

CADUET®
(amlodipine besylate/atorvastatin calcium) Tablets

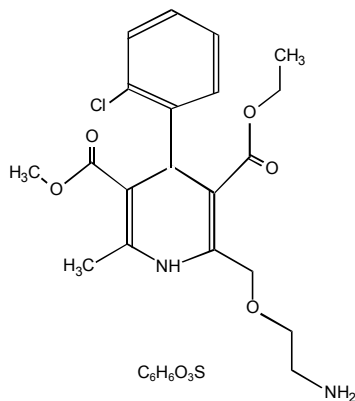
DESCRIPTION

CADUET® (amlodipine besylate and atorvastatin calcium) tablets combine the long-acting calcium channel blocker amlodipine besylate with the synthetic lipid-lowering agent atorvastatin calcium.

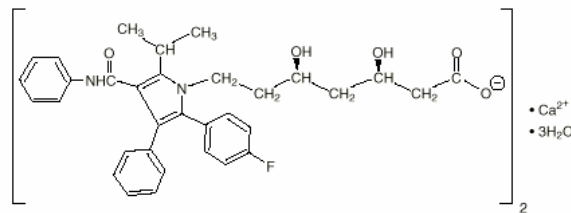
The amlodipine besylate component of CADUET is chemically described as 3-Ethyl-5-methyl (\pm)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

The atorvastatin calcium component of CADUET is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Its empirical formula is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$.

The structural formulae for amlodipine besylate and atorvastatin calcium are shown below.



Amlodipine besylate



Atorvastatin calcium

CADUET contains amlodipine besylate, a white to off-white crystalline powder, and atorvastatin calcium, also a white to off-white crystalline powder. Amlodipine besylate has a molecular weight of 567.1 and atorvastatin calcium has a molecular weight of 1209.42. Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol. Atorvastatin calcium is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol, and freely soluble in methanol.

CADUET tablets are formulated for oral administration in the following strength combinations:

Table 1: CADUET Tablet Strengths

	5mg/ 10mg	5mg/ 20mg	5mg/ 40mg	5mg/ 80mg	10mg/ 10mg	10mg/ 20mg	10mg/ 40mg	10mg/ 80mg
amlodipine equivalent (mg)	5	5	5	5	10	10	10	10
atorvastatin equivalent (mg)	10	20	40	80	10	20	40	80

Each tablet also contains calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicon dioxide (anhydrous), magnesium stearate, Opadry® II White 85F28751 (polyvinyl alcohol, titanium dioxide, PEG 3000 and talc) or Opadry® II Blue 85F10919 (polyvinyl alcohol, titanium dioxide, PEG 3000, talc and FD&C blue #2). Combinations of atorvastatin with 5 mg amlodipine are film coated white, and combinations of atorvastatin with 10 mg amlodipine are film coated blue.

CLINICAL PHARMACOLOGY

Mechanism of Action

CADUET

CADUET, is a combination of two drugs, a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) amlodipine (antihypertensive/antianginal agent) and an HMG-CoA reductase inhibitor atorvastatin (cholesterol lowering agent). The amlodipine component of CADUET inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of CADUET is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

The Amlodipine Component of CADUET

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A₂ analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

The Atorvastatin Component of CADUET

Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor.

Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

The effect of atorvastatin on cardiovascular morbidity and mortality has not been determined.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not

of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacokinetics and Metabolism

Absorption

Studies with amlodipine: After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine when administered alone is not altered by the presence of food.

Studies with atorvastatin: After oral administration alone, atorvastatin is rapidly absorbed; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see **DOSAGE AND ADMINISTRATION**).

Studies with CADUET: Following oral administration of CADUET peak plasma concentrations of amlodipine and atorvastatin are seen at 6 to 12 hours and 1 to 2 hours post dosing, respectively. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from CADUET are not significantly different from the bioavailability of amlodipine and atorvastatin administered separately (see above).

The bioavailability of amlodipine from CADUET was not affected by food. Although food decreases the rate and extent of absorption of atorvastatin from CADUET by approximately 32% and 11%, respectively, as it does with atorvastatin when given alone. LDL-C reduction is similar whether atorvastatin is given with or without food.

Distribution

Studies with amlodipine: *Ex vivo* studies have shown that approximately 93% of the circulating amlodipine drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Studies with atorvastatin: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk (see **CONTRAINDICATIONS, Pregnancy and Lactation, and PRECAUTIONS, Nursing Mothers**).

Metabolism

Studies with amlodipine: Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism.

Studies with atorvastatin: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see **PRECAUTIONS, Drug Interactions**). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Studies with amlodipine: Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Ten percent of the parent amlodipine compound and 60% of the metabolites of amlodipine are excreted in the urine.

Studies with atorvastatin: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric

Studies with amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose of amlodipine may be required.

Studies with atorvastatin: Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of atorvastatin in the elderly population compared to younger adults. (see **PRECAUTIONS section, Geriatric Use**).

Pediatric

Studies with amlodipine: Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Studies with atorvastatin: Pharmacokinetic data in the pediatric population are not available.

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