Comments on evidence summary:

The introduction section clearly states the purpose of preparing the review and offers a comprehensive overview of the role and properties of the synthetic gestogen, norethisterone, along with its pharmaceutical history. Current clinical indications for using norethisterone, along with contraindications and precautions, and commonly reported adverse events associated with norethisterone usage are included.

From a methodological perspective, the search strategy applied appears appropriate, thorough, and up-to-date. It would have been helpful to provide greater detail on the statistical significance of the results reported in the systematic review on 5mg norethisterone for the treatment of menopausal symptoms (Table 1). Recording the length of follow-up for all of the trials of hormone replacement therapy would have been useful, as well. Finally, it is not clear why the systematic review authored by Furness et al was not included among the data presented in the review, as information from this review was extensively referenced within the narrative of the review. Was this review one of the excluded reviews highlighted in the flow diagram used to identify systematic reviews for inclusion? Additional detail on why this review was either excluded and yet referenced, would be helpful.

Regarding the evidence summarized in the systematic reviews of dysfunctional uterine bleeding (DUB), consistent reporting in Table 3 of the characteristics of women (i.e., age) studied would facilitate interpretation of the data. It is difficult to distinguish what and how each systematic review presented in Table 3 contributes to the overall conclusions of the review. Evidence provided in Table 4 enables the reader to examine the role of 5mg norethisterone compared with other treatments, and provides greater details of the trial results.

The assessment of bias was thoroughly conducted and clearly presented; however additional discussion of the methodological quality of the studies included in the review would have been helpful (such as Table 2). The assessment of bias highlights the methodological limitations of many of the trials that satisfied the inclusion criteria for the review, and is usefully in underscoring the limitations of the available evidence.

The conclusions drawn from the summary of published data on the topic are sound and appropriate.
Response to the proposal:

Norethisterone (5 mg tablet) is currently listed on the WHO Model List of Essential Medicines as a medicine used for contraception, dysfunctional uterine bleeding, and hormone replacement therapy. The public health relevance, comparative efficacy, and safety of this item for continued inclusion on the WHO Model List of Essential Medicines has been questioned.

As part of the World Health Organization's effort to improve access to quality of care in family planning, two evidence-based guidelines - the Medical eligibility criteria for contraceptive use (MEC) and the Selected practice recommendations for contraceptive use (SPR) - were developed to provide guidance regarding 'who' can use contraceptive methods safely and 'how' to use contraceptive methods safely and effectively (WHO 2010, WHO 2005). Within these two guidelines, WHO publishes recommendations on the use of contraceptive methods, including a progestogen-only injectable contraceptive method containing 200 mg norethisterone enantate (NET-EN) for healthy women, as well as women with selected medical conditions and personal characteristics. In particular, the Selected practice recommendations for contraceptive use (SPR) offers recommendations on how to manage bleeding abnormalities among women using progestogen-only injectable contraception, including NET-EN. For NET-EN users experiencing light or heavy bleeding, the Selected practice recommendations for contraceptive use recommends the use of nonsteroidal anti-inflammatory drugs (NSAIDS) such as mefenamic acid or valdecoxib, or estrogens for short-term treatment.

WHO's Department of Reproductive Health and Research does not promulgate recommendations on the use of norethisterone 5mg for the treatment of dysfunctional uterine bleeding or hormone replacement therapy. In 1994, the Department convened an expert Working Group to advise WHO on areas for research on the menopause. The report from this meeting offers recommendations on areas for research related to menopausal symptoms, epidemiology and treatment. However, recommendations on specific therapies and/or formulations to treat menopausal symptoms were not determined at this meeting. The most extensive sections of the report attempt to resolve some of the controversy surrounding the use of hormone therapy to reduce the risks of osteoporotic fractures and cardiovascular diseases while also answering the question of whether hormone therapy increases the risk of breast cancer, endometrial cancer, and other gynaecological cancers. Information ranges from advice on calcium and vitamin D supplementation for the prevention of osteoporosis, to estimates of the increase in relative risk of breast cancer among women using estrogens alone for different lengths of time.

During 21-25 March 2011, the 18th Expert Committee on the Selection and Use of Essential Medicines, which will convene in Accra, Ghana to determine whether peroral dose of 5 mg norethisterone should remain listed on the WHO Model List of Essential Medicines for the treatment of dysfunctional uterine bleeding and
hormone replacement therapy. A systematic review of the published literature was prepared to evaluate the efficacy of peroral 5mg norethisterone for such uses.

According to a comprehensive search of multiple bibliographic databases, data from three randomized controlled trials (RCTs) and one systematic review provided evidence to evaluate the efficacy of 5 mg norethisterone for treatment of menopausal symptoms. However, only limited data was available on the norethisterone dose of interest (5 mg), as results on 5 mg norethisterone were rarely mentioned in these studies. According to the summarized evidence, 5 mg norethisterone was consistently not effective at reducing menopausal symptoms, and was not effective compared with other therapies as a hormone replacement therapy, including lower doses (i.e., 1 mg) of norethisterone. RCTs repeatedly demonstrated the superior efficacy of alternative therapies for this purpose. Moreover, the use of norethisterone 5 mg produced several side effects such as bloating and break-through bleeding, when administered as a hormone replacement therapy. The assessment of bias within these studies highlighted a variety of methodological limitations, particularly regarding unclear allocation sequence generation, allocation concealment of treatment groups, and blinding of researcher-assessed outcomes.

Eight systematic reviews and 10 randomized controlled trials evaluating the effectiveness of progestogens, including peroral 5 mg norethisterone, in the management of dysfunctional uterine bleeding (DUB) were identified through a comprehensive search of the published literature. The trials randomized women with dysfunctional uterine bleeding, also known as menorrhagia (mean blood loss [MBL] ≥80 ml/cycle) when not associated with pelvic or systemic disease, to various treatments. Evidence comparing the effectiveness of norethisterone with danazol, tranexamic acid, the levonorgestrel-releasing intrauterine system, and NSAIDS (naproxen, mefenamic acid) showed that norethisterone significantly reduced mean blood loss, but was less effective at reducing blood loss compared with the comparison treatments in the majority of trials. Although danazol treatment was significantly more effective at reducing menstrual blood loss than norethisterone, a higher rate of adverse events were reported among women assigned to take danazol. Further one trial reported higher satisfaction scores among women using the LNG-IUS compared with women assigned to take norethisterone. The assessment of bias within these studies highlighted a variety of methodological limitations, particularly regarding unclear allocation sequence generation, allocation concealment of treatment groups, and blinding of researcher-assessed outcomes.

Norethisterone in peroral dose of 5 mg does not feature in any guidelines produced by the Department of Reproductive Health and Research.

Owing to the limited evidence identified, it can be recommended that peroral norethisterone 5 mg for hormone replacement therapy as it is not observed to alleviate menopausal symptoms. This dose is five-fold higher than is currently used in standard practice for the treatment of menopausal symptoms (1 mg norethisterone),
For the treatment of dysfunctional uterine bleeding, however, it may be retained in the Essential Medicines List for this indication for the following reasons:

- Evidence shows peroral norethisterone (5 mg) significantly reduces anovulatory and ovulatory dysfunctional uterine bleeding.

- Even if other therapies are more effective in reducing bleeding and better tolerated, there are some issues to be considered:

  1. LNG-IUS is still not available in many countries, and where it is available, it is very expensive, and many patients will not be able to afford this. While it may be very effective, its price will not make it a first option for treatment.

  2. Danazol may be better in reducing menstrual blood compared to norethisterone, but there are many unpleasant side effects as mentioned in the summary of the review (page 21). Some of these effects include growing of facial hair, acne, skin dryness. Many women do not tolerate these side effects.

  3. Tranexamic acid is also effective in reducing menstrual blood but as the summary mentions, there is a risk for thromboembolic events. It is also regarded as symptomatic treatment, with good and rapid results, but its mechanism does not target the hormone related pathologic changes in the endometrium of women with DUB, which norethisterone may take care of in the long run.

  4. The summary of the review mentions that norethisterone and NSAIDS have similar effects on the amount of blood loss, and mentions these are most commonly used drugs for menorrhagia.

References

