine University of Düsseldorf, Germany, in an editorial published in the same issue.

However, he suggested “it seems premature to recommend specific insulin regimens for patients with newly diagnosed disease.”

**CADUET® (amlodipine besylate/atorvastatin calcium) Tablets**  
**Brief Summary of Prescribing Information**  
**INDICATIONS AND USAGE:** CADUET (amlodipine and atorvastatin) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate. **Amlodipine:** **1. Hypertension:** Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents; **2. Coronary Artery Disease (CAD): Chronic Stable Angina:** Amlodipine is indicated for the treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal or antihypertensive agents; **Vasospastic Angina (Prinzmetal's or Variant Angina):** Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs. **Angiographically Documented CAD:** In patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%, amlodipine is indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure. **AND Atorvastatin:** **1. Prevention of Cardiovascular Disease:** In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:  
-Reduce the risk of myocardial infarction  
-Reduce the risk of stroke  
-Reduce the risk for revascularization procedures and angina  
In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:  
-Reduce the risk of myocardial infarction  
-Reduce the risk of stroke;  
In patients with clinically evident coronary heart disease, LIPITOR is indicated to:  
-Reduce the risk of non-fatal myocardial infarction  
-Reduce the risk of fatal and non-fatal stroke  
-Reduce the risk for revascularization procedures  
-Reduce the risk of hospitalization for CHF  
-Reduce the risk of angina  
**2. Heterozygous Familial and Nonfamilial Hypercholesterolemia:** Atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb); **3. Elevated Serum TG Levels:** Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV); **4. Primary Dysbetalipoproteinemia:** Atorvastatin is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet; **5. Homozygous Familial Hypercholesterolemia:** Atorvastatin is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable; **6. Pediatric Patients:** Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:  
a. LDL-C remains ≥ 190 mg/dL or  
b. LDL-C remains ≥ 160 mg/dL and:  
· there is a positive family history of premature cardiovascular disease or  
· two or more other CVD risk factors are present in the pediatric patients.  
Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used, in addition to a diet restricted in saturated fat and cholesterol, only when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines*, summarized in Table 1).

**Table 1. NCEP Treatment Guidelines: LDL-C Goals and Outpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories**

Risk Category	LDL-C Goal (mg/dL)	LDL-C Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL-C Level at Which to Consider Drug Therapy (mg/dL)
CHD <sup>a</sup> or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) <sup>b</sup>
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk Factor <sup>c</sup>	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

<sup>a</sup> CHD, coronary heart disease. <sup>b</sup> Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory. <sup>c</sup> Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still > 200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category. Prior to initiating therapy with atorvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 x [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. The antilipidemic component of CADUET has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V). The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

**Table 2. NCEP Classification of Cholesterol Levels in Pediatric Patients**

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

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

**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. **Liver Dysfunction:** HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** In clinical trials in patients taking atorvastatin the following has been observed. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients, with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CADUET is recommended. CADUET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of CADUET (see **CONTRAINDICATIONS**). **Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the atorvastatin component of CADUET and with other drugs in the HMG-CoA reductase inhibitor class.** Uncomplicated myalgia has been reported in atorvastatin-treated patients (see **ADVERSE REACTIONS**). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values

>10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in the HMG-CoA reductase inhibitor class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, combination of ritonavir plus saquinavir or lopinavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with CADUET and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (See **DRUG INTERACTIONS**). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **In patients taking CADUET, therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

**PRECAUTIONS: General:** Since the vasodilation induced by the amlodipine component of CADUET is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering CADUET as with any other peripheral vasodilator particularly in patients with severe aortic stenosis. Before instituting therapy with CADUET, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see **INDICATIONS AND USAGE**). **Use in Patients with Congestive Heart Failure:** In general, calcium channel blockers should be used with caution in patients with NYHA Class III or IV heart failure. The amlodipine component of CADUET (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see **CLINICAL PHARMACOLOGY**) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class I/II heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. **Beta-Blocker Withdrawal:** The amlodipine component of CADUET is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker. **Endocrine Function:** HMG-CoA reductase inhibitors, such as the atorvastatin component of CADUET interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity: Studies with atorvastatin:** Brain hemorrhage was seen in a female dog treated with atorvastatin calcium for 3 months at a dose equivalent to 120 mg atorvastatin/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses of atorvastatin calcium equivalent to up to 280 mg atorvastatin/kg/day. The 120 mg/kg dose of atorvastatin resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated with atorvastatin calcium at a dose equivalent to 10 mg atorvastatin/kg/day and one at a dose equivalent to 120 mg atorvastatin/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses of atorvastatin calcium equivalent to up to 400 mg atorvastatin/kg/day or in rats at doses equivalent to up to 100 mg atorvastatin/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg atorvastatin/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of the HMG-CoA reductase class. A chemically similar drug in this class produced optic nerve degeneration (Wallerman degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Information for Patients:** Due to the risk of myopathy with drugs of the HMG-CoA reductase class, to which the atorvastatin component of CADUET belongs, patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions:** Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are coadministered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the C<sub>max</sub>: 91% (90% confidence interval: 80 to 103%), but the AUC of atorvastatin increased by 18% (90% confidence interval: 109 to 127%) in the presence of amlodipine. No drug interaction studies have been conducted with CADUET and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below. **Studies with Amlodipine:** *In vitro* data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). **Cimetidine:** Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine. **Antacid:** Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine. **Sildenafil:** A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect. **Digoxin:** Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. **Ethanol (Alcohol):** Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol. **Warfarin:** Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time. In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digibin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. **Studies with Atorvastatin:** The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g. cyclosporine, erythromycin, clarithromycin, and azole antifungals) (see **WARNINGS, Skeletal Muscle**). **Inhibitors of cytochrome P450 3A4:** Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4. **Clarithromycin:** Concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) resulted in a 4.4-fold increase in atorvastatin AUC (see **WARNINGS, Skeletal Muscle**, and **DOSE AND ADMINISTRATION**). **Erythromycin:** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with co-administration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see **WARNINGS, Skeletal Muscle**). **Combination of Protease Inhibitors:** Concomitant administration of atorvastatin 40 mg with ritonavir plus saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg+100 mg twice daily) resulted in a 5.9-fold increase in atorvastatin AUC (see **WARNINGS, Skeletal Muscle**, and **DOSE AND ADMINISTRATION**). **Itraconazole:** Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with a 2.5-3.3-fold increase in atorvastatin AUC. **Diltiazem hydrochloride:** Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin. **Cimetidine:** Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine. **Grapefruit juice:** Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day). **Cyclosporine:** Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an 8.7-fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with cyclosporine is necessary, the dose of atorvastatin should not exceed 10 mg (see **WARNINGS, Skeletal Muscle**). **Inducers of cytochrome P450 3A4:** Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. **Antacid:** When atorvastatin and Maalox TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. **Antipyrene:** Because atorvastatin does not affect the pharmacokinetics of antipyrene, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. **Colestipol:** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. **Digoxin:** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. **Oral Contraceptives:** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking CADUET. **Warfarin:** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. **Amlodipine:** In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful. **Amlodipine:** In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful. **Drug/Laboratory Test Interactions:** None known. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with amlodipine:** Rats and mice treated



The 4-T multicenter, open-label trial included 708 patients who had inadequate glycemic control on dual oral metformin and sulfonylurea therapy. The patients were a mean age of 61.7 years, with a mean disease duration of 9 years. They were randomized to one of three supplemental insulin regimens in the first year: prandial insulin aspart (NovoRapid) three times daily, biphasic insulin aspart (NovoMix 30) twice daily, or basal detemir (Levemir) once daily, or twice if needed.

In the second year, sulfonylureas were replaced by a second insulin if hyper-

glycemia became unacceptable, which was the case in almost 90% of the patient population, said Dr. Holman.

For such patients who had started on biphasic insulin, a midday prandial dose was added. For those who had started on either basal or prandial regimens, their treatments converged, so that the basal group added prandial doses (10% of the daily basal dose with a minimum and maximum limit) and the prandial group added a basal dose (10 units at bedtime). “The importance here is the temporal sequence—they are not identical,” said Dr. Holman. “So basal plus prandial was

not the same as prandial plus basal. They started at a different place and so the percentages were different. So those who started with prandial had substantially more prandial than basal at the end, and those who started with the basal and then added prandial ended up with about 50/50.”

Preliminary results published after the first year of the study did not favor the basal insulin regimen, which was the least successful at bringing hemoglobin A<sub>1c</sub> levels to 6.5% or less (N. Engl. J. Med. 2007;357:1716-30). “The addition of biphasic or prandial insulin aspart re-

duced levels more than the addition of basal insulin detemir but was associated with greater risks of hypoglycemia and weight gain,” the authors concluded at that time.

However, “the difference in outcomes from the first to the third year is startling,” Dr. Roden remarked in his editorial.

Final results showed that fewer than 45% of all patients achieved the HbA<sub>1c</sub> target of 6.5% or less. In addition, significantly fewer patients on the biphasic regimen (31.9%) compared to the prandial (44.7%) and basal (43.2%) groups, reached the target.

Furthermore, the basal group gained significantly less weight (3.6 kg) than did the biphasic and prandial groups (5.7 and 6.4 kg, respectively), and the median number of hypoglycemic events per

‘It shows that if you use insulin systematically it doesn’t really matter which way you start. You can get to the same glucose level, but there are other important differences.’

patient per year was lowest in the basal group (1.7), compared to the biphasic (3.0) and prandial groups (5.5).

“Median glycated hemoglobin levels converged after 1 year and remained stable in all groups, for an overall value at 3 years of 6.9%,” wrote the authors (7.1% for biphasic, 6.8% for prandial, and 6.9% for basal, with no significant differences). The final mean reduction from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group.

In an interview, Dr. Matthew Riddell commented that the 4-T results confirm the current guidelines from the American Diabetes Association and the European Association for the Study of Diabetes. “It shows that if you use insulin systematically it doesn’t really matter which way you start. You can get to the same glucose level, but there are other important differences in treatments. The 4-T gives us a clue that maybe the meal-time insulin treatments shouldn’t be the mainstay,” said the professor of medicine at Oregon Health and Science University in Portland.

“The overall message of the [final 4-T results] is that you need complex insulin regimens to obtain adequate glycemic control, which is still not reached in a substantial number of subjects,” Dr. Roden said in an interview.

The 4-T study was supported by Novo Nordisk A/S and Diabetes UK.

Dr. Holman reported receiving grants and consulting fees from pharmaceutical companies that included Novartis and Novo Nordisk, lecture fees from pharmaceutical companies, and royalties from sale of the Unistik single-use safety lancet. Dr. Roden reported receiving consulting and lecture fees from several drug makers, including Novo Nordisk. Dr. Riddle reported paid lecturing from and advisory board work with several drug companies.

with amliodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amliodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m<sup>2</sup> basis, similar to the maximum recommended human dose of 10 mg amliodipine/day\*. For the rat, the highest dose level was, on a mg/m<sup>2</sup> basis, about twice the maximum recommended human dose\*. Mutagenicity studies conducted with amliodipine maleate revealed no drug related effects at either the gene or chromosome levels. There was no effect on the fertility of rats treated orally with amliodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amliodipine/kg/day (8 times\* the maximum recommended human dose of 10 mg/day on a mg/m<sup>2</sup> basis). *Studies with atorvastatin:* In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females; in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for two years. \*Based on patient weight of 50 kg. **Pregnancy: Pregnancy Category X (see CONTRAINDICATIONS):** Safety in pregnant women has not been established with CADUET. CADUET should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking CADUET, it should be discontinued and the patient advised again as to the potential hazards to the fetus. *Studies with amliodipine:* No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amliodipine maleate at doses up to 10 mg amliodipine/kg/day (respectively 8 times\* and 23 times\* the maximum recommended human dose of 10 mg/day on a mg/m<sup>2</sup> basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amliodipine maleate at 10 mg amliodipine/kg/day for 14 days before mating and throughout mating and gestation. Amliodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. \*Based on patient weight of 50 kg. *Studies with atorvastatin:* Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses of atorvastatin calcium equivalent to up to 300 mg atorvastatin/kg/day or in rabbits at doses of atorvastatin calcium equivalent to up to 100 mg atorvastatin/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m<sup>2</sup>). In a study in rats given atorvastatin calcium at doses equivalent to 20, 100, or 225 mg atorvastatin/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity for pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 for pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses of atorvastatin correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. **Labor and Delivery:** No studies have been conducted in pregnant women on the effect of CADUET, amliodipine or atorvastatin on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amliodipine has been shown to prolong the duration of labor in rats. **Nursing Mothers:** It is not known whether the amliodipine component of CADUET is excreted in human milk. Nursing rat pups taking atorvastatin had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking CADUET should not breast-feed (see **CONTRAINDICATIONS**). **Pediatric Use:** There have been no studies conducted to determine the safety or effectiveness of CADUET in pediatric populations. *Studies with amliodipine:* The effect of amliodipine on blood pressure in patients less than 6 years of age is not known. *Studies with atorvastatin:* Safety and effectiveness in patients 1-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months' duration in adolescent boys and postmenarcheal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. See **CLINICAL PHARMACOLOGY, Clinical Studies** section; **ADVERSE REACTIONS, Pediatric Patients;** and **DOSAGE AND ADMINISTRATION, Pediatric Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia.** Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see **CONTRAINDICATIONS** and **PRECAUTIONS, Pregnancy**). **Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.** Clinical efficacy with doses of atorvastatin up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. See **CLINICAL PHARMACOLOGY, Clinical Studies, Atorvastatin Effects in Homozygous Familial Hypercholesterolemia. Geriatric Use:** There have been no studies conducted to determine the safety or effectiveness of CADUET in geriatric populations. *In studies with amliodipine:* Clinical studies of amliodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection of the amliodipine component of CADUET for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amliodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**). *In studies with atorvastatin:* The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (>65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin calcium 10 mg. Of these, 835 were elderly (>65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin calcium 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group. The rates of discontinuation in patients on atorvastatin due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups. *In studies with Atorvastatin: Use in Patients with Recent Stroke or TIA:* In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where LIPITOR 80 mg vs placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo. Subjects with hemorrhagic stroke on study entry appeared to be at increased risk for hemorrhagic stroke.

**ADVERSE REACTIONS: CADUET:** CADUET (amliodipine besylate/atorvastatin calcium) has been evaluated for safety in 1092 patients in double-blind placebo controlled studies treated for co-morbid hypertension and dyslipidemia. In general, treatment with CADUET was well tolerated. For the most part, adverse experiences have been mild or moderate in severity. In clinical trials with CADUET, no adverse experiences peculiar to this combination have been observed. Adverse experiences are similar in terms of nature, severity, and frequency to those reported previously with amliodipine and atorvastatin. The following information is based on the clinical experience with amliodipine and atorvastatin. **The Amliodipine Component of CADUET:** Amliodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amliodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amliodipine were of mild or moderate severity. In controlled clinical trials directly comparing amliodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amliodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Adverse Event	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.0

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-controlled Studies Adverse Event	amliodipine (%) (N=1730)	Placebo (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	4.6
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amliodipine treatment as shown in the following table:

Adverse Event	amliodipine M=1% (N=1218)	Placebo F=1% (N=326)
Edema	14.6	9.1
Flushing	1.5	0.9
Palpitations	1.4	0.9
Somnolence	1.3	0.3

The following events occurred in <1% but >0.1% of patients treated with amliodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia,\*\* dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia,\*\* back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease. **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps,\*\* myalgia. **Psychiatric:** sexual dysfunction (male\*\* and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** dyspnea,\*\* epistaxis. **Skin and Appendages:** angioedema, erythema multiforme, pruritus,\*\* rash,\*\* rash erythematous, rash maculopapular. \*\*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. **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hematologic:** leukopenia, purpura, thrombocytopenia. The following events occurred in <0.1% of patients treated with amliodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertension, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina. Amliodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. In the CAMELOT and PREVENT studies (see **CLINICAL PHARMACOLOGY Clinical Studies, Clinical Studies with Amliodipine**) the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema. The following postmarketing event has been reported infrequently with amliodipine treatment where a causal relationship is uncertain: glycemiasia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amliodipine. Amliodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. **The Atorvastatin Component of CADUET:** Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences:** Adverse experiences reported in <2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 3.

	atorvastatin 20 mg N=36	40 mg N=79	80 mg N=94
<b>Body System/ Adverse Event</b>			
<b>BODY AS A WHOLE</b>			
Infection	10.0	10.3	7.4
Headache	7.0	5.4	6.4
Accidental Injury	3.7	4.2	3.2
Flu Syndrome	1.9	2.2	3.2
Abdominal Pain	0.7	2.8	2.1
Back Pain	3.0	2.8	1.1
Allergic Reaction	2.6	0.9	1.3
Asthenia	1.9	2.2	0.0
<b>DIGESTIVE SYSTEM</b>			
Constipation	1.8	2.1	1.1
Dyspepsia	4.1	2.3	5.3
Flatulence	3.3	2.1	1.1
<b>RESPIRATORY SYSTEM</b>			
Sinusitis	2.6	2.8	6.4
Pharyngitis	1.5	2.5	2.1
<b>SKIN AND APPENDAGES</b>			
Rash	0.7	3.9	1.1
<b>MUSCULOSKELETAL SYSTEM</b>			
Arthralgia	1.5	2.0	0.0
Myalgia	1.1	3.2	0.0

*Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT):* In ASCOT (see **CLINICAL PHARMACOLOGY, Clinical Studies, Clinical Studies with Atorvastatin**) involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up. *Collaborative Atorvastatin Diabetes Study (CARDS):* In CARDS (see **CLINICAL PHARMACOLOGY, Clinical Studies, Clinical Studies with Atorvastatin**) involving 2838 subjects with type 2 diabetes treated with LIPITOR 10 mg daily (n=1428) or placebo (n=1410), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported. *Treating to New Targets Study (TNT):* In TNT (see **CLINICAL PHARMACOLOGY, Clinical Studies**) involving 10,001 subjects with clinically evident CHD treated with LIPITOR 10 mg daily (n=5006) or LIPITOR 80 mg daily (n=4995), there were more serious adverse events and discontinuations due to adverse events in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4-10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%). *Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL):* In IDEAL (see **CLINICAL PHARMACOLOGY, Clinical Studies**) involving 8,888 subjects treated with LIPITOR 80 mg/day (n=4439) or simvastatin 20-40 mg daily (n=4449), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 4.8 years. The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients. **Body as a Whole:** Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. **Respiratory System:** Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis. **Nervous System:** Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypoesthesia, hypertension. **Musculoskeletal System:** Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinosis contracture, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. **Urogenital System:** Urinary tract infection, hematuria, albuminuria, urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Echinymosis, anemia, lymphadenopathy, thrombocytopenia, petechia. **Postintroduction Reports with Atorvastatin:** Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, and hepatic failure. **Pediatric Patients (ages 10-17 years):** In a 26-week controlled study in boys and postmenarcheal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies** section and **PRECAUTIONS, Pediatric Use**). Please see full prescribing information for additional information about CADUET.

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