Conclusions

The MHRA Drug Safety Update (August 2012) highlights changes to the simvastatin SmPC regarding interactions that can increase the risk of myopathy and/or rhabdomyolysis. When used with amlodipine, the maximum dose of simvastatin is now 20mg; higher doses are ‘off-label’.

For patients taking amlodipine and simvastatin 40mg consider:

1. **Reducing simvastatin dose to 20mg**—most patients can be managed this way as the interaction with amlodipine leads to an increase in simvastatin exposure that is similar to taking simvastatin 40mg alone.
2. **Staying on simvastatin 40mg**— discuss the risks and benefits of this ‘off-label’ option with the patient. Be aware that, due to the interaction with amlodipine, exposure to adverse effects is similar to that associated with simvastatin 80mg when given alone.
3. **Change to an alternative statin**
   - Pravastatin, fluvastatin or rosuvastatin do not interact with amlodipine.
   - Atorvastatin (20mg or 40mg daily) is an option if a more potent statin is needed. The risk of an interaction with amlodipine is much lower with atorvastatin than simvastatin.
4. **Change to an alternative calcium channel blocker**—do not change therapy in patients who are well controlled with amlodipine. Altering the calcium channel blocker is clinically less desirable. Note: the maximum dose of simvastatin is also 20mg with verapamil and diltiazem.

Consider each patient individually taking into account:

- multiple drug therapy and the possibility of drug interactions,
- co-morbidities, including liver function,
- following a change in therapy monitor patients for efficacy and adverse effects.

**Why has the simvastatin dosing guidance changed?**

Myopathy is an adverse effect associated with statins. The risk of myopathy increases with higher plasma levels associated with high-dose therapy (simvastatin 80mg) or concurrent use of interacting drugs. Following changes to SmPCs, the MHRA Drug Safety Update August 2012 highlights updated advice on simvastatin interactions.

**Key change:** the maximum dose for simvastatin in conjunction with amlodipine is now 20mg daily.

**What is the basis for the interaction?**

- Simvastatin is metabolised by the cytochrome P-450 isoenzyme CYP3A4 and is very sensitive to the effects of CYP3A4 inhibitors, leading to many well recognised drug interactions.
- Amlodipine is a weak inhibitor of CYP3A4.
- Concurrent use of amlodipine and simvastatin causes a significant increase in blood levels of simvastatin such that, in practice, the effect is double that compared to uninhibited simvastatin. Therefore, in patients on amlodipine 10mg plus simvastatin 20mg, the effect is similar to receiving simvastatin 40mg alone. The same applies for higher doses of simvastatin where the risk of adverse effects is much greater.
- Fluvastatin, pravastatin and rosuvastatin are not metabolised by CYP3A4 to any significant extent and they do not interact with amlodipine.
- Atorvastatin is also metabolised by CYP3A4 but is less susceptible to interaction with CYP3A4 inhibitors than simvastatin due to its structure. No clinically significant interaction between amlodipine and atorvastatin has been reported.
Do other calcium channel blockers have similar effects on simvastatin?
Verapamil and diltiazem are known inhibitors of CYP3A4; the maximum dose of simvastatin is 20mg daily in patients taking these. Other calcium channel blockers do not interact with simvastatin.

What does the manufactures’ data say?
The current MHRA recommendations reflect updates to the SmPCs for amlodipine and simvastatin.

Istin® (amlodipine)
- Co-administration of multiple doses of 10mg of amlodipine with 80mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin to 20mg daily in patients on amlodipine.
- In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin.

Zocor® (simvastatin)
- Amlodipine - Do not exceed 20mg simvastatin daily. Administration of amlodipine can cause a 1.6-fold increase in exposure to simvastatin.

NOTE: use of the combination of simvastatin 40mg + amlodipine is now ‘off-label’.

Lipitor® (atorvastatin)
There have been no changes to the SmPC for atorvastatin.
- Amlodipine 10mg (single dose) + atorvastatin 80mg (single dose) results in an 18% increase in the area under the curve; no clinical recommendation is made.

What does NICE say about pharmacotherapy for lipid lowering?
NICE guidelines on Lipid modification (CG67) and Management of type 2 diabetes (CG87) state:
- Use 40mg simvastatin or drug of similar efficacy and acquisition cost.
- If there are potential drug interactions or 40mg simvastatin is contraindicated, offer a lower dose of simvastatin or pravastatin.

NOTE:
- Simvastatin 20mg has similar efficacy to simvastatin 40mg, when given in combination with amlodipine.
- Generic atorvastatin is now available substantially lowering its acquisition cost.

What are the costs of statin + calcium channel blocker combinations?

<table>
<thead>
<tr>
<th>Calcium channel blocker</th>
<th>Statin</th>
<th>Comparative costs for 28 days treatment (Drug Tariff September 2012)</th>
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<tbody>
<tr>
<td></td>
<td>Simvastatin 40mg</td>
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<tr>
<td>Amlodipine 10mg</td>
<td>Simvastatin 20mg</td>
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<td>Pravastatin 20mg</td>
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<td>Nicardipine 45mg bd</td>
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</tr>
</tbody>
</table>

Further reading
- MHRA Statins: interactions, and updated advice for atorvastatin (Drug Safety Update, Jan 2008)
- FDA. Drug development and drug interactions: Table of substrates, inhibitors and inducers