Simvastatin prescribing Recommendations following revised safety advice

The MHRA issued revised guidance on the prescribing of simvastatin in August 2012.[1] This follows on from a previous communication on the increased risk of myopathy associated with use of high-dose simvastatin (80 mg daily).[2]
Considering the risk of myopathy associated with simvastatin, recent analysis of clinical trial data, spontaneously reported cases and drug-drug interaction studies has resulted in further changes to the simvastatin prescribing information. The changes include:

- contraindications to concomitant use with certain medicines
- maximum dose recommendations when simvastatin is taken with a number of other medicines

These **interactions may increase plasma concentrations of simvastatin** which is associated with an increased risk of myopathy and/or rhabdomyolysis.[1]

Key points:

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

Important: Drug interactions can occur with all statins, and therefore prescribers are reminded to check the Summary of Product Characteristics (SPC) for the individual agents if prescribing outside of the recommendations made below.

Recommendations for prescribers:

1. Identify all patients prescribed simvastatin and ciclosporin, danazol or gemfibrozil. For these patients, simvastatin must be stopped with a view to switching to an alternative statin.
   Recommended alternative statins are:
   - **With ciclosporin**: Atorvastatin at a maximum dose of 10mg (higher atorvastatin doses are contraindicated with ciclosporin); OR pravastatin up to 40mg daily
   - **With gemfibrozil or danazol**: Atorvastatin initiated at 10mg daily, increasing as required to control lipids, with careful monitoring; OR pravastatin up to 40mg daily

2. Identify all patients prescribed **simvastatin 40mg and either amlodipine or diltiazem**.

Current Lipid Treatment Targets
Primary prevention: no targets, use generic agent
Secondary Prevention for Stable CVD: Total cholesterol ≤ 5mmol/L and LDL ≤ 3mmol/L
Diabetics and Patients Post - Acute Coronary Syndrome: Total cholesterol ≤ 4mmol/L or LDL ≤ 2mmol/L

For these patients, the simvastatin should be reviewed with a view to either:

a. **Reducing the dose of simvastatin to 20mg daily**
   Note; this is still an effective dose – simvastatin 20mg daily will deliver on average 90% of the lipid lowering efficacy of simvastatin 40mg daily, such that overall an approximate 0.2mmol/L increase in LDL cholesterol level can be expected as a result of this dose reduction.[3,4] Where this small change in LDL level is unlikely to affect achievement of lipid treatment targets, and the patient is tolerating simvastatin - this option may be preferable.

OR

b. **Switching to atorvastatin 20mg daily**
   This dose has approximately the same lipid lowering efficacy as simvastatin 40mg daily.
   Patients NOT currently achieving recommended lipid treatment targets, as per table above, should be switched to atorvastatin, with a view to dose titration in line with SLCSN lipid modification guidance, which can be found at: http://www.slcsn.nhs.uk/prescribing.html

3. Changes at an individual patient level should be made at or before the patient next requests a repeat prescription.

Updated list of drugs interactions with simvastatin

Drug interactions associated with increased risk of myopathy / rhabdomyolysis	
Interacting agents	**Prescribing recommendations**
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (eg, nelfinavir) Nefazodone Ciclosporin Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Amiodarone Amlodipine Verapamil Diltiazem	Do not exceed 20 mg 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

Detailed SLCSN lipid modification guidance can be found at:
http://www.slcsn.nhs.uk/prescribing.html

References

1. MHRA Drug Safety Update August 2012. Simvastatin: updated advice on drug interactions - updated contraindications.
2. MHRA Drug Safety Update May 2010. Simvastatin: increased risk of myopathy at high dose (80mg)
3. Jones PH et al. Comparison of the efficacy, safety, or rosuvastatin, versus atorvastatin, simvastatin and pravastatin across Doses (STELLAR trial). Am J Cardiol 2003;93:152–160
4. Law et al. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003 Jun 28;326(7404):1423.