

Caduet® Monograph

Brand Name: Caduet®

Generic Name: Amlodipine/Atorvastatin

Manufacturer: Pfizer

Year introduced: The FDA approved amlodipine/atorvastatin on January 30, 2004.

Mechanism of Action:

Amlodipine is a dihydropyridine calcium antagonist (calcium channel blocker). It inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The result is a reduction in peripheral vascular resistance and reduction in blood pressure.

Atorvastatin 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. Atorvastatin lowers plasma cholesterol and lipoprotein levels. The effect of atorvastatin on cardiovascular morbidity and mortality has not been determined.

FDA-approved indications:

Amlodipine/atorvastatin is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine indications

1. Hypertension
2. Chronic stable angina
3. Vasospastic angina (Prinzmetal's or variant angina)
4. Angiographically documented CAD

Atorvastatin indications

1. Reduce the risk of myocardial infarction (MI), reduce the risk of stroke, and reduce the risk for revascularization procedures and angina in adult patients without clinically evident coronary heart disease (CHD), but with multiple risk factors for CHD
2. Reduce risk of MI and stroke in patients with type 2 diabetes, and without clinically evident CHD, but with multiple risk factors for CHD
3. Reduce the risk of non-fatal MI, reduce the risk of fatal and non-fatal stroke, reduce the risk for revascularization procedures, reduce the risk of hospitalization for CHF, and reduce the risk of angina in patients with clinically evident CHD
4. Heterozygous familial and nonfamilial hypercholesterolemia
5. Elevated serum triglyceride levels
6. Primary dysbetalipoproteinemia
7. Homozygous familial hypercholesterolemia
8. Heterozygous familial hypercholesterolemia in boys and postmenarchal girls 10-17 years of age

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Contraindications:

- Known hypersensitivity to the product or any component of the product
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy and lactation

Pharmacokinetics:

Following oral administration of amlodipine/atorvastatin, peak plasma concentrations of amlodipine and atorvastatin occur at 6-12 hours and 1-2 hours post dosing, respectively. The bioavailability of amlodipine and atorvastatin in the combination product is not significantly different from the agents administered separately.

| | Amlodipine | Atorvastatin |
|--------------|--|---|
| Absorption | The absolute bioavailability is estimated to be between 64% and 90%. The bioavailability is not affected by food. | The absolute bioavailability of atorvastatin (parent drug) is approximately 14%. The systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. Food decreases the rate and extent of drug absorption, but the LDL-C reduction is similar whether given with or without food. |
| Distribution | Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients. | Atorvastatin is ≥98% bound to plasma proteins. |
| Metabolism | Amlodipine is extensively (~90%) converted to inactive metabolites via hepatic metabolism. | Atorvastatin is extensively metabolized by cytochrome P450 (CYP) 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulating HMG-CoA reductase inhibitory activity is attributed to active metabolites. |
| Elimination | Elimination of amlodipine is biphasic with a terminal elimination half-life of 30-50 hours. Ten percent of the parent compound and 60% of the metabolites are excreted in the urine. | Atorvastatin and its metabolites are eliminated primarily in the bile following hepatic and/or extra-hepatic metabolism. The mean plasma elimination half-life is ~14 hours; the half-life of the inhibitory activity for HMG-CoA reductase is 20-30 hours. Less than 2% of a dose is recovered in the urine. |

Adverse Effects:

Per prescribing information, amlodipine/atorvastatin has been evaluated for safety in 1,092 patients in double-blind placebo controlled studies as treatment for co-morbid hypertension and dyslipidemia. However, none of the data were included in the prescribing information, and none of the studies were published at the time of this writing. Also per the prescribing

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information, observed adverse experiences in terms of nature, severity, and frequency were similar to those previously reported with amlodipine and atorvastatin. Adverse events noted with the individual components are reported below.

Amlodipine

The most common adverse events with amlodipine are headache and edema.

**Amlodipine Dose-Related Adverse Events:
Incidence in Placebo-Controlled Clinical Studies**

| Adverse Event (%) | Amlodipine 2.5 mg (N=275) | Amlodipine 5 mg (N=296) | Amlodipine 10 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 |
| Palpitation | 0.7 | 1.4 | 4.5 | 0.6 |

**Amlodipine Adverse Events – Not Clearly Dose-Related:
Incidence >1% in Placebo-Controlled Clinical Studies**

| Adverse Event (%) | Amlodipine (N=1730) | Placebo (N=1250) |
|-------------------|------------------------|---------------------|
| Headache | 7.3 | 7.8 |
| Fatigue | 4.5 | 2.8 |
| Nausea | 2.9 | 1.9 |
| Abdominal Pain | 1.6 | 0.3 |
| Somnolence | 1.4 | 0.6 |

Several drug- and dose-related adverse events occurred at a greater incidence in women than in men.

| Adverse Event (%) | Amlodipine Men (N=1218) | Amlodipine Women (N=512) | Placebo Men (N=914) | Placebo Women (N=336) |
|-------------------|-------------------------------|--------------------------------|---------------------------|-----------------------------|
| Edema | 5.6 | 14.6 | 1.4 | 5.1 |
| Flushing | 1.5 | 4.5 | 0.3 | 0.9 |
| Palpitation | 1.4 | 3.3 | 0.9 | 0.9 |
| Somnolence | 1.3 | 1.6 | 0.8 | 0.3 |

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Atorvastatin

The most frequent adverse events in atorvastatin clinical trials that were thought to be related to the drug were constipation, flatulence, dyspepsia, and abdominal pain.

**Atorvastatin Adverse Events:
Incidence ≥2% in Placebo-Controlled Clinical Studies**

| Adverse Event (%) | Placebo (N=270) | Atorvastatin 10 mg (N=863) | Atorvastatin 20 mg (N=36) | Atorvastatin 40 mg (N=79) | Atorvastatin 80 mg (N=94) |
|-------------------------------|-----------------|----------------------------|---------------------------|---------------------------|---------------------------|
| Body as a Whole | | | | | |
| Infection | 10.0 | 10.3 | 2.8 | 10.1 | 7.4 |
| Headache | 7.0 | 5.4 | 16.7 | 2.5 | 6.4 |
| Accidental Injury | 3.7 | 4.2 | 0.0 | 1.3 | 3.2 |
| Flu Syndrome | 1.9 | 2.2 | 0.0 | 2.5 | 3.2 |
| Abdominal Pain | 0.7 | 2.8 | 0.0 | 3.8 | 2.1 |
| Back Pain | 3.0 | 2.8 | 0.0 | 3.8 | 1.1 |
| Allergic Reaction | 2.6 | 0.9 | 2.8 | 1.3 | 0.0 |
| Asthenia | 1.9 | 2.2 | 0.0 | 3.8 | 0.0 |
| Digestive System | | | | | |
| Constipation | 1.8 | 2.1 | 0.0 | 2.5 | 1.1 |
| Diarrhea | 1.5 | 2.7 | 0.0 | 3.8 | 5.3 |
| Dyspepsia | 4.1 | 2.3 | 2.8 | 1.3 | 2.1 |
| Flatulence | 3.3 | 2.1 | 2.8 | 1.3 | 1.1 |
| Respiratory System | | | | | |
| Sinusitis | 2.6 | 2.8 | 0.0 | 2.5 | 6.4 |
| Pharyngitis | 1.5 | 2.5 | 0.0 | 1.3 | 2.1 |
| Skin and Appendages | | | | | |
| Rash | 0.7 | 3.9 | 2.8 | 3.8 | 1.1 |
| Musculoskeletal System | | | | | |
| Arthralgia | 1.5 | 2.0 | 0.0 | 5.1 | 0.0 |
| Myalgia | 1.1 | 3.2 | 5.6 | 1.0 | 0.0 |

Drug Interactions:

No drug interaction studies have been conducted with amlodipine/atorvastatin and other drugs. Studies with the individual components are summarized below.

| Precipitant Drug | Object Drug | | Description |
|-------------------|---------------------|---|--|
| Atorvastatin | Digoxin | ↑ | Steady-state plasma digoxin concentrations increased by ~20%. |
| Atorvastatin | Oral contraceptives | ↑ | AUC values for norethindrone and ethinyl estradiol increased by approximately 30% and 20%, respectively. |
| Azole antifungals | Atorvastatin | ↑ | Increased risk of myopathy with concurrent administration |
| Clarithromycin | Atorvastatin | ↑ | Increased risk of myopathy with concurrent administration |
| Cyclosporine | Atorvastatin | ↑ | Increased risk of myopathy with concurrent administration |
| Diltiazem | Atorvastatin | ↑ | Increased risk of myopathy with concurrent administration |

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| Precipitant Drug | Object Drug | | Description |
|-------------------------|--------------|---|---|
| Erythromycin | Atorvastatin | ↑ | Increased risk of myopathy with concurrent administration; increased atorvastatin plasma concentrations by ~40% |
| Fibric acid derivatives | Atorvastatin | ↑ | Increased risk of myopathy with concurrent administration |
| Niacin (nicotinic acid) | Atorvastatin | ↑ | Increased risk of myopathy with concurrent administration |
| Protease Inhibitors | Atorvastatin | ↑ | Increased risk of myopathy with concurrent administration |
| Sildenafil | Amlodipine | ↑ | Additive blood pressure lowering |

Warnings/Precautions:

Cardiovascular Morbidity and Mortality

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

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 upon starting calcium channel blocker therapy or at the time of dosage increase.

Liver Dysfunction

HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the ULN occurring on two or more occasions) in serum transaminases have occurred with atorvastatin therapy. Jaundice developed in one patient.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin. Uncomplicated myalgia and myopathy have also been reported.

Hypotension

Rarely, hypotension may occur with amlodipine therapy. Caution should be exercised when administering amlodipine/atorvastatin to a patient with severe aortic stenosis.

Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and, theoretically, might blunt adrenal and/or gonadal steroid production.

Myopathy

The risk of myopathy is increased when HMG-CoA reductase inhibitors are coadministered with CYP 3A4 inhibitors, fibric acid derivatives, or niacin. Lower starting and maintenance doses of atorvastatin are imperative when coadministered with these products to ensure that the lowest dose necessary of atorvastatin is administered.

Pregnancy/Lactation:

- Pregnancy Category X
- HMG-CoA reductase inhibitors are contraindicated in pregnancy and lactation

Usual Dosage:

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The dosage of Caduet (amlodipine/atorvastatin) must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia.

Amlodipine – 5-10 mg QD

Atorvastatin – 10-80 mg QD (pediatric patients – 10-17 years of age – 10-20 mg/day)

Availability:

5/10 mg, 10/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, 10/40 mg, 5/80 mg, 10/80 mg, 2.5/10 mg, 2.5/20 mg, 2.5/40 mg

Clinical Studies:

There are no published clinical trials with amlodipine/atorvastatin. Information below is found in the Clinical Studies section of the product prescribing information

In a double-blind, placebo-controlled study, 1660 patients with co-morbid hypertension and dyslipidemia received once daily treatment with one of eight dose combinations of amlodipine and atorvastatin (5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, or 10/80 mg), amlodipine alone (5 or 10 mg), atorvastatin alone (10, 20, 40, or 80 mg), or placebo. At eight weeks, all combination treatment groups demonstrated “statistically significant” (p-values not reported) dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP), and LDL-C compared to placebo, with no overall modification of effect of either component on SBP, DBP, and LDL-C (see tables below).

AML = amlodipine; ATO = atorvastatin

Effect on SBP

| | | Placebo | ATO 10 mg | ATO 20 mg | ATO 40 mg | ATO 80 mg |
|-----------|--------------------|---------|--------------|--------------|--------------|--------------|
| Placebo | Mean change (mmHg) | -3.0 | -4.5 | -6.2 | -6.2 | -6.4 |
| | Vs. placebo (mmHg) | -- | -1.5 | -3.2 | -3.2 | -3.4 |
| AML 5 mg | Mean change (mmHg) | -12.8 | -13.7 | -15.3 | -12.7 | -12.2 |
| | Vs. placebo (mmHg) | -9.8 | -10.7 | -12.3 | -9.7 | -9.2 |
| AML 10 mg | Mean change (mmHg) | -16.2 | -15.9 | -16.1 | -16.3 | -17.6 |
| | Vs. placebo (mmHg) | -13.2 | -12.9 | -13.1 | -13.1 | -14.6 |

Effect on DBP

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| | | Placebo | ATO 10 mg | ATO 20 mg | ATO 40 mg | ATO 80 mg |
|-----------|-----------------------|---------|--------------|--------------|--------------|--------------|
| Placebo | Mean change (mmHg) | -3.3 | -4.1 | -3.9 | -5.1 | -4.1 |
| | Vs. placebo (mmHg) | -- | -0.8 | -0.6 | -1.8 | -0.8 |
| AML 5 mg | Mean change (mmHg) | -7.6 | -8.2 | -9.4 | -7.3 | -8.4 |
| | Vs. placebo (mmHg) | -4.3 | -4.9 | -6.1 | -4.0 | -5.1 |
| AML 10 mg | Mean change (mmHg) | -10.4 | -9.1 | -10.6 | -9.8 | -11.1 |
| | Vs. placebo (mmHg) | -7.1 | -5.8 | -7.3 | -6.5 | -7.8 |

Effect on LDL-C

| | | Placebo | ATO 10 mg | ATO 20 mg | ATO 40 mg | ATO 80 mg |
|-----------|------------------|---------|--------------|--------------|--------------|--------------|
| Placebo | Mean % change | -1.1 | -33.4 | -39.5 | -43.1 | -47.2 |
| AML 5 mg | Mean % change | -0.1 | -38.7 | -42.3 | -44.9 | -48.4 |
| AML 10 mg | Mean % change | -2.5 | -36.6 | -38.6 | -43.2 | -49.1 |

Conclusion

Efficacy of the combination of amlodipine and atorvastatin in the treatment of co-morbid hypertension and dyslipidemia was demonstrated in one clinical trial (non-published). To date, only summary information is provided in the product prescribing information. Questions regarding the duration of treatment, study design, inclusion/exclusion criteria, patient population demographics, and significance levels remain unknown. The combination lowered blood pressure and LDL cholesterol as expected with the components individually; there was no apparent decrease in efficacy with either agent. However, the advantage of a combination product over co-administration of the two ingredients separately has not yet been established.

References

1. Pfizer Ireland Pharmaceuticals. Caduet® (amlodipine and atorvastatin) prescribing information. Dublin (Ireland): 2005.

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