A Single Tablet To Help Manage Patients With Hypertension and Other Cardiovascular Risk Factors
Managing Patients With Hypertension And Other Cardiovascular Risk Factors

Hypertension, an independent risk factor for coronary heart disease (CHD), is highly prevalent in the United States. The most recent data from the National Health and Nutrition Examination Survey (NHANES) indicate that at least 61 million U.S. adults — 29 percent — had high blood pressure (systolic ≥140 mm Hg or diastolic ≥90 mm Hg) in 1999–2002.

Hypertension is among the well-known modifiable risk factors for CHD, along with other risk factors such as dyslipidemia, smoking, obesity, and physical inactivity. The majority of hypertensive patients have dyslipidemia as an additional risk factor, according to NHANES 1999–2002.

The Multiple Risk Factor Intervention Trial (MRFIT), in which middle-aged white men without CHD were followed for a mean of 12 years, showed that in nonsmoking patients with hypertension (n=202,619), the risk of a CHD death increases as cholesterol levels increase (Figure). Furthermore, the joint effect of hypertension and dyslipidemia on CHD mortality rates is greater than that of either risk factor alone.

This makes managing blood pressure (BP) and dyslipidemia even more important, in terms of CHD events.

Results of a large retrospective cohort study of patients with hypertension in a managed care population showed that among patients who initially were given an antihypertensive (AH) and a lipid-lowering (LL) therapy within a 91-day period as an addition to their existing prescription medication, the more medications patients took, the less likely they were to refill their newly prescribed antihypertensive and lipid-lowering medications adequately. In this managed care population study, patients were considered adherent to AH and LL therapy if they had sufficient AH and LL therapies to cover at least 80 percent of days per 91-day period; however, whether patients actually took the medication was not determined.

In the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA), which involved 10,305 treated hypertensive patients with additional risk factors and without CHD, Lipitor® (atorvastatin calcium) reduced the relative risk of nonfatal myocardial infarction (MI) by 45 percent (P=.0002) and stroke by 26 percent (P=.033). Although the reduction of fatal and nonfatal stroke did not reach a predefined significance level (P=.01), a favorable trend was observed. Relative risk reduction in the primary end point, a composite of time to first occurrence of nonfatal MI or fatal CHD, was 36 percent (P=.0005). Patients in each treatment

These data did not include Caduet® (amlodipine besylate/atorvastatin calcium). No conclusion about Caduet, Norvasc® (amlodipine besylate), or Lipitor® (atorvastatin calcium) can be made about these data.

FIGURE In hypertensive patients, risk of CV event increases as cholesterol levels increase

An examination of data from patients screened for the Multiple Risk Factor Intervention Trial (MRFIT), a primary prevention trial studying the combined influence of BP, serum cholesterol level, and smoking on age-adjusted CHD mortality in 316,099 white men aged 35 to 57 years. This figure depicts data on the correlation of CHD mortality to varying levels of BP and cholesterol in 202,619 nonsmoking white subjects followed up for an average of 12 years.

SOURCE: NEATON 1992
Managing Patients With Hypertension: Is Lowering Blood Pressure Enough?  

Managed care analysis by Steven Peskin, MD  
Corporate Medical Director, MediMedia USA

Compelling data from landmark clinical trials, such as the Multiple Risk Factor Intervention Trial (MRFIT), demonstrate the presence of hypertension, as well as additional cardiovascular risk factors, including hypercholesterolemia, increases the risk of CVD in patients with hypertension.

For physicians and other clinical executives responsible for population health management, the message is clear. Interventions — lifestyle, behavioral, or pharmacologic — that address more than one risk factor may lead to greater risk reduction in the cardiovascular morbidity and mortality of hypertensive patients.

Simplifying medication regimen — for example, by reducing pill count — may result in improved adherence.

This clinical brief summarizes important key clinical data on the blood-pressure lowering efficacy of Norvasc and cardiovascular benefits of Lipitor, the two components of Caduet that help support the rationale of Caduet treatment, which through Lipitor, helps to reduce CV risk in patients with hypertension without CHD and additional risk factors, including dyslipidemia.

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### Important Safety Information

Caduet is a combination of two medications, Norvasc® (amlodipine besylate) and Lipitor® (atorvastatin), and is modification of effect of either component on SBP, DBP, and LDL-C.¹⁰

In clinical trials enrolling patients with comorbid hypertension and dyslipidemia, these agents have been generally well tolerated. Caduet adverse experiences are similar in nature, severity, and frequency to those reported previously with Norvasc and Lipitor taken separately.

Used with diet and exercise, Caduet is a single, once-daily tablet for hypertensive patients with additional CV risk factors without CHD who need the blood pressure lowering of amlodipine and the cardiovascular benefits of atorvastatin. With this single pill formulation, Caduet may simplify patients’ medication regimen by reducing the number of prescriptions to refill, and eliminating one copayment,¹ while treating two CV risk factors.

¹Compared to amlodipine and atorvastatin administered separately.
indicated in patients for whom treatment with both Norvasc and Lipitor is appropriate. Norvasc is indicated for the treatment of hypertension and chronic stable or vasospastic angina. Lipitor is indicated as an adjunct to diet and exercise to reduce the risk of MI, revascularization procedures, and angina in adult patients with multiple risk factors but without clinically evident CHD; and to reduce elevated total-C, LDL-C, apo B, TG levels; and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

Caduet is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women who are pregnant or may become pregnant and/or nurse; in patients with hypersensitivity to any component of this medication.

Rare cases of rhabdomyolysis have been reported with the Lipitor component of Caduet and with other statins. With any statin, tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected, if creatine phosphokinase (CPK) levels rise markedly, or if the patient has risk factors for rhabdomyolysis.

Due to increased risk of myopathy seen with the Lipitor component of Caduet and other statins, physicians should carefully consider combined therapy with fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or niacin and carefully monitor patients for signs or symptoms of myopathy early during therapy and when titrating dose of either drug.

It is recommended that liver function tests be performed prior to and 12 weeks following the initiation of Caduet therapy and any elevation in dose of the Lipitor component, and periodically thereafter. If ALT or AST values >3X ULN persist, dose reduction or withdrawal of Lipitor is recommended.

Generally CCBs should be used with caution in patients with heart failure. In studies with Norvasc, there has been no evidence of worsened heart failure.

In a controlled clinical trial, the most common adverse events were edema, headache, and dizziness. These were similar to those reported previously with Norvasc and/or Lipitor.

Please see brief summary of prescribing information.
CADUET® (amlodipine besilate/atorvastatin calcium) Tablets

Brief Summary: for full prescribing information, see package insert.

INDICATIONS AND USAGE: CADUET® (amlodipine besilate/atorvastatin calcium) 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. Constipative Analgesia: Amlodipine is indicated for the treatment of chronic stable angina. For this indication, amlodipine is not recommended for use in patients with other antihypertensive drugs. Atorvastatin: 1. Prevention of Cardiovascular Disease: In adults, CADUET® is indicated as an adjunct to diet in the management of hypercholesterolemia (Fredrickson Types Ia and IIa and IIb) and as an adjunct to diet and other lipid-lowering therapies in the management of hypercholesterolemia (Fredrickson Types IV and V).

Primary Dyslipidemia/ Hypercholesterolemia: CADUET® is indicated for the treatment of adults with primary dyslipidemia (Fredrickson Types Ia and IIa). It may be used alone or in combination with other lipid-lowering therapies. Amlodipine: 1. Hypertension: Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive drugs. Amlodipine may be used in patients who have had a myocardial infarction or who have congestive heart failure. It has also been used in patients with stable angina, hypertension, and diabetes. It has also been used in patients with other antihypertensive drugs. Atorvastatin: 1. Prevention of Cardiovascular Disease: In adults, CADUET® is indicated as an adjunct to diet in the management of hypercholesterolemia (Fredrickson Types Ia and IIa) and as an adjunct to diet and other lipid-lowering therapies in the management of hypercholesterolemia (Fredrickson Types IV and V).

PRECAUTIONS: General: Since the coadministration of the amlodipine component of CADUET® is a moderate CYP3A4 inhibitor, moderate inhibition of CYP3A4 may occur and could result in a clinically significant increase in plasma concentrations of drugs that are highly dependent on CYP3A4 for their metabolism. As with any drug that is highly dependent on CYP3A4 for its metabolism, the use of drugs that are CYP3A4 substrates with CADUET® may require a reduction in the dose of one or both of the components of CADUET®. The effects of these drugs on atorvastatin metabolism should be reviewed, and, if necessary, the dose of atorvastatin should be adjusted. The use of drugs that are CYP3A4 substrates with CADUET® may also require an increase in the dose of one or both of the components of CADUET®. The effects of these drugs on amlodipine metabolism should be reviewed, and, if necessary, the dose of amlodipine should be adjusted. The use of drugs that are CYP3A4 substrates with CADUET® may also require an increase in the dose of one or both of the components of CADUET®. The effects of these drugs on atorvastatin metabolism should be reviewed, and, if necessary, the dose of atorvastatin should be adjusted. The use of drugs that are CYP3A4 substrates with CADUET® may also require an increase in the dose of one or both of the components of CADUET®. The effects of these drugs on amlodipine metabolism should be reviewed, and, if necessary, the dose of amlodipine should be adjusted.

CONTRAINDICATIONS: CADUET® contains amlodipine and atorvastatin and is contraindicated in patients with active liver disease, renal impairment, and any known hypersensitivity to either component of this medication. Pregnanate and lactating females are also contraindicated in the use of CADUET®. The use of CADUET® is not recommended in patients with severe aortic stenosis. Before instituting therapy with CADUET®, an attempt should be made to determine the serum creatinine level. Amlodipine: 1. Hypertension: Amlodipine is contraindicated in patients with severe aortic stenosis. It is not recommended for use in patients with severe aortic stenosis. Before instituting therapy with CADUET®, an attempt should be made to determine the serum creatinine level. Atorvastatin: 1. Prevention of Cardiovascular Disease: In adults, CADUET® is indicated as an adjunct to diet in the management of hypercholesterolemia (Fredrickson Types Ia and IIa) and as an adjunct to diet and other lipid-lowering therapies in the management of hypercholesterolemia (Fredrickson Types IV and V).

Drug Interaction: CADUET® contains amlodipine and atorvastatin. Both amlodipine and atorvastatin are metabolized by CYP3A4. The use of drugs that are CYP3A4 substrates with CADUET® may require a reduction in the dose of one or both of the components of CADUET®. The effects of these drugs on atorvastatin metabolism should be reviewed, and, if necessary, the dose of atorvastatin should be adjusted. The use of drugs that are CYP3A4 substrates with CADUET® may also require an increase in the dose of one or both of the components of CADUET®. The effects of these drugs on amlodipine metabolism should be reviewed, and, if necessary, the dose of amlodipine should be adjusted. The use of drugs that are CYP3A4 substrates with CADUET® may also require an increase in the dose of one or both of the components of CADUET®. The effects of these drugs on atorvastatin metabolism should be reviewed, and, if necessary, the dose of atorvastatin should be adjusted. The use of drugs that are CYP3A4 substrates with CADUET® may also require an increase in the dose of one or both of the components of CADUET®. The effects of these drugs on amlodipine metabolism should be reviewed, and, if necessary, the dose of amlodipine should be adjusted.