Drug monograph of CADUET®

Generic name: Amlodipine and Atorvastatin
Brand name: Caduet
Manufacturer: Pfizer
Classification: Prescription only medicine
Strength (amlodipine mg/atorvastatin mg): 2.5/10, 2.5/20, 2.5/40, 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, 10/80
Availability in HK: Registered in Hong Kong as a P1S1S3 poison.
Pharmacologic action:
Amlodipine: Amlodipine inhibits the influx of extracellular calcium across cardiac muscle and vascular smooth muscle cell membranes and cause arterial. This increases coronary blood flow and oxygen delivery. Amlodipine exerts its effects mainly on arteriolar vasculature but has no significant effect on sinus node function or cardiac conduction and no negative inotropic effects at clinical doses.
Atorvastatin: Atorvastatin inhibits HMG-CoA reductase, which is the rate limiting enzyme in the liver that converts HMG-CoA to mevalonate. Atorvastatin decreases total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), TG, and increases high-density lipoprotein cholesterol (HDL-C).
Indication:
Caduet is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

<table>
<thead>
<tr>
<th>Amlodipine:</th>
<th>Atorvastatin:</th>
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</thead>
<tbody>
<tr>
<td>1. Hypertension</td>
<td>1. Primary Heterozygous</td>
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<tr>
<td>2. Chronic Stable Angina</td>
<td>Hypercholesterolemia (Familial or Nonfamilial)</td>
</tr>
<tr>
<td>4. (Prinzmetal's or Variant)</td>
<td>3. Hypertriglyceridemia</td>
</tr>
<tr>
<td></td>
<td>4. Primary Dysbetalipoproteinemia</td>
</tr>
<tr>
<td></td>
<td>5. Homozygous Familial Hypercholesterolemia</td>
</tr>
</tbody>
</table>

Bioavailability/Pharmacokinetics:
*Amlodipine:
Absorption: Oral bioavailability ranges from 52—88%. Peak plasma concentrations are achieved between 6—9 hours post-dose, and maximum hypotensive effects are correspondingly delayed.
Distribution: The drug is approximately 93% bound to plasma proteins
Metabolism: Amlodipine is primarily metabolized by CYP3A4 isoenzymes.
Elimination: Amlodipine is extensively metabolized to inactive compounds, and 10% of the parent compound and 60% of the inactive metabolites are excreted in the urine.
The mean terminal half-life of amlodipine is 35 hours following single dose administration.

**Atorvastatin:**

**Absorption:** After oral administration, the drug is rapidly absorbed with peak plasma concentrations occurring within 1—2 hours. The absolute bioavailability is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%.

**Distribution:** Atorvastatin is > 98% bound to plasma proteins.

**Metabolism:** Atorvastatin undergoes extensive metabolism to active metabolites.

**Elimination:** Atorvastatin and its metabolites occur primarily in bile following hepatic and/or extrahepatic metabolism. The mean plasma elimination half-life of atorvastatin is approximately 14 hours, however, the half-life of HMG-CoA reductase inhibitory activity is 20—30 hours because of the active metabolites.

**Dosage:**

The dose range of the individual drug entities: amlodipine 5 to 10 mg and atorvastatin 10 to 80 mg

Dosage of caduet should be individualized on the basis of effectiveness and tolerance for patient who is starting the drug.

For patient who is on both drugs can directly continue on the existing treatment regimen at mg/mg basis of individual component.

**Maximum Dosage Limits:**

- **Adults:** 10 mg/day PO amlodipine and 80 mg/day PO atorvastatin.
- **Elderly:** 5—10 mg/day PO amlodipine (based on tolerance and clinical response) and 80 mg/day PO atorvastatin.
- **Adolescents and children >= 10 years:** 5 mg/day PO amlodipine and 20 mg/day PO atorvastatin.
- **Children < 10 years:** Safe and effective use has not been established.

**Patients with hepatic impairment:**

Not recommended in patients with hepatic disease (see Contraindications).

**Patients with renal impairment:**

No dosage adjustment is needed.

**Intermittent hemodialysis:**

Amlodipine and atorvastatin are highly protein bound, and are not likely to be significantly removed by hemodialysis.
Drug Interaction:
No drug interaction studies have been conducted with caduet and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components.

Amlodipine:
1. Antifungals (itraconazole, ketoconazole, fluconazole), erythromycin and other inhibitors of cytochrome P450 isoenzyme 3A4 may inhibit amlodipine’s metabolism.
2. Rifampin, rifabutin, rifapentine, carbamazepine, barbiturates (e.g., phenobarbital or primidone), and may induce the CYP3A4 metabolism of amlodipine and thereby reduce their oral bioavailability. The dosage requirements of amlodipine may be increased.
3. In vitro studies have not shown any effect of amlodipine on the protein binding of digoxin, phenytoin, warfarin and indomethacin.
4. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Atorvastatin:
1. Atorvastatin should not be administered along with other HMG-CoA reductase inhibitors because of increase risk of myopathy. It should be administer cautiously with fibrin acid derivatives due to increase risk of myopathy.
2. When multiple doses of atorvastatin and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored.
5. Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Food/herb-drug interactions:
1. Grapefruit juice should be avoided in patients taking atorvastatin and amlodipine because it inhibits metabolism of the drug
2. St John’s wort induce metabolism of amlodipine and atorvastain and it should be avoided.
3. Melatonin impairs efficacy of calcium channel through an unknown mechanism.
**Efficacy:**
1. Single-pill amlodipine/atorvastatin is effective in achieving BP and LDL-L goals in 58% of patients with concomitant hypertension and dyslipidemia but remains inconclusive since the study is non-comparative and not placebo-controlled.¹
2. Amlodipine 5mg /atorvastatin 10mg in patients with concomitant hypertension and hyperlipidemia is superior to amoldipine 5 mg in the treatment of hyperlipidemia and atorvastatin 10 mg in the treatment of hypertension.²
3. A variety of combinations of amlodipine/atorvastatin (as separate pills) are all more effective in reducing LDL and reducing systolic blood pressure than atorvastatin alone and amlodipine alone respectively.³
4. Neither amlodipine nor atorvastatin modifies the treatment effect of the other when both are administered in combination.²,³
5. Absorption of the amlodipine/atorvastatin single-pill is bioequivalent to its components when individually administer. AUC and Cmax of atorvastatin and amlodipine are not significantly different in amlodipine 10mg/ atorvastatin 80mg compared with both alone.⁴
6. Both large artery elasticity and small artery elasticity were significantly increased with amlodipine/atorvastatin and amlodipine alone compared with placebo, but the increase in elasticity in small arteries are significantly greater in the amlodipine/atorvastatin group when compared with amlodipine alone.⁵
7. Some regulatory authorities were not convinced with the efficacy of Caduet® demonstrated and Pfizer had withdrawn its application to market Caduet® in 12 European countries in 2005.⁶

**Table1: Study details of atorvastatin/amlodipine.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Duration</th>
<th>Interventions</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemini</td>
<td>1220</td>
<td>14 weeks</td>
<td>Eight dosage strengths of amlodipine/atorvastatin single pill</td>
<td>open-label, noncomparative, multicentre trial</td>
</tr>
<tr>
<td>AVALON</td>
<td>847</td>
<td>8 weeks</td>
<td>Amlodipine5mg/Atorvastatin10mg vs Atorvastatin 10mg vs Amlodipine 5 mg</td>
<td>Phase 3 double-blind placebo controlled, randomised, open labelled, multi centre study in North America</td>
</tr>
<tr>
<td>AVALON-A WC</td>
<td>667</td>
<td>8 weeks</td>
<td>Amlodipine/atorvastatin vs amlodipine vs placebo</td>
<td></td>
</tr>
<tr>
<td>RESPOND</td>
<td>1594</td>
<td>60 weeks</td>
<td>Different dosages of: Amlodipine/atorvastatin vs Atorvastatin vs amlodipine vs placebo</td>
<td>Multinational, randomized, double-blind, multi-center, double dummy, placebo controlled</td>
</tr>
</tbody>
</table>
Safety:
1. Single-pill amlodipine/atorvastatin is well-tolerated with 4.8% and 5.6% patients discontinued use due to adverse effects.\textsuperscript{1,3}
2. The most common adverse effects in amlodipine/atorvastatin group were respiratory tract infection, peripheral oedema, headache and myalgia. \textsuperscript{1,3}
3. Co-administration of amlodipine/atorvastatin does not result in increase in adverse events compared with amlodipine and atorvastatin alone.\textsuperscript{3}

<table>
<thead>
<tr>
<th>Study</th>
<th>Gemini</th>
<th>RESPOND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to adverse events</td>
<td>4.8%</td>
<td>5.6% ( placebo 4.5%)</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>11.9%</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>8.8%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Headache</td>
<td>5.4%</td>
<td>4.5%</td>
</tr>
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</table>

Adverse reaction:
Adverse reactions are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin.

Atorvastatin
Reversible myositis, headache, altered liver-function tests (rarely, hepatitis), paraesthesia, and gastro-intestinal effects including abdominal pain, flatulence, constipation, diarrhoea, nausea and vomiting. Rash and hypersensitivity reactions (including angioedema and anaphylaxis) have been reported rarely. Chest pain, angina; insomnia, dizziness, hypoesthesia, arthralgia; back pain; \textit{less commonly} anorexia, malaise, weight gain, amnesia, impotence, thrombocytopenia, tinnitus, and alopecia;

Amlodipine
Adominal pain, nausea; palpitation, flushing, oedema; headache, dizziness, sleep disturbances, fatigue; \textit{less commonly} gastro-intestinal disturbances, dry mouth, taste disturbances, hypotension, syncope, chest pain, dyspnoea, rhinitis, mood changes, tremor, paraesthesia, urinary disturbances, impotence, gynaeacomastia, weight changes, myalgia, visual disturbances, tinnitus, pruritus, rashes (including isolated reports of erythema multiforme), alopecia, purpura, and skin discolouration.
**Contraindications:**
Caduet is contraindicated in patients
1. with active liver disease or unexplained persistent elevations of serum transaminases;
2. in women who are pregnant or may become pregnant and/or nurse
3. in patients with hypersensitivity to any component of this medication.

**Precautions:**
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.

Liver Dysfunction:
HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function.
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. Caduet should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Skeletal muscle:
Rare cases of rhabdomyolysis have been reported with the atorvastatin component of Caduet and with other statins. Discontinue drug if myopathy is suspected, if creatine phosphokinase (CPK) levels rise markedly, if the patient has risk factors for rhabdomyolysis, or if the patient is having a risk factor predisposing to the development of renal failure secondary to 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.

Vascular:
Vasodilation induced by the amlodipine component of Caduet is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Caution should be exercised when administering Caduet as with any
other peripheral vasodilator particularly in patients with severe aortic stenosis.

Heart failure:
Calcium channel blockers should be used with caution in patients with heart failure.

Endocrine:
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. 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.

References:
5. Cohn JN, Neutel J, Houston M, et al. Early improvements in vascular compliance following coadministration of amlodipine and atorvastatin in patients with concomitant hypertension and dyslipidemia. The Avalon Arterial Wall Compliance (AWC) trial. Program and abstracts from the 20th Annual Scientific Meeting of the American Society of Hypertension; May 14-18, 2005; San Francisco,
California. Late Breaking Clinical Trials

6. Pfizer withdraws Caduet in 12 Euro countries 11-11-2005 by Pharamtimes
   www.pharmatimes.com (accessed on 16-01-2006)

Other references:

- Drug monograph of caduet, amlodipine and atorvastatin on clinical pharmacology http://cpip.gsm.com/ (accessed on 19-1-2006)
- Drug Facts and comparison 2005
- BNF 50
- Prescribing information of Caduet by Pfizer www.caduet.com (accessed on 19-1-2006)