

# Atorvastatin (Lipitor) for the management of lipid disorders

(a-TOR-va-stat-in)

## Summary

- Atorvastatin is more potent at lowering plasma cholesterol levels compared with simvastatin and pravastatin.
- If existing treatment with simvastatin or pravastatin achieves target cholesterol levels, it is not necessary to switch to a more potent statin.
- High doses of atorvastatin (40 mg, 80 mg) achieve reductions in cholesterol that are not possible with the recommended doses of simvastatin.
- There are currently no head-to-head studies comparing the clinical outcomes of atorvastatin with equipotent doses of other statins.
- Choose the lowest effective dose of atorvastatin to achieve the current recommended target cholesterol level.
- All statins can cause myopathy or rhabdomyolysis, but this is rare.
- Elevated liver transaminase levels can occur with statins, particularly at high doses.

## PBS listing

Atorvastatin is listed on the PBS as a restricted benefit for use in patients who meet the criteria set out in the General Statement for Lipid-Lowering Drugs Prescribed as Pharmaceutical Benefits (refer to the *Schedule of Pharmaceutical Benefits*). On 1 August 2005, new generic brands of simvastatin were listed on the PBS, resulting in a 12.5% price reduction across the statin class to brands of simvastatin, pravastatin and fluvastatin.<sup>1</sup> Atorvastatin was exempt from this price reduction and has maintained its price on the PBS.<sup>1</sup>

## Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee accepted that atorvastatin is more effective than simvastatin in lowering cholesterol levels and that this justifies a price difference.<sup>1</sup> Economic analyses were based on percentage changes in lipid parameters derived from a meta-analysis of atorvastatin and its comparator, simvastatin. Head-to-head studies of the clinical outcomes of atorvastatin compared with simvastatin were not available, so the economic analysis was validated using the clinical outcomes from placebo-controlled studies.

## Place in therapy

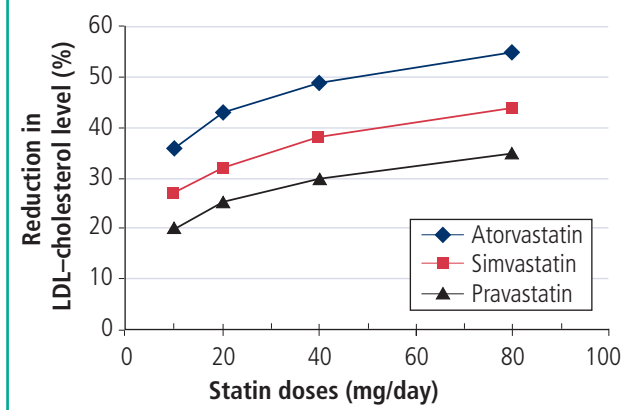
Atorvastatin is an HMG-CoA reductase inhibitor (statin) that lowers plasma cholesterol levels. Statins are first line for the treatment of hypercholesterolaemia.<sup>2,3</sup> In patients with coronary heart disease and in others at high cardiovascular risk, statins reduce the risk of death, myocardial infarction, revascularisation or stroke.<sup>3,4</sup> Aim for a target LDL-cholesterol level < 2.5 mmol/L (total cholesterol < 4.0 mmol/L).<sup>5-7\*</sup> Any step towards the target is likely to be beneficial.<sup>7,8</sup>

## Atorvastatin lowers cholesterol levels across its dose range

Atorvastatin is more potent at lowering cholesterol levels on a milligram-for-milligram basis compared with either simvastatin or pravastatin (see Figure 1).<sup>3,6,9</sup> Similar reductions in cholesterol can be achieved with equipotent doses, but across its dose range atorvastatin reduces LDL-cholesterol about 5–20% more than the reductions achieved with simvastatin or pravastatin.

\* Recommended for coronary heart disease, diabetes, stroke, transient ischaemic attack, peripheral vascular disease, microalbuminuria, renal disease, familial hypercholesterolaemia, 15% cardiovascular risk over 5 years, and in indigenous Australians.<sup>5-7</sup>

**Figure 1: Percentage reduction in plasma LDL-cholesterol levels with recommended doses of atorvastatin, simvastatin and pravastatin<sup>6,9-11</sup>**



The dose equivalency of atorvastatin and simvastatin is reported to be between 1:2 (i.e. 10 mg is similar to 20 mg)<sup>6,9</sup> and 1:4 (i.e. 10 mg is similar to 40 mg).<sup>11</sup> However, a meta-analysis that reported the equivalency of 1:4<sup>11</sup> did not assess potential differences between studies. Atorvastatin reduces plasma triglyceride levels more than simvastatin, and simvastatin elevates plasma HDL-cholesterol levels more than atorvastatin.<sup>9</sup> The clinical significance of these differences is unknown.

### Lowering cholesterol with atorvastatin, simvastatin or pravastatin reduces the risk of cardiovascular events

There are currently no head-to-head studies that directly compare the effectiveness of atorvastatin with equipotent doses of other statins for reducing the risk of cardiovascular events. The PROVE-IT<sup>12</sup> trial of intensive versus moderate lipid modification in acute coronary syndromes is the only head-to-head study comparing the clinical outcomes of statins. The absolute risk of a major cardiovascular event or death from any cause was reduced by 3.9% more with atorvastatin 80 mg (mean LDL-cholesterol 1.6 mmol/L) compared with pravastatin 40 mg (mean LDL-cholesterol 2.5 mmol/L).<sup>12</sup> This was largely due to reductions in revascularisation and unstable angina.<sup>12</sup>

Indirect comparison of atorvastatin, simvastatin and pravastatin using the clinical outcomes from placebo-controlled studies is difficult, as there are significant differences between the study populations\*.<sup>13-24</sup>

Statins provided greater absolute benefits in patients with a history of cardiovascular events (secondary prevention) compared with those without (primary prevention).<sup>4,8</sup> In some studies, patients treated with placebo or 'usual care' were also prescribed lipid-lowering drugs, so differences between treatment groups were reduced.<sup>13-21,24</sup> This predominantly occurred in the HPS<sup>13</sup> (simvastatin) and ALLHAT-LLT<sup>18</sup> (pravastatin) studies, where statins were prescribed on average in 17% of patients receiving placebo or 'usual care'.

Choose atorvastatin, simvastatin or pravastatin when initiating treatment with a statin.<sup>2</sup> If maximum recommended doses do not achieve treatment goals, switch to a statin that is more potent at lowering cholesterol (see Figure 1 and Dosing issues). Combining a statin with another lipid-modifying (non-statin) drug can also help reduce cholesterol.<sup>2,3,6</sup>

### Aggressively lowering cholesterol below the current recommended targets continues to be debated

In the Treating to New Targets (TNT) study<sup>25</sup>, treatment with atorvastatin 80 mg daily (mean LDL-cholesterol 2.0 mmol/L) reduced the absolute risk of myocardial infarction and stroke by 1.3% and 0.8%, respectively, more than atorvastatin 10 mg daily (mean LDL-cholesterol 2.6 mmol/L). However, higher statin doses increase the risk of adverse effects (see Safety issues). Intensive lipid modification (mean LDL-cholesterol 1.6–2.0 mmol/L) with atorvastatin 80 mg or simvastatin 40 mg/80 mg did not reduce overall mortality compared with less intensive treatment (LDL-cholesterol 2.0–2.6 mmol/L).<sup>12,25-27</sup> Studies were not powered to detect differences in mortality, thus the benefits are unclear. The threshold below which lowering of cholesterol becomes harmful, or has little added benefit, is unknown.

\* See additional content on page 06 for more information on the effects of atorvastatin, simvastatin and pravastatin in placebo-controlled studies

## Safety issues

Atorvastatin is well tolerated and its safety profile is similar to that of other statins.<sup>28</sup> Adverse effects include myalgia, mild gastrointestinal symptoms, elevated transaminase levels and headache.<sup>2,3</sup> Rarely, myopathy or rhabdomyolysis can occur.<sup>3</sup>

### Atorvastatin poses a similarly low risk of myopathy and rhabdomyolysis to that of other statins

Stop treatment with atorvastatin if patients develop persistent symptoms of muscle aches, mild to severe pain, or stiffness or weakness, even when plasma creatine kinase levels are normal.<sup>29</sup> Symptoms are usually reversible within a few days to weeks of stopping treatment.<sup>29</sup> Consider restarting atorvastatin at a lower dose after at least 4 weeks if symptoms were mild and when plasma creatine kinase levels have returned to normal.<sup>3</sup> If the reaction recurs, stop atorvastatin permanently.<sup>3</sup> An alternative statin may be considered but continue to monitor for signs of muscle toxicity.<sup>3</sup>

Studies have rarely reported myopathy or rhabdomyolysis with atorvastatin<sup>12,14,20,23,25,26</sup> but these are strongly associated with certain risk factors (see Box 1). Patients most likely to develop muscle disorders, such as those with multiple comorbidities or taking interacting drugs, are usually excluded from statin trials and thus cases may have been underreported.

In 2004 the Adverse Drug Reactions Advisory Committee (ADRAC) reported that risk factors existed in nearly half of the cases of statin-induced myalgia, myopathy or raised plasma creatine kinase levels, and in more than 75% of cases of rhabdomyolysis.<sup>30</sup> A postmarketing analysis reported that simvastatin caused more adverse effects related to muscle than atorvastatin, but patients taking simvastatin on average received higher doses and more concomitant interacting drugs.<sup>32</sup>

In the A to Z trial<sup>27</sup>, 9 of 2263 patients developed muscle disorders (including three cases of rhabdomyolysis) with simvastatin 80 mg. Risk factors were evident in three cases and included renal failure, use of verapamil, or alcohol abuse. In the TNT study<sup>25</sup>, although there were no reports

of elevated plasma creatine kinase levels (> 10 times upper limit of normal) or rhabdomyolysis related to atorvastatin 80 mg, 197 patients with adverse reactions to the 10 mg dose during the run-in phase (35 with myalgia) did not continue the study.

#### Box 1: Factors that increase the risk of muscle disorders with statins<sup>2,3,29–31</sup>

##### High plasma levels of statins due to high doses

- 40 mg daily, particularly with other coexisting risk factors

##### Concomitant drugs that may increase plasma levels of statins by inhibiting CYP3A4 hepatic or gut metabolism\*

- Calcium-channel blockers (diltiazem, verapamil)
- Macrolide antibiotics (clarithromycin, erythromycin)
- Azole antifungals (fluconazole, itraconazole, ketoconazole)
- SSRIs (fluvoxamine, fluoxetine)
- Protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)
- Others: amiodarone, cyclosporin, delavirdine, grapefruit juice

##### Concomitant drugs that may cause muscle damage

- Cyclosporin, gemfibrozil, fenofibrate, nicotinic acid

##### Concurrent illness or disease states

- Infection, trauma or major surgery
- Metabolic disorder (e.g. diabetes, hypothyroidism)
- Renal or hepatic disease
- Previous muscle damage with a statin

##### Patient demographics

- Older age ( $\geq$  70 years), female gender, low body weight

\* Does not apply to pravastatin, as it is not metabolised by CYP enzymes<sup>3,31</sup>

### Monitor liver transaminases with statins, particularly at high doses

Elevations in liver transaminase levels (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) with statins are dose dependent but uncommon and rarely develop into serious hepatic reactions (e.g. hepatitis, cholestatic jaundice).<sup>3,28</sup> Stop atorvastatin if ALT and/or AST levels are persistently three or more times the upper limit of normal.<sup>3</sup> Elevations usually resolve with a lower dose or alternative statin.<sup>3,14</sup>

In studies, patients taking atorvastatin 80 mg daily had a 1–3% greater absolute risk of elevated liver transaminase levels (ALT and/or AST > 3 times the upper limit of normal) compared with placebo<sup>26</sup>, pravastatin 40 mg<sup>12</sup> or atorvastatin 10 mg.<sup>25</sup>

### Dosing issues

Start with a low dose of atorvastatin and titrate if necessary to achieve treatment goals (dose range 10–80 mg once daily).<sup>33</sup> Measure the cholesterol level within 4 weeks of initiating atorvastatin, or after dose titration.<sup>33</sup> Higher doses (40–80 mg daily) may be required to reduce cholesterol levels by  $\geq$  50%. Atorvastatin can be taken at any time of the day, with or without food.<sup>33</sup>

### Changing from other statins to atorvastatin

Before switching treatment to atorvastatin, check that the patient has been compliant with taking their statin treatment. Monitor the patient for adverse effects, which can occur when treatments change, especially if titrating atorvastatin to a higher dose (see Safety issues).<sup>30</sup>

### Information for patients

Advise patients that:

- atorvastatin can lower cholesterol more than other 'statin' drugs
- atorvastatin must be taken every day in conjunction with lifestyle changes such as diet and exercise
- the cost of atorvastatin to the patient is the same as for most other statins
- adverse effects of the muscle or liver are rare and more likely to occur if blood levels of atorvastatin are increased (e.g. interacting drugs)
- persistent muscle aches, mild to severe pain, or stiffness or weakness must be reported promptly, especially after any change in treatment.

Suggest or provide the Lipitor consumer medicine information (CMI) when prescribing or supplying atorvastatin.

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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.

## Additional content - Atorvastatin (Lipitor) for the management of lipid disorders

### Studies of atorvastatin, simvastatin and pravastatin compared with placebo or usual care: plasma LDL-cholesterol reduction and major coronary events

| Study population*: statin versus placebo or usual care   | Primary prevention study | Secondary prevention study | Mean % LDL-C reduction (level, mmol/L) | % ARR of major coronary events† | NNT (to prevent one major coronary event) |
|--|--------------------------|----------------------------|--|---------------------------------|---|
| <b>Atorvastatin versus placebo</b>   |                          |                            |  |                                 |   |
| <b>ASCOT-LLA</b> <ul style="list-style-type: none"> <li>Atorvastatin 10 mg</li> <li>Hypertension plus at least three other CV risk factors</li> </ul>                              | ✓                        | ✓ ‡                        | 33% (2.3)                              | 1.1%                            | 91  |
| <b>CARDS</b> <ul style="list-style-type: none"> <li>Atorvastatin 10 mg</li> <li>Type 2 diabetes mellitus plus at least one other CV risk factor</li> </ul>                         | ✓                        |                            | 36% (2.0)                              | 1.9%§                           | 53§                                       |
| <b>Atorvastatin versus usual care</b>  |                          |                            |  |                                 |   |
| <b>GREACE</b> <ul style="list-style-type: none"> <li>Atorvastatin 10–80 mg</li> <li>CHD</li> </ul>   |                          | ✓                          | 46% (2.5)                              | 3.8, 2.3%‡‡                     | 26, 43‡‡                                  |
| <b>ALLIANCE</b> <ul style="list-style-type: none"> <li>Atorvastatin 10–80 mg</li> <li>CHD</li> </ul>   |                          | ✓                          | 34% (2.5)                              | 3.5%¶                           | 29¶                                       |
| <b>Simvastatin versus placebo</b>  |                          |                            |  |                                 |   |
| <b>4S</b> <ul style="list-style-type: none"> <li>Simvastatin 10–40 mg</li> <li>Angina, MI</li> </ul>   |                          | ✓                          | 35% (3.2)                              | 9.0%                            | 11  |
| <b>HPS</b> <ul style="list-style-type: none"> <li>Simvastatin 40 mg</li> <li>CHD, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, hypertension</li> </ul> | ✓                        | ✓                          | 32% (2.3)                              | 3.1%                            | 32  |
| <b>Pravastatin versus placebo</b>  |                          |                            |  |                                 |   |
| <b>WOSCOPS</b> <ul style="list-style-type: none"> <li>Pravastatin 40 mg</li> <li>Hypercholesterolaemia (men only)</li> </ul>   | ✓                        |                            | 26% (3.7)                              | 2.2%                            | 45  |
| <b>CARE</b> <ul style="list-style-type: none"> <li>Pravastatin 40 mg</li> <li>Acute MI</li> </ul>  |                          | ✓                          | 32% (2.5)                              | 3.0%                            | 33  |

|  |   |   |             |        |       |
|--|---|---|-------------|--------|-------|
| <b>LIPID</b> <ul style="list-style-type: none"> <li>Pravastatin 40 mg</li> <li>MI, unstable angina</li> </ul>  |   | ✓ | 25% (2.9)   | 3.6%   | 28    |
| <b>PROSPER</b> <ul style="list-style-type: none"> <li>Pravastatin 40 mg</li> <li>Risk factors for, or existing, vascular disease (elderly, age 70–82 years)</li> </ul> | ✓ | ✓ | 27% (2.8)** | 2.1%   | 48    |
| <b>Pravastatin versus usual care</b>   |   |   |             |        |       |
| <b>ALLHAT-LLT</b> <ul style="list-style-type: none"> <li>Pravastatin 10–40 mg</li> <li>Hypertension plus at least one other CV risk factor</li> </ul>                  | ✓ | ✓ | 27% (2.8)   | 0.7%†† | 143†† |
| <b>GISSI</b> <ul style="list-style-type: none"> <li>Pravastatin 10–40 mg</li> <li>Acute MI</li> </ul>  |   | ✓ | 15% (3.3)   | 0.8%†† | 125†† |

**Key:** LDL-C = LDL-cholesterol, ARR = absolute risk reduction, NNT = number needed to treat (number of patients who need to be treated to prevent one event), CV = cardiovascular, CHD = coronary heart disease, MI = myocardial infarction

\* Patient populations, study durations (2–6 years) and trial designs varied between studies thus interpretation of results must be undertaken with caution

† Non-fatal MI and death related to CHD (primary endpoint in most studies)

‡ History of stroke or transient ischaemic attack (study excluded patients with MI or angina)

§ Includes unstable angina

‡‡ ARR 3.8% (NNT 26) non-fatal MI, ARR 2.3% (NNT 43) death related to CHD

¶ Includes unstable angina and revascularisation

\*\* At 2 years follow-up, not study average

†† Not statistically significant

**Date prepared: September 2005**

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