

Pandemic Flu Vaccine Under Study for Asthmatics

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A new phase II trial will test the safety and efficacy of the pandemic influenza A(H1N1) vaccine on patients with mild to severe asthma.

Although the vaccine has already been approved as safe and effective in the general population, additional studies are necessary to confirm its effect on those with asthma—especially those who take

glucocorticoid medications, Dr. Anthony Fauci said in a statement.

“People with severe asthma often take high doses of glucocorticoids that can suppress their immune system, placing them at greater risk for infection and possibly serious disease caused by 2009 H1N1 influenza virus,” said Dr. Fauci, director of the National Institute of Allergy and Infectious Disease (NIAID). “We need to determine the optimal dose of

2009 H1N1 influenza vaccine that can be safely administered to this at-risk population and whether one or two doses are needed to provide an immune response that is predictive of protection.”

The study, sponsored by NIAID and the National Heart, Lung, and Blood Institute, plans to enroll 350-400 healthy subjects aged 12 years and older with mild, moderate, or severe asthma. Participants will be stratified into two

groups: those with mild to moderate versus those with severe asthma. All participants will be randomly assigned to receive either a high-dose (30 mcg) or low-dose (15 mcg) H1N1 vaccine. Both vaccine dosages will be administered in two intramuscular injections 21 days apart. Participants assigned to the higher dose (30 mcg) will receive two injections of the 15-mcg vaccine at each administration. ■

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

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) 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 postmenarcheal 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 \geq 190 mg/dL or
- b. LDL-C remains \geq 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 Cutpoints 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 ^a or CHD risk equivalents (10-year risk \geq 20%)	<100	\geq 100	\geq 130 (100-129: drug optional) ^b
2+ Risk Factors (10-year risk \approx 20%)	<130	\geq 130	10-year risk 10%-20%: \geq 130 10-year risk \geq 20%: \geq 160
0-1 Risk Factor ^c	<160	\geq 160	\geq 190 (160-189: LDL-lowering drug optional)

^a CHD, coronary heart disease. ^b 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 fibrates. Clinical judgment also may call for deferring drug therapy in this subcategory. ^c 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	\geq 200	\geq 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 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 II/III 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. **Endrupt Beta-Blocker:** 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, spiroinolactone, 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 (mice) and 8 to 16 times (rats) 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 (Wallerian 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 atorvastatin showed no effect on the C_{max}: 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. **Atorvastatin:** Co-administration of the antagonist, Maelox with a single dose of amlodipine had no significant effect on the pharmacokinetics of atorvastatin. **Sildenafil:** A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of atorvastatin. 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, digoxin, 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. **Atorvastatin and Maelox:** When atorvastatin and Maelox TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. **Atorvastatin:** Because atorvastatin does not affect the pharmacokinetics of antipyrine, 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