

Amlodipine with atorvastatin (Caduet) for dyslipidaemia with concomitant hypertension or angina

(am-LOD-i-peen with a-TOR-va-stat-in)

Summary

- Amlodipine with atorvastatin (Caduet) is a fixed-dose combination preparation pairing drugs to treat different indications concurrently — hypertension or angina, and dyslipidaemia.
- Do not initiate antihypertensive, anti-angina and/or statin therapy with the combination preparation.
- Establish the effective and tolerated dose of each component as single drugs before changing to the combined preparation.
- Before prescribing, ask 'Would these be the drugs of choice as individual agents?' A combination preparation can cost patients less but this should not be the primary consideration.
- For patients responding well to therapy with other drugs there is no reason to change to this fixed-dose combination.
- Do not prescribe Caduet unless the patient has previously tolerated amlodipine 5 mg daily. There is no dose strength of Caduet equivalent to amlodipine 2.5 mg — this is the recommended starting dose in frail, small or elderly people, or in those at risk of hypotension.
- Be aware of the potential for confusion that may arise with the differently named medicine and its 8 different dose combinations. Explain to the person being treated which medicines are being replaced by Caduet and tell them to discard any unneeded medicines.

PBS listing

Restricted benefit

Amlodipine with atorvastatin fixed-dose combination (Caduet) can be prescribed for people with hypertension and/or angina who also meet the Pharmaceutical Benefits Scheme lipid-lowering criteria.

The restriction allows a dihydropyridine calcium-channel blocker to be prescribed*:

- in place of a currently prescribed dihydropyridine calcium-channel blocker (amlodipine [Norvasc], felodipine [Plendil, Felodur], lercanidipine [Zanidip], nifedipine [e.g. Adefin, Adalat])
- in addition to another antihypertensive and/or anti-anginal agent when hypertension or angina are inadequately controlled

- instead of another antihypertensive and/or anti-anginal agent whose adverse effects are poorly tolerated.²

The listing does not allow for prescribing to treatment-naive patients with hypertension and/or angina.

Reason for PBS listing

Caduet was listed on the basis of cost minimisation compared with amlodipine and atorvastatin as separate medicines. Costs and efficacy of other antihypertensive–statin combinations were not considered as part of this listing.³

*Dihydropyridine calcium-channel blockers differ from non-dihydropyridine calcium-channel blockers (verapamil and diltiazem) in their sites of action, and their therapeutic and adverse effects. They are therefore not interchangeable.¹

Place in therapy

Caduet is a new type of fixed-dose combination preparation that combines drugs to treat two or more different indications concurrently — hypertension and/or angina, and dyslipidaemia. The usual considerations that apply to combination preparations remain important (see Principles of using fixed-dose combination preparations, below).⁴

Caduet as fixed-dose combination therapy

Choose antihypertensive and lipid-modifying therapy according to the clinical needs of the individual rather than possible compliance, convenience or cost advantages of the combined preparation. Out-of-pocket costs for the patient will be lower with Caduet than with amlodipine and atorvastatin as separate medicines. However, for patients who are responding well to another antihypertensive–statin combination there is no reason to change to Caduet.

A potential but unproven compliance benefit does not override therapeutic considerations. Compliance is influenced by individual patient characteristics^{5–7} as well as the total number of drugs or doses in the regimen.^{5,8} Simplifying dosage regimens can improve compliance, but the evidence suggests a small relative improvement of between 8% and 20%.⁹ There are multiple other strategies for improving compliance in patients for whom this is known to be a problem (e.g. exploring the reasons for non-compliance, increased follow-up, patient education, using dose administration aids such as Webster packs).¹⁰

Do not initiate amlodipine or atorvastatin therapy with Caduet. Establish the dose of each drug that is effective and well tolerated using the single medicines, before prescribing the combination (see Box 1, page 12).

Amlodipine as an antihypertensive agent

Amlodipine is a dihydropyridine calcium-channel blocker; these drugs are considered one of several reasonable first-line choices in uncomplicated hypertension, when there are no compelling indications for using another drug (e.g. coexisting

conditions or the need for target-organ protection).^{11–13} Blood pressure control has a more important effect on cardiovascular outcomes than the class of antihypertensive used.^{12,14}

In head-to-head clinical outcome trials, calcium-channel blockers have been associated with an increased risk of new heart failure compared with ACE inhibitors and thiazide diuretics.^{14–16} Use amlodipine with caution in people with existing chronic heart failure.¹⁷

Calcium-channel blockers vary in their therapeutic effects and individual adverse-effect profiles; consider this if changing to Caduet from a dihydropyridine calcium-channel blocker other than amlodipine. Substitute amlodipine as an individual drug first, to establish dose and tolerance before introducing the combination.

Atorvastatin compared with other statins

For most patients with hyperlipidaemia, the aim of therapy is to reduce low-density lipoprotein–cholesterol (LDL-C) levels to recommended targets. There is no reason to choose atorvastatin over other statins for initiating statin therapy because equipotent doses of statins achieve similar reductions in cholesterol levels. A change to atorvastatin might be considered when maximally tolerated doses of pravastatin or simvastatin do not reduce cholesterol levels sufficiently in patients who are compliant with statin therapy; atorvastatin is more potent in lowering LDL-C levels on a milligram-for-milligram basis than simvastatin or pravastatin¹⁸ (see the December 2005 *NPS RADAR* review of atorvastatin).

There are no head-to-head trials comparing the effects of atorvastatin with those of equipotent doses of other statins on clinical outcomes.

Principles of using fixed-dose combination preparations

Box 1 (page 12) lists the uses of Caduet that are consistent with quality use of medicines principles for combined preparations. Consider the questions in Table 1 when assessing the usefulness of any fixed-dose combination preparation.

Table 1: Questions to ask about fixed-dose combination preparations

Questions to ask	Answer for Caduet
Is it a sensible combination?	
<ul style="list-style-type: none"> Will the drug combination have an additive or synergistic effect, or does one drug counteract the adverse effects of the other? Is the combination bioequivalent to the individual components? 	<ul style="list-style-type: none"> Treats two conditions concurrently; there is no additive or synergistic effect compared with treatment with the individual drugs Accepted as bioequivalent to similar doses of the individual components³
Is the dosing compatible?	
<ul style="list-style-type: none"> Are the pharmacokinetics similar (e.g. absorption, duration of action)? How likely are dose changes? Will increasing the dose of one component result in an unnecessary dose increase in the other component? 	<ul style="list-style-type: none"> Both components are administered once daily Hypertension and angina are both conditions that change over time, so dose adjustments are likely No — but while the dose can be titrated using the 8 dose combinations available, a new strength must be prescribed, which may cause confusion. Tablets cannot be halved
What will be the impact on adverse effects?	
<ul style="list-style-type: none"> Will there be more adverse effects? Will it be possible to identify which drug is causing adverse effects? 	<ul style="list-style-type: none"> Adverse effects appear similar to those of the individual components^{17,19} There is no Caduet strength that allows a dose of amlodipine 2.5 mg. Prescribing amlodipine 5 mg to small, frail or elderly people, or those at risk of hypotension, may increase the risk of adverse effects (e.g. peripheral oedema, hypotension) Some adverse effects (e.g. headache) are common to both drugs and it may be hard to identify which drug is responsible It would be difficult to temporarily withdraw one drug to assess its contribution to adverse effects (e.g. atorvastatin and muscle pain)
What is the place in therapy of the combination preparation?	
<ul style="list-style-type: none"> Should this combination preparation be used for initiating therapy?* Would the components be the drugs of choice as separate medicines? Does the patient need both medicines? Does evidence show advantages for the combination compared with monotherapy? 	<ul style="list-style-type: none"> Do not use to initiate therapy with either amlodipine or atorvastatin — only consider it for patients who have been stabilised on regular doses of the individual drugs (See Box 1, page 12) See Amlodipine as an antihypertensive agent (page 10), and Atorvastatin compared with other statins (page 10) Studies suggest that the combination preparation has similar lipid-modifying and antihypertensive effects as occur with the individual medicines.¹⁷ No therapeutic or compliance advantage has been shown with Caduet
What is the potential for confusion and medication error?	
<ul style="list-style-type: none"> What will be the consequences for the patient? 	<ul style="list-style-type: none"> There is potential for confusion because: <ul style="list-style-type: none"> there are 8 strengths of Caduet available (covering most amlodipine/atorvastatin dose combinations) Caduet's brand name differs from those of the component drugs. (See Information for patients, page 12)

* There are some occasions when prescribing of a combination preparation as initial therapy is necessary — for example, combined oral contraceptive preparations, some combination antibiotics, some medicines for Parkinson's disease

Box 1: Which uses of Caduet are consistent with quality use of medicines (QUM)?

QUM-recommended use of Caduet

- Changing from regular stable doses of amlodipine and atorvastatin as single drugs:
 - when either amlodipine or atorvastatin is being used for the first time, prescribe these as single medicines before changing to the combination preparation

Non-recommended uses of Caduet (according to QUM)

- Initiating in patients who have not previously tolerated amlodipine 5 mg or more
- Initiating concomitant antihypertensive and statin therapy
- Initiating either amlodipine or atorvastatin, even if the patient is already taking one of these drugs. To titrate dose a different strength will need to be prescribed.
- Switching any patient who is well controlled on another regimen to Caduet

Safety issues

There are no apparent differences in adverse effects with Caduet compared with its individual components. The most common treatment-related adverse effects with the combination are peripheral oedema (7%), myalgia (2%) and headache (2%).¹⁹

It may be difficult for healthcare providers who are unfamiliar with a patient to determine which of the 8 strengths of Caduet they are taking (e.g. after hospital admission or discharge). Patients who move frequently between different healthcare providers might be at greater risk of error.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Dosing issues

Caduet should not be used unless the patient has previously tolerated amlodipine 5 mg or more. There is no Caduet dose strength equivalent to amlodipine 2.5 mg;

this dose is often used as a starting dose and is the recommended starting dose in small, frail or elderly people, or those at risk of hypotension.²⁰

Caduet tablets should not be halved.

A disadvantage of fixed-dose combination tablets is that to change the dose of one component a different strength preparation must be prescribed (see Information for patients).

Information for patients

Advise patients which of their existing medicines (if any) are being replaced by Caduet and tell them to discard these unneeded medicines to avoid double dosing. There is potential for confusion because:

- Caduet has a completely different brand name to either of its components (amlodipine [Norvasc], atorvastatin [Lipitor])
- changes in strength may not be obvious to the patient because of similarities in the appearance of tablets, which are coloured according to the amlodipine strength.

Tell patients which active ingredients their medicines contain and their strengths, rather than relying on brand names. Encourage patients to carry a medicines list and keep it up to date.

Patients prescribed amlodipine (Norvasc) incur an additional cost because of a Therapeutic Group premium with Norvasc; this cost does not apply to Caduet.³

Suggest or provide the Caduet consumer medicine information (CMI) leaflet.

Table 2: Dose strengths of Caduet available*

Amlodipine/atorvastatin	Tablet colour
5 mg/10 mg 5 mg/20 mg 5 mg/40 mg 5 mg/80 mg	White
10 mg/10 mg 10 mg/20 mg 10 mg/40 mg 10 mg/80 mg	Blue

* The strength is marked on the pack, but not on the tablets

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.