Norethisterone

NOT RECOMMENDED AS AN ESSENTIAL MEDICINE

Section: 18. Medicines for endocrine disorders > 18.4. Progestogens

ATC codes: G03DC02

Indication	Excessive menstruation with irregular cycle ICD11 code: GA22
INN	Norethisterone
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid: 5 mg
EML status history	First added in 1977 (TRS 615) Changed in 1979 (TRS 641) Changed in 1984 (TRS 722) Removed in 2011 (TRS 965)
Sex	All
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	Norethisterone
DrugBank	Norethisterone

Summary of evidence and Expert Committee recommendations

In 2003, the Expert Committee raised a question about the public health relevance of continuing to include medroxyprogesterone acetate (MPA) on the EML for hormone replacement therapy (HRT). In 2005 this was extended to include uncertainty of the need for ethinylestradiol and also norethisterone. The Secretariat has therefore commissioned reviews of all three products for the current meeting. They were added to the List in 1979 for use in HRT and although the safety of medroxyprogesterone acetate has been subsequently evaluated, the efficacy and safety of all three medicines for HRT have not been reassessed since the publication of the large studies of HRT demonstrating no cardiovascular benefit as well as the increased risk of breast cancer. WHO therefore commissioned reviews from the University of Split as a branch of the Italian Cochrane Centre. The Department of Reproductive Health Research, WHO, recommends retention of MPA for HRT and deletion of ethinylestradiol and norethisterone. The reviews provide a comprehensive literature search for each medicine in relation to potential benefits of HRT, in terms of symptomatic relief and effects on surrogate markers. For ethinylestradiol, the review includes also a RCT and systematic review (1), showing effects on bone density that were used as the basis of the claim for reduction in postmenopausal osteoporosis. For MPA, the reviews cite the studies measuring effect on bleeding patterns, bone density, lipid concentrations, mammographic findings, cardiovascular effects, menopausal symptoms, metabolism, overall efficacy and safety as well as 'other effects'. For norethisterone, the review presents a systematic review and 3 RCTs of use of norethisterone as HRT, and 8 systematic reviews and 10 RCTs for use in the treatment of dysfunctional uterine bleeding. Norethisterone was generally less effective than alternatives for the latter indication. The reviews do not provide any information about the potential harms of HRT. The main risks that have been identified are the increased risk of breast cancer (from the Million Women Study; 2), RR for current users 1.66 (95% CI 1.58–1.75), and the increased risk of thromboembolic events (3): pooled RR 2.15 (95% CI 1.61–2.86), pulmonary embolus RR 2.15 (95% CI 1.41–3.28), and stroke RR 1.44 (95% CI 1.10–1.89). There is also no evidence to support reduction in risk of cardiovascular disease (4) – one of the main

claims for HRT – and the evidence for reduction in fractures is limited to change in bone mineral density, an uncertain surrogate. However, there is continuing controversy about the overall risk benefit balance. Most guidelines today recommend HRT for short-term use only, for symptom relief. WHO does not have a treatment guideline for menopausal symptoms. The benefits and risks of use of HRT have to be assessed on a case-by-case basis. There is still considerable uncertainty about the optimal short term symptomatic management of menopause. While there are options for the management of vasomotor effects, including clonidine, there are questions about the safest and most effective way to use hormonal preparations to manage urogenital symptoms. No comparative cost information was provided. The Committee noted that long-term hormone replacement treatment of menopause is no longer considered appropriate, notwithstanding individuals' possible need for treatment of symptoms. The Committee therefore decided to delete all three medicines for this indication, but to signal the need for a review of the short-term symptomatic management of menopause and the development of guidelines in this regard. For this reason, the section subheading would be retained until a proposal for inclusion of an alternative estrogen is received and reviewed. However, as progestins are needed for the management of dysfunctional uterine bleeding, MPA was retained, with a square box symbol, in the 5 mg oral solid dosage form, for this purpose. This would allow for the procurement of norethisterone in settings where this is the only product available.

References: 1. Doren M, Nilsson JA, Johnell O. Effects of specific post-menopausal hormone therapies on bone mineral density in post-menopausal women: a meta-analysis. Human Reproduction, 2003, 18(8):1737–1746. 2. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. The Lancet, 2003, 362:429–437. 3. Gabriel SR et al. Hormone replacement therapy for preventing cardiovascular disease in postmenopausal women. Cochrane Database of Systematic Reviews, 2005, (2): CD002229. 4. Waters DD et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women. A randomized controlled trial. Journal of the American Medical Association, 2002, 288:2432–2440.