Simvastatin

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 18. Medicines for endocrine disorders

ATC codes: C10AA01

Indication	Polycystic ovary syndrome ICD11 code: 5A80.1
INN	Simvastatin
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 20 mg
EML status history	Application rejected in 2021 (TRS 1035)
Sex	Female
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Simvastatin
DrugBank	Simvastatin

Expert Committee recommendation

The Expert Committee noted that polycystic ovary syndrome is a frequent disease in women worldwide. It is associated with infertility, obesity, metabolic syndrome, hypertension, type 2 diabetes, cardiovascular disease and some gynaecological cancers, and has important psychosocial effects, highlighting the need for appropriate treatment. The Committee also acknowledged that repurposing of old drugs for new indication is important and should be further investigated. However, the available evidence shows that while simvastatin can improve biochemical markers in patients with polycystic ovary syndrome, there is no evidence that these improvements result in better clinical outcomes. Moreover, the evidence seems to suggest statins may differ with regard to their effect on surrogate markers, such as hormone levels, with atorvastatin possibly being superior to simvastatin. The Committed noted that simvastatin should not be used in pregnancy as studies in animals and humans have shown fetal abnormalities or the risk of human fetal abnormalities. This an important issue as polycystic ovary syndrome mainly affects women of reproductive age and one aim of treatment of polycystic ovary syndrome is to improve fertility. Therefore, the Expert Committee did not recommend the addition of simvastatin for polycystic ovary syndrome due to an absence of evidence for clinical benefits.

Background

Simvastatin was added to the EML in 2007 for the secondary prevention of cardiovascular disease in high-risk populations with a square box listing giving pravastatin, lovastatin, fluvastatin and atorvastatin as possible alternatives, with the choice to be made at the national level. The Committee acknowledged that there was high-

quality clinical evidence from many large randomized trials and systematic reviews that established the clinical benefits of statins, in conjunction with lifestyle modification, for this indication (1). Simvastatin has not previously been considered by the Expert Committee for use in the treatment of polycystic ovary syndrome. Generally, polycystic ovary syndrome presents as a spectrum of heterogeneous disorders of reproduction and metabolism in women with frequent symptoms, such as abnormal menstruation, infertility, obesity, hirsutism, acanthosis nigricans, acne and ovarian cysts. Expert groups commonly recommend using the Rotterdam criteria for diagnosis of polycystic ovary syndrome (2,3). The Rotterdam criteria require that the patient exhibits two of three of the following characteristics: oligo- and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; and/or ultrasound evidence of polycystic ovaries (4).

Public health relevance

Polycystic ovary syndrome is the most common endocrinopathy affecting women of reproductive age globally, with a prevalence of about 8–13% (5). Due to discrepancies between diagnostic criteria and symptom presentation, the prevalence may be as high as 20% (6). The prevalence and disease presentation vary widely by ethnicity and geographical location (7,8). Polycystic ovary syndrome is a leading cause of infertility. Furthermore, women with polycystic ovary syndrome are at a higher risk of developing impaired glucose tolerance, type 2 diabetes, cardiovascular disease, hypertension, metabolic syndrome and certain gynaecological cancers (5,9). Women with polycystic ovary syndrome have a substantially lower quality of life compared with control groups and population data (10). Visible signs of excess androgens (such as hirsutism, acne and alopecia) have noticeable effects on physical appearance that can affect neuropsychological status. Obesity also has an important psychosocial effect (11). Women, especially adolescents, with polycystic ovary syndrome are at increased risk of anxiety and depression (12–14). Associations between socioeconomic status and polycystic ovary syndrome prevalence vary; however, women of low socioeconomic status during adulthood, or low socioeconomic status during childhood but high personally attained socioeconomic status during adulthood, are more likely to have polycystic ovary syndrome (13,15).

Benefits

Systematic reviews and meta-analyses Five systematic reviews and meta-analyses were identified that included an evaluation of simvastatin for the management of polycystic ovary syndrome (16–20). Variation in inclusion criteria (e.g. any statin), search approach, analytical techniques and outcomes of interest produced variability in conclusions on the usefulness of simvastatin and other statins for this indication. Three reviews focused on the evaluation of pharmacological class (16,19,20), and concluded simvastatin may provide some benefit with regard to biochemical markers such as lipid and testosterone levels. Two reviews included a comparison of atorvastatin, simvastatin and rosuvastatin and found atorvastatin to be superior in terms of effects on testosterone or dehydroepiandrosterone levels. However, small sample sizes limit the clinical usefulness of these findings (17,18). Further studies are needed to assess clinical outcomes. Randomized clinical trials Fifteen randomized controlled trials compared the effectiveness of regimens containing simvastatin with one or two other treatment options. Most trials had small sample sizes. Trial data indicated positive effects of simvastatin therapy on lipids, hormone levels and other measures of disease activity in women with polycystic ovary syndrome. Two trials compared simvastatin with placebo. A trial in 61 women with polycystic ovary syndrome pursuing in vitro fertilization found positive effects on testosterone and cholesterol but did not find benefit in terms of fertilization success (21). Another trial in 200 women with polycystic ovary syndrome found positive effects of simvastatin compared with placebo on hormone levels, lipids, menstrual regularity, hirsutism, acne, ovarian volume, body mass index and waist-to-hip ratio, but did not on fasting glucose, fasting insulin or measures of insulin resistance (22). Two trials compared simvastatin with metformin in women with polycystic ovary syndrome (23,24). One trial included 400 women and found simvastatin was superior to metformin in improving total cholesterol, low-density lipoprotein, C-reactive protein and acne; metformin was superior in improving fasting blood sugar and insulin measures (23). The second trial included 40 women with polycystic ovary syndrome pursuing in vitro fertilization; both regimens were associated with beneficial effects on biochemical parameters, but neither regimen affected fertilization outcomes (24). Three trials with a total of 401 women with polycystic ovary syndrome compared simvastatin, metformin and

the combination of simvastatin and metformin (25–28). In one of the trials, neither metformin nor simvastatin were found to affect levels of free fatty acid binding protein-4 or retinol binding protein-4, known to contribute to metabolic syndrome (26). In another trial, women treated with simvastatin had significantly better responses than women treated with metformin alone for outcomes including number of spontaneous menses in 6 months, ovulation, ovarian volume, body mass index, waist-to-hip ratio, hirsutism score, acne, total and free testosterone, and other metabolic parameters (25). In the third trial, no significant differences were found between treatment groups for reduction in total testosterone, reduction in body mass index, or improvements in markers of systemic inflammation and endothelial function. Simvastatin treatment was superior to metformin alone (27,28). One trial compared simvastatin, metformin and flutamide plus oral contraceptives in 102 women with polycystic ovary syndrome and metabolic syndrome (29). After 6 months, simvastatin was superior to the other two regimens for reductions in waist circumference, body mass index and triglyceride levels. Metformin was superior to the other regimens for effects on fasting blood sugar. Two trials compared simvastatin to atorvastatin in 116 women with polycystic ovary syndrome (30,31). Both trials found the statin regimens lead to improvements in lipid levels and other measures of disease activity, while benefits attributed to the individual agents varied to some extent; the data suggest possible greater effects of simvastatin on hormone levels, while atorvastatin may have a greater effect on measures of insulin resistance. Two trials evaluated simvastatin plus metformin versus metformin alone in 192 women with polycystic ovary syndrome (32,33). Both trials found the regimen containing simvastatin-led to greater improvements in hormone levels (e.g. testosterone, follicle stimulating hormone and luteinizing hormone) and lipids. One trial evaluated simvastatin plus oral contraceptives versus oral contraceptives alone in 48 women with polycystic ovary syndrome (34). The combination regimen significantly reduced serum testosterone, other hormone levels (e.g. follicle stimulating hormone and luteinizing hormone), reduced total cholesterol and low-density lipoprotein levels, and increased high-density lipoprotein levels. The hirsutism score was also slightly reduced.

Harms

The safety and tolerability profile of simvastatin as a treatment for hyperlipidaemia is well known. The literature describing the use of simvastatin or atorvastatin in the treatment of women with polycystic ovary syndrome indicates a safety profile comparable to that observed in the substantial evidence on statin use for hyperlipidaemia. Simvastatin is contraindicated in pregnancy and breastfeeding. It should only be used in women of childbearing potential when they are highly unlikely to conceive.

Additional evidence

Comments were received from Dr Barbara Stegmann, Clinical Lead for Women’s Health, Organon & Co. (marketing authorization holder for Zocor brand of simvastatin), highlighting concerns about the of use of statins (including simvastatin) during pregnancy and in women of childbearing potential, including a category X designation by the United States Food and Drug Administration for use in pregnancy (drugs that can cause birth defects and developmental abnormalities in humans), and the contraindications for use during pregnancy and breastfeeding issued by the Food and Drug Admiration, European Medicines Agency and other regulatory agencies (35–37).

Cost / cost effectiveness

No cost–effectiveness data were presented in the application. Simvastatin is widely used globally and is generally affordable. A national cost analysis using United States data, noted that the estimated annual national health care cost associated with polycystic ovary syndrome was US$ 1.16 billion, with the greatest contributors being treatment for diabetes, oral contraceptives, initial evaluation, medical costs associated with obesity, and infertility treatment (38). An analysis from the United Kingdom of Great Britain and Northern Ireland focused on the costs associated with diabetes in women with polycystic ovary syndrome, and estimated the annual health care burden of the condition was at least £ 237 million (39).

WHO guidelines

WHO guidelines for the treatment of women with polycystic ovary syndrome are not currently available.

Availability

Simvastatin is widely available globally in branded and generic forms. Currently, it does not have regulatory approval for the treatment of polycystic ovary syndrome.

Other considerations

The applicants reviewed data from a phenome-wide association study. Such studies can identify diseases or conditions (phenotypes) that are associated with a specific gene or genetic variant (40). Phenome-wide association studies make use of existing data from the ExomeChip genotyping platform (about 250 000 coding variants across the protein coding region of the genome) and electronic health records of about 35 000 patients. Because the rationale of phenome-wide association studies can be extended to predict phenotypic manifestations of pharmacological targeting (such as with simvastatin) of a given gene product in humans, these methods are used for drug repurposing (41). As a hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin reduces cholesterol. The phenotypes associated with the missense single nucleotide polymorphism (SNP) (Ile638Val) in the HMGCR gene are risk-causing, so in this regard, the SNP is functioning as an HMG-CoA reductase activator (the opposite of the drug). This SNP is associated with increased risk of cholesterol disorders, and is also associated with oophorectomy and ovarian cysts. The applicants assert this evidence supports the proposal to treat polycystic ovary syndrome with simvastatin. The application noted that current evidence does not confirm that there is a true pharmacological class effect for statins in polycystic ovary syndrome. In addition, statins have a pharmacological variation that might plausibly suggest different outcomes with polycystic ovary syndrome.

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