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Dr. Benedikt Huttner
Secretary of the Expert Committee

World Health Organization
Expert Committee on the Selection and Use of Essential Medicines
Medicines Selection, IP and Affordability
Department of Health Products Policy and Standards
20 Avenue Appia
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Dear Dr. Huttner:

The World Health Organization (WHO) recently received a proposal to add a new indication for use of simvastatin (tradename Zocor) for the treatment of Polycystic Ovarian Syndrome (PCOS) to the core Essential Medicines List (I.14 Simvastatin-polycystic ovary syndrome – EML). This request is being made through Project Remedi (Repurposing Essential Medicines Internationally) by Jill M Pulley, MBA and Rebecca Jerome, MLIS, MPH of the Vanderbilt Institute for Clinical and Translational Research in Nashville Tennessee. Simvastatin is an HMG-CoA reductase inhibitor that lowers cholesterol levels by blocking the action of HMG-CoA reductase, the rate limiting step in cholesterol synthesis.[1] While women with PCOS can indeed have increased cholesterol levels, PCOS is a complex endocrine condition with alterations across the hypothalamic-pituitary-ovarian axis. Often, but not always, women with PCOS have elevated levels of free and total testosterone resulting in abnormal menstrual cycles and impaired fertility. Cholesterol is a required substrate for testosterone synthesis, so by reducing cholesterol levels the amount of substrate available for testosterone production is reduced and levels decline [2]. The proposal by Pulley and Jerome concludes that use of simvastatin could therefore lower testosterone leading to the resumption of normal menstrual cycles, enhanced fertility, and improved cardiovascular health. [3].However, preclinical and clinical trial data on simvastatin in men suggest that the small decline is testosterone seen with the use of testosterone was unlikely to be clinically significant. The impact of this small decline in testosterone in premenopausal women has not been determined. [4]

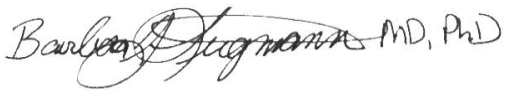
Despite these potentially beneficial effects in a woman suffering from PCOS, it is critically important to recognize that many women with PCOS have the potential to become pregnant even without treatment and this possibility increases if the underlying metabolic abnormalities are corrected. The possibility of pregnancy must be addressed as all statins, including simvastatin, are considered by FDA as “Category X” (drugs that can cause birth defects and developmental abnormalities in humans) and therefore are contraindicated for use during pregnancy and lactation specifically because of the negative impact the above-mentioned actions have on the developing fetus [5]. Both cholesterol and testosterone are essential for normal fetal development. Lack of adequate testosterone levels in the male fetus results in abnormal genitourinary development, including undescended testes, a reduction in the amount of testicular tissue and reduced sperm production leading to infertility in adulthood. [6, 7]

There are no adequate and well-controlled studies of use with simvastatin during pregnancy; however, in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In a review of 100 women who reported exposure in pregnancy, the level of adverse events did not exceed what was expected in the general population but the smallest risk of congenital malformations this study could

detect was 3-4 fold above the background rates and rates below this level could have gone unrecognized. Though not confirmed with simvastatin, teratogenicity studies with other structurally related statins in rats and mice have shown skeletal malformations.

In summary, the use of statins to treat women with PCOS may improve the health of the women and could possibly improve their fertility. As a result, the number of fetuses exposed to statins in-utero could increase substantially, specifically in early pregnancy when the potential for negative impact of the exposure appears to be greatest. At this time, all statins are contraindicated for use during pregnancy and lactation by both the FDA and EMA. No regulatory agency nor professional association has opposed this classification or endorsed the use of statins in pregnancy [5, 8], and we believe that simvastatin should be administered to women of childbearing age ONLY when such patients are highly unlikely to conceive. [4] Whilst the unmet medical needs of women with PCOS are recognized, we would nevertheless recommend that the WHO take the contraindication of statins in pregnancy into account in their deliberations on the use simvastatin in treatment of PCOS, especially in areas of the world with limited prenatal and neonatal care,

Sincerely,



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Organon & Co.

This letter is being submitted on behalf of Organon LLC, a subsidiary of Organon & Co. (collectively, "Organon"). Organon & Co. is a wholly owned subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, known as MSD outside of the U.S. and Canada (hereinafter, "MSD"). Organon is scheduled to spin off as a separate company in 2021 and the marketing authorization for ZOCOR (simvastatin) is being transferred from MSD to Organon as a part of the intended spin off of Organon.

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3. Pulley, J. and R. Jerome, *Simvastatin for management of polycystic ovary syndrome (PCOS).* Project Remidi, 2021.
4. *Zocor (simvastatin) [package insert]. Whitehouse Station, NJ: MERCK & CO., INC. 1991.*
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