

## Area Prescribing/Drugs and Therapeutic Committee:

Date of next meeting:

Decision: Yes  No

Restricted use:

## Drug name

**Simvastatin 20 mg/5 ml and 40 mg/5 ml oral suspension**

## Indication

For patients unable/unwilling to swallow simvastatin tablets.

For treatment of: primary hypercholesterolaemia or mixed dyslipidaemia, if response to dietary change and other non-pharmacological treatments is inadequate; and for homozygous familial hypercholesterolaemia, as an adjunct to diet and other lipid-lowering treatments, or if such treatments are not appropriate.

For cardiovascular prevention: in patients with manifest atherosclerotic CVD or diabetes mellitus, with normal/increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy.

## Dosage

Please refer to the Summary of Product Characteristics (SPC) which can be found at [www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)

## Mode of action

- Blocks HMG-CoA reductase (linked to cholesterol production in the liver), inhibiting production of LDL
- This causes an increase in the number of LDL receptors on the hepatocyte surface, resulting in greater removal of cholesterol from the bloodstream.

## NICE recommendations

- Treatment for the primary and secondary prevention of CVD should be initiated with simvastatin 40 mg (or generic statin with the lowest acquisition costs)
- Patient preference should guide the review of drug therapy.<sup>1</sup>

## Evidence for use

- Simvastatin is one of the 50 most prescribed drugs for the elderly<sup>2</sup>
- Almost 60% of patients aged >65 years experience some difficulty swallowing solid medications<sup>3</sup>
- CVD is the leading cause of death in England and Wales<sup>4</sup>
- Key risk factors for CVD can be used to identify (using Framingham and/or QRISK2) and treat those at risk: age is the main determinant of CVD risk, with smoking, raised blood pressure, and raised cholesterol also making a major contribution.<sup>5</sup> Identifiable groups at particular risk include women (due to longevity and increased stroke risk when >75 years of age),<sup>6</sup> South Asian men,<sup>1</sup> and individuals with a family history of premature CHD.<sup>1</sup>

## Cost effectiveness

- Compliance rates associated with long-term statin use can be poor<sup>7</sup> and the medical and economic consequences may be considerable
- Swallowing difficulties might be one factor that adversely affects compliance, particularly in elderly and stroke patients
- Stroke currently costs the NHS £2.8 billion/year<sup>8</sup>
- Liquid simvastatin might be more appropriate and more cost effective for patients with poor compliance, or swallowing difficulties (e.g. the elderly and stroke patients<sup>3</sup>).

## Contraindications

Hypersensitivity to simvastatin or to any of the excipients; active liver disease or unexplained persistent elevations of serum transaminases; pregnancy and lactation; concomitant administration of potent CYP3A4 inhibitors.

## Precautions

Please refer to the SPC at [www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)

## Side-effects

Please refer to the SPC at [www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/)

CVD=cardiovascular disease; HMG-CoA=3-hydroxy-3-methyl-glutaryl coenzyme A; LDL=low density lipoprotein; CHD=coronary heart disease

## Key points

The following patients who may become non-adherent benefit from simvastatin oral suspension:

- Patients aged >60 years who might have difficulty swallowing simvastatin (or other statin) tablets
- Children with familial hypercholesterolaemia who may prefer a liquid
- Stroke patients, who are likely to have evidence of post-stroke dysphagia and who require treatment for secondary prevention of a cardiovascular event.

If patients cannot swallow their tablets and become non-adherent, they will not obtain the clinical benefits—a liquid simvastatin can help these patients.

## References

1. National Institute for Health and Clinical Excellence. *Lipid modification—Updated 2010*. Clinical Guideline 67. London: NICE, 2010. Available at: [guidance.nice.org.uk/CG67](http://guidance.nice.org.uk/CG67)
2. Wright D. *Oral liquid formulary—guidance for healthcare professionals*. Norwich: University of East Anglia, 2006.
3. Strachan I, Greener M. Medication-related swallowing difficulties may be more common than we realise. *Pharmacy in Practice* 2005; **15** (9): 411–414.
4. [www.statistics.gov.uk/downloads/theme\\_health/hsq33web.pdf](http://www.statistics.gov.uk/downloads/theme_health/hsq33web.pdf) (accessed 22 June 2010).
5. Emberson J, Whincup P, Morris R et al. Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: impact of regression dilution bias. *Eur Heart J* 2003; **24**: 1719–1726.
6. Seshadri S, Beiser A, Kelly-Hayes M et al. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke* 2006; **37**: 345–350.
7. Benner J, Glynn R, Mogun H et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002; **288** (4): 455–461.
8. National Institute for Health and Clinical Excellence. *Stroke*. Clinical Guideline 68. London: NICE, 2008. Available at: [guidance.nice.org.uk/CG68](http://guidance.nice.org.uk/CG68).

## Abbreviated Prescribing Information: Simvastatin 20mg/5ml and 40mg/5ml Oral Suspension. Consult Summary of Product Characteristics before prescribing.

**Presentation:** White to off-white oral suspensions. **Therapeutic Indications:** Hypercholesterolaemia:- Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments is inadequate. Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments or if such treatments are not appropriate. Cardiovascular prevention:- Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy. **Posology and Method of Administration: Adults:** The dosage range is 5–80mg/day depending on condition given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80mg/day given as a single dose in the evening. The 80mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications. No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency, dosages above 10mg/day should be carefully considered. **Children:** (10–17 years of age, boys Tanner Stage II and above and girls who are at least one year post-menarche) with heterozygous familial hypercholesterolaemia, starting dose is 10mg once a day in the evening. The recommended dosing range is 10–40 mg/day. Adjustments should be made at intervals of 4 weeks or more. The experience of simvastatin in pre-pubertal children is limited. **Elderly:** No dosage adjustment is necessary. **Contra-indications:** Hypersensitivity to simvastatin or to any of the excipients. Active liver disease or unexplained persistent elevations of serum transaminases. Pregnancy and lactation. Concomitant administration of potent CYP3A4 inhibitors. **Precautions:** Myopathy/Rhabdomyolysis: risk of myopathy is increased by high levels of HMG CoA reductase inhibitory activity in plasma. Hepatic effects; persistent increases (to > 3 x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels. The product should be used with caution in patients who consume substantial quantities of alcohol. Interstitial lung disease; exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Diabetes Mellitus; some evidence suggests that statins as a class can raise blood glucose level. Excipient Warnings; parahydroxybenzoates which may cause allergic reactions. **Interactions:** The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates. There is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels. Rare cases of myopathy/rhabdomyolysis have

been associated with simvastatin co-administered with lipid-modifying doses ( $\geq 1$ g/day) of niacin. Drug interactions associated with increased risk of myopathy/rhabdomyolysis: Potent CYP3A4 inhibitors - Contraindicated with simvastatin. Gemfibrozil - Avoid but if necessary, do not exceed 10mg simvastatin daily. Cyclosporin, danazol, other fibrates (except fenofibrate) - Do not exceed 10mg simvastatin daily. Amiodarone, verapamil - Do not exceed 20mg simvastatin daily. Diltiazem - Do not exceed 40mg simvastatin daily. Fusicid acid - Patients should be closely monitored. Grapefruit juice - Avoid grapefruit juice when taking Simvastatin. Effects of other medicinal products on simvastatin. Combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. Cyclosporin - the dose of simvastatin should not exceed 10mg daily. Very rare cases of elevated INR have been reported. **Pregnancy and Lactation:** Simvastatin Oral Suspension is contraindicated during pregnancy. It is not known whether simvastatin or its metabolites are excreted in human milk. Women taking Simvastatin Oral Suspension should not breast-feed their infants. **Effects on Ability to Drive and Use Machines:** Simvastatin Oral Suspension has no or negligible influence on the ability to drive and use machines. **Undesirable Effects:** Blood and lymphatic system disorders: Rare: anaemia. Psychiatric disorders: Very rare: insomnia. Not known: depression. Nervous system disorders: Rare: headache, paresthesia, dizziness, peripheral neuropathy. Very rare: memory impairment. Respiratory, thoracic and mediastinal disorders: Not known: interstitial lung disease. Gastrointestinal disorders: Rare: constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis. Hepato-biliary disorders: Rare: hepatitis/ jaundice. Very rare: hepatic failure. Skin and subcutaneous tissue disorders: Rare: rash, pruritus, alopecia. Musculoskeletal, connective tissue and bone disorders: Rare: myopathy, rhabdomyolysis, myalgia, muscle cramps. Reproductive system and breast disorders: Not known: erectile dysfunction. General disorders and administration site conditions: Rare: asthenia, apparent hypersensitivity syndrome. Investigations: Rare: increases in serum transaminases, elevated alkaline phosphatase; increase in serum CK levels. **Overdose:** There is no specific treatment in the event of overdose. **Shelf Life and Storage:** 12 months unopened, 1 month opened. Do not store above 25°C. **Pack Size and NHS Price:** 20mg/5ml, 150ml – £99.50, 40mg/5ml, 150ml – £152.00. **Legal Category:** POM. **Marketing Authorisation Number and Holder:** 20mg/5ml PL 00427/0146, 40mg/5ml PL 00427/0147. Rosemont Pharmaceuticals Ltd, Rosemont House, Yorkdale Industrial Park, Braithwaite Street, Leeds, LS11 9XE, UK. **Date of Preparation:** August 2013

Information about adverse event reporting can be found at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk).

Adverse events should also be reported to Rosemont Pharmaceuticals Ltd on 0113 244 1400