PRAC recommendation
HMG-CoA Reductase Inhibitors – Simvastatin – Risk of myopathy and rhabdomyolysis associated with high doses

This is a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA).

1. Administrative details

<table>
<thead>
<tr>
<th>Substance (invented name)</th>
<th>Simvastatin (Zocor and associated brand names)</th>
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<tbody>
<tr>
<td>Authorisation procedure</td>
<td>Non-centralised</td>
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<tr>
<td>Signal (EPITT No)</td>
<td>HMG-CoA Reductase Inhibitors: simvastatin – risk of myopathy and rhabdomyolysis associated with high doses – follow-up of previous PhVWP review (13849)</td>
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<tr>
<td>PRAC meeting date</td>
<td>7-10 April 2014</td>
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<td>Signal identifier</td>
<td>UK</td>
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<td>PRAC rapporteur(s)</td>
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<td>Status</td>
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<td>Date of adoption</td>
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2. Prioritisation and recommendation

Evidence evaluated and prioritisation/public health importance

The safety of statins has been under constant review over past years. In 2012 a preliminary review of the data from the SEARCH trial by the PhVWP concluded that this trial provided a safety signal for 80mg simvastatin treatment but that further work was required to define the risk benefit balance of intensive
dose statin therapy and to characterise the patients prescribed high dose statins and whether benefits were similar across all patient populations.

In November 2013 the PRAC reviewed the brand leader MAH’s response to the PhVWP list of questions, including further information on the SEARCH trial, together with detailed information on UK usage of simvastatin generated from the CPRD. The PRAC considered that the data generally supported what is already known about the dose dependent risk of myopathy and rhabdomyolysis and which is reflected in the current product information for statins. The PRAC noted that the use of 80mg simvastatin is low in the UK but considered it would be informative to gather further information on the overall pattern of statin use especially at high doses in the EU. The PRAC also noted the potential importance of genetic polymorphisms (such as variants of the SLCO1B1 gene), which may help identify patients predisposed to myopathy/rhabdomyolysis with statin use. Consequently the brand leader MAH for simvastatin was asked to provide further data on biomarkers for myopathy related to statins.

The focus of the current assessment is on usage data for statins generated by the National Competent Authorities (NCAs) of Member States (MS) and the EMA and on the MAH response to the PRAC request for further data on biomarkers for myopathy related to statins.

Fourteen NCAs and the EMA provided information on statin usage following the NUI (non-urgent request for information) circulated in December 2013. The data show a diverse pattern of usage across Europe, with use of one statin predominating in some MS compared to a fairly even spread of use of 3 to 4 statins in other MS. Likewise, the use of simvastatin in particular has shown different patterns of use. Although it is authorised in all MS, absolute use of simvastatin has remained stable or increased steadily between 2006 and 2011 in some MS, whereas in other MS absolute use of simvastatin has declined steadily over the same time period. Use of simvastatin 80mg appears to be a very small proportion of all statin use in all MS.

In general, the product information for other statins contain less detailed warnings on myopathy and rhabdomyolysis than the product information for simvastatin. Given the differing usage patterns of the various statins across member states it was discussed that individual MS may wish to use national communication mechanisms to remind prescribers that an increased risk of myopathy and rhabdomyolysis is associated with use of high dose statins.

A number of potential biomarkers for myopathies in association with statin use have been identified. The genetic polymorphism SLCO1B1*5 has been mostly associated with cases of rhabdomyolysis seen with simvastatin use. Some, but not all, studies have found an increased risk of rhabdomyolysis with other statins when this variant of SLCO1B1 is present. Conversely, SLCO1B1*5 polymorphisms appear to account for about 40 to 50% of cases of rhabdomyolysis with simvastatin. Thus, a significant number of cases are not associated with this polymorphism. A number of other potential biomarkers for myopathy have been proposed but the evidence supporting these is sparse.

**Recommendation**

The genetic polymorphism SLCO1B1*5 increases the risk of myopathy, due to increased plasma levels of simvastatin. SLCO1B1*5 occurs in ~15-18% of Europeans and was found in about 45% of myopathy cases seen with simvastatin in the SEARCH trial, and accounted for 50-60% of myopathy cases seen in the SEARCH and HPS clinical trials. Screening for SLCO1B1*5 is not established in routine clinical practice but may be conducted in some specialist centres.

Given the increased risk of myopathy that occurs with carriers of the SLCO1B1 gene c.521T>C allele, it is appropriate to include information on this genetic subpopulation in the simvastatin SmPC as a risk factor
for myopathy and also highlight the importance of considering the impact of the SLCO1B1 genotype as part of an individual risk:benefit assessment where the genotype is available or already known.

The MAHs for simvastatin-containing products should submit a variation within two months to the relevant NCAs (National Competent Authority) to include the following text in the Summary of Product Characteristics (new text underlined):

Section 4.4 Special warnings and precautions for use

Reduced function of transport proteins

Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin and increase the risk of myopathy and rhabdomyolysis. Reduced function can occur as the result of inhibition by interacting medicines (eg ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1% in general, without genetic testing. Based on the results of the SEARCH trial, homozygote C allele carriers (also called CC) treated with 80 mg have a 15% risk of myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1.5%. The corresponding risk is 0.3% in patients having the most common genotype (TT) (See section 5.2). Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this gene upon genotyping does not exclude that myopathy can still occur.

Section 5.2 Pharmacokinetic properties

Elimination

Simvastatin is taken up actively into the hepatocytes by the transporter OATP1B1.

Special populations

Carriers of the SLCO1B1 gene c.521T>C allele have lower OATP1B1 activity. The mean exposure (AUC) of the main active metabolite, simvastatin acid is 120% in heterozygote carriers (CT) of the C allele and 221% in homozygote (CC) carriers relative to that of patients who have the most common genotype (TT). The C allele has a frequency of 18% in the European population. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of simvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4).