NHS Lincolnshire

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SIMVASTATIN: UPDATED ADVICE ON DRUG INTERACTIONS AND CONTRAINDICATIONS

The Medicines and Healthcare Products Regulatory Agency (MHRA) have updated and expanded their advice on drug interactions which may increase plasma concentrations of simvastatin and consequently increase the risk of myopathy and/or rhabdomyolysis. Specifically:

- **Simvastatin is now contraindicated with ciclosporin, danazol and gemfibrozil.**
- **The maximum recommended dose for simvastatin in conjunction with amlodipine or diltiazem is now 20mg/day.**

PACEF have reviewed the updated MHRA advice on simvastatin and consulted additional material including the Summaries of Product Characteristics (SPCs) for each affected product, further information provided by the MHRA and standard sources on drug interactions. Our advice is as follows:

(1) All patients taking simvastatin concurrently with amlodipine, diltiazem or verapamil should be reviewed at their next routine appointment to ensure that their dose of simvastatin is not in excess of 20mg daily. The MHRA have emphasized that urgent review of patients on these combinations is not required. Review at the next routine appointment is sufficient.

(2) For patients receiving simvastatin for primary prevention of cardiovascular disease (CVD), step-down to simvastatin 20mg is the simplest option. Simvastatin is licensed for the primary prevention of CVD at a dose of 20mg once daily. In most patients this should be sufficient. Alternatively, for patients taking concurrent amlodipine, generic atorvastatin 10mg could also be considered; atorvastatin is licensed for primary prevention of CVD at the 10mg dose. For patients taking concurrent diltiazem or verapamil, generic pravastatin 40mg is preferred; pravastatin is licensed for primary prevention of CVD at the 40mg dose. Generic atorvastatin could also be considered, although careful clinical monitoring is recommended particularly at the higher doses or if the dosage of the concurrent diltiazem or verapamil is changed or stopped. Rosuvastatin (*Crestor*) is licensed for purpose but is high-cost and not cost-effective in most scenarios; it should only be considered where all other alternatives have been poorly tolerated.

(3) For patients receiving simvastatin for secondary prevention of CVD, the importance of keeping TC and LDL-C below target levels will necessitate monitoring of lipid control after dose reduction or product switching. The options are to reduce the simvastatin dose to 20mg and monitor the effect or to consider switching to an equivalent dose of an alternative statin. For

patients taking concurrent amlodipine, generic atorvastatin 10mg or 20mg should be considered; atorvastatin is licensed for the secondary prevention of CVD. For patients taking concurrent diltiazem or verapamil, generic pravastatin 40mg is preferred; pravastatin is licensed for secondary prevention of CVD at the 40mg dose. Generic atorvastatin could also be considered, although careful clinical monitoring is recommended particularly at the higher doses or if the dosage of the concurrent diltiazem or verapamil is changed or stopped. Rosuvastatin (*Crestor*) is licensed for purpose but is high-cost and not cost-effective in most scenarios; it should only be considered where all other alternatives have been poorly tolerated or insufficiently effective.

(4) Although interactions between simvastatin and alternative dihydropyridine CCBs (those other than amlodipine) have never been formally documented in practice, they remain possible in theory. As a result of this, prescribers are urged to concentrate on optimising appropriate statin therapy as detailed above rather than switching patients from amlodipine to an alternative once daily dihydropyridine CCB, such as felodipine.

MHRA Advice

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The following table summarizes the drug interactions associated with an increased risk of myopathy/rhabdomyolysis with simvastatin:

Interacting agents	**Prescribing recommendations**
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Nefazodone Ciclosporin Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10mg simvastatin daily
Amiodarone Amlodipine Verapamil Diltiazem	Do not exceed 20mg simvastatin daily
Fusidic acid	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Frequently asked questions?

What is the mechanism of these interactions?

The MHRA report a clear increase in the number of reported cases of rhabdomyolysis with 40mg of simvastatin when administered with either amlodipine or diltiazem; this is not observed when the same drugs are administered with simvastatin 20mg. The mechanism through which most statin drug interactions occur involves the inhibition or induction of the hepatic enzymes of the cytochrome P450 system, especially CYP3A4. Each of the statins differs in their potential for drug interactions. Lipophilic statins, such as atorvastatin, fluvastatin and simvastatin, depend to varying degrees on the P450 system for metabolism to more hydrophilic compounds for renal excretion: hydrophilic statins, such as pravastatin and rosuvastatin, are much less dependent on P450 enzymes for metabolism. 90% of an amlodipine dose is metabolised hepatically by CYP3A4 and is thought to compete with simvastatin for this enzyme; diltiazem and verapamil are modest inhibitors of CYP3A4 and are thought to compromise simvastatin metabolism accordingly. Both mechanisms result in increased plasma concentrations of simvastatin when taken concurrently with amlodipine, diltiazem or verapamil.

Is simvastatin 20mg sufficient for primary and secondary prevention of CVD?

Simvastatin is licensed for the primary prevention of CVD at a dose of 20mg once daily; it is also licensed for secondary prevention of CVD. The MHRA have highlighted the flat dose response curve with simvastatin and have stated that the majority of the LDL-C lowering effect is apparent at lower simvastatin doses than 40mg; they quote a 6% difference between the LDL-C lowering effect of simvastatin 20mg and 40mg (simvastatin 20mg has approximately 90% of the lipid lowering capacity of simvastatin 40mg). They have also postulated that the effect of concurrent prescribing of simvastatin with either amlodipine or diltiazem may be to increase simvastatin plasma levels, boost the effect of the simvastatin 20mg dose and partially mitigate against this reduced LDL-C reduction capacity.

In addition, the MHRA use the SEARCH study to substantiate the use of simvastatin 20mg as a standard fire-and-forget dose in primary prevention of CVD where the patient is taking concurrent amlodipine, diltiazem or verapamil. SEARCH was a multicentre, double blind trial which evaluated over 6.7 years the number of major vascular events (MVEs) (heart attack, revascularisation, and CV death) in 6,031 post-MI patients taking 80mg simvastatin compared to 6,033 post-MI patients taking 20mg simvastatin. The results showed that treatment with simvastatin 80mg did not provide any significant benefits over simvastatin 20mg; the incidence of MVEs was similar for both groups and there was no evidence of increased total or cause-specific mortality, vascular mortality, non-vascular mortality or higher risk of cancer or haemorrhagic stroke with the high dose simvastatin. Hence, in this study population, in a secondary prevention context, there was no evidence of improved outcomes with simvastatin 80mg compared to simvastatin 20mg. The MHRA extrapolate this finding to provide reassurance around step-down from simvastatin 40mg to 20mg in both a primary and secondary prevention context.

Does atorvastatin provide a potential alternative to simvastatin for patients taking concurrent amlodipine?

Yes. Atorvastatin is not specifically contra-indicated with amlodipine, nor is dose reduction recommended. To date there have been no published case reports of

rhabdomyolysis associated with concurrent use of atorvastatin and a dihydropyridine CCB (such as amlodipine) at any dose. There is a statement in the atorvastatin (*Lipitor*) SPC that an increase in atorvastatin plasma concentration (equivalent to an 18% increase in area under the curve) occurs when 80mg atorvastatin is given with 10mg amlodipine. This is predictable based on the lipophilicity of atorvastatin and the dependency of atorvastatin on the cytochrome P450 metabolic pathway (see above). However, even at the 80mg dose of atorvastatin, this effect on plasma concentration is unlikely to be clinically significant. As a result of this, PACEF have judged atorvastatin to be an appropriate alternative to simvastatin for patients taking concurrent amlodipine, although they have recommended caution in doses of atorvastatin higher than 40mg.

Does atorvastatin provide a potential alternative to simvastatin for patients taking concurrent diltiazem or verapamil?

Atorvastatin is a less appropriate alternative to simvastatin in patients taking concurrent diltiazem or verapamil. The atorvastatin (*Lipitor*) SPC gives specific guidance on concurrent use with diltiazem and verapamil which are known to be moderate inhibitors of CYP3A4 (see above). One study has shown an increase in atorvastatin plasma concentration equivalent to a 51% increase in area under the curve when a stat dose of atorvastatin 40mg was given concurrently with diltiazem 240mg; no similar studies have been done with verapamil, but a comparable effect is likely based on similar moderate CYP3A4 inhibition. Guidance from the *Lipitor* SPC states that: ‘a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the CYP3A4 inhibitor’. Prescribers are advised to step down to 20mg simvastatin in the first instance. If secondary prevention of CVD patients fail to reach target at this dose, an alternative statin will need to be considered. In terms of its interaction profile, generic pravastatin 40mg is the preferred alternative. Atorvastatin is not specifically contra-indicated with diltiazem and verapamil, nor has this interaction formed part of an MHRA drug safety alert, but care will need to be taken, particularly at higher doses and if the dose of the diltiazem or verapamil is changed. As a result of this, PACEF have judged atorvastatin to be a less appropriate alternative to simvastatin for patients taking concurrent diltiazem or verapamil.

Is there a role for pravastatin and rosuvastatin?

Yes. Hydrophilic statins, such as pravastatin and rosuvastatin, appear to be free of these interactions and should be considered, particularly in patients insufficiently responsive to simvastatin 20mg and taking concurrent diltiazem or verapamil (see above). Generic pravastatin 40mg is preferred as it is licensed for purpose, evidence based, well tolerated and available as a low cost generic. Rosuvastatin (*Crestor*) is also licensed for purpose and evidence based, but is high-cost and not cost-effective in most scenarios: it should only be considered where all other alternatives have been poorly tolerated or have delivered inadequate lipid control.

Would it not be easier to leave patients on simvastatin and switch the concurrent amlodipine to felodipine or an alternative dihydropyridine CCB?

In common with amlodipine, the other dihydropyridine CCBs (felodipine, isradipine, lacidipine and lercanidipine) are also thought to compete with simvastatin for the CYP3A4 enzyme metabolic pathway. However, interactions between these dihydropyridine CCBs and lipophilic statins are not mentioned in any of the product

SPCs except for lercanidipine (*Zanidip*) (where caution is advised when co-prescribing lercanidipine with other substrates of CYP3A4 (e.g. simvastatin and atorvastatin)). Although interactions between simvastatin and dihydropyridine CCBs (other than amlodipine) have never been formally documented in practice, they remain possible in theory. As a result of this, prescribers are urged to concentrate on optimising statin therapy as detailed above rather than switching patients from amlodipine to an alternative once daily dihydropyridine CCB, such as felodipine.

Most of my patients are well established on simvastatin/amlodipine or simvastatin/diltiazem concurrent therapy with no discernible problems, do I really need to change their therapy?

Approximately half of the myopathy cases identified with simvastatin 80mg in SEARCH study (see above) occurred within the first year of treatment; the incidence of myopathy in each subsequent year was approximately 0.1%. This emphasizes that the bulk of the risk of myopathy with simvastatin is with new initiations and within the first year of treatment. Patients established on simvastatin for more than a year without a problem are at a much lower risk of going on to develop myopathy. This tends to confirm the view that established patients without a problem are likely to remain problem free. However, medico-legally, for the small number of patients that are likely to go on to develop problems later in therapy, it would be difficult for a prescriber to escape censure for failing to implement changes instigated by an MHRA drug safety alert. As a result of this, our advice to all prescribers is to make the required changes even in those that are stable with no discernible problems.

References

MHRA, *Drug Safety Update*, Vol 6 No 1 (August 2012), *Simvastatin: updated advice on drug interactions – updated contraindications*.

A wide range of published and unpublished sources have been used in the compilation of this advice. In addition to the MHRA *Drug Safety Update*, three email responses by the MHRA to specific questions have significantly contributed to the text. A full review of the SPCs for each of the key products has enabled us to confirm marketing authorisations and interaction profiles. Advice from our Regional Medicines Information Centre was also invaluable. Some elements from advice published elsewhere have also been incorporated into the text.

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