South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Gynaecology

MEDICINE REVIEW

1. Executive Summary

Date: September 2017
Medicine (INN): Venlafaxine
Medicine (ATC): N06AX16
Indication (ICD10 code): Menopausal and female climacteric states (N95.1/N95.9)
Patient population: Women with severe menopausal symptoms who have a contra-indication to taking hormone replacement therapy (e.g. hormone-dependent cancer survivors, thrombo-embolism. Liver disease or unacceptable side-effects to hormone replacement therapy (e.g. exacerbation of depression, enlargement of uterine fibroids, exacerbation of endometrioses)
Prevalence of condition: About 25% of all post-menopausal women < 60 years of age (36).
Level of Care: Regional level
Prescriber Level: Obstetrician, gynaecologist
Current standard of Care: Hormone replacement therapy
Efficacy estimates: (preferably NNT) Not available
Motivator/reviewer name(s): Prof GS Gebhardt, Dr S Takuva
PTC affiliation: Prof Gebhardt: Tygerburg Hospital PTC

2. Name of author(s)/motivator(s): Prof GS Gebhardt, Dr S Takuva

3. Author affiliation and conflict of interest details:

Prof GS Gebhardt: Stellenbosch University, Committee member of the National Committee for Confidential Enquiry into Maternal Deaths (NCCEMD); Adult Hospital Level Committee (2017-2020); no conflict of interests declared.

Dr S Takuva: Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand and HIV Vaccine Trials Network; Adult Hospital Level Committee (2017-2020); no conflict of interests declared.

4. Introduction/ Background

Menopausal hormone replacement therapy (HRT) including tibolone and conjugated equine estrogens are the most effective treatment for vasomotor symptoms (VMS) associated with menopause at any age(1). Long-term follow up studies from the Women's Health Initiative Randomized Trials have shown that hormone replacement therapy in post-menopausal women was not associated with an increased risk of all-cause, cardiovascular or cancer mortality(2).Treatment of gynaecologic cancers generally involves surgery and/or radiation therapy. These therapies often result in loss of ovarian function and induced menopause(3) and HRT are contra-indicated due to its effect on tumour growth (most breast cancers express estrogen and/or progesterone receptors(4). When there are contra-indications to HRT, selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors such as paroxetine, escitalopram, venlafaxine and desvenlafaxine have been shown to be effective in randomized controlled trials.

5. **Purpose/Objective:** In women with post-menopausal symptoms who have contra-indications to take hormonal replacement therapy (HRT), does venlafaxine relieve symptoms when compared to placebo or standard non-hormonal treatment?

6. **Methods:**
   a. **Data sources:** Pubmed, Cochrane database of systematic reviews, ScienceDirect, NICE, Google scholar, EMBASE, SCOPUS, ISRCTN registry, EBSCOhost and SUNSearch.
   b. **Search strategy**
   (("Clinical Trial"[Publication Type]) OR ("Phase I Clinical Trial" OR "Phase II Clinical Trial" OR "Phase III Clinical Trial" OR "Phase IV Clinical Trial" OR "Controlled Clinical Trial" OR "Multicenter Study" OR "Randomized Controlled Trial" OR "Pragmatic Clinical Trial"))
   AND (("Breast Neoplasms"[Mesh] NOT "Breast Neoplasms, Male"[Mesh]) OR ("Breast cancer" OR "Breast Neoplasms"))
   AND (("Hot Flashes"[Mesh]) OR (“hot flashes” OR “hot flush” OR “vasomotor symptoms” OR “night sweats” OR “menopausal symptoms”))

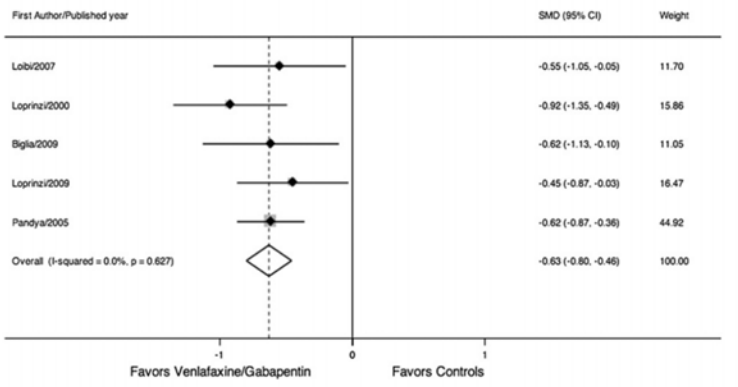
   From the literature search, there were 12randomized trails identified that compared venlafaxine to either placebo or another drug/intervention ((5–16), 4 systematic reviews with meta-analysis (17–20) and 6 systematic reviews without a metaanalysis (21–23) and 13 international guidelines or review articles on the management of the menopause with specific reference to non-hormonal treatment of menopausal symptoms (1, 3, 4, 24–32).

   c. **Evidence synthesis**
   Of the five systematic reviews which attempted meta-analysis, the included studies were as follows:
      1. **Cochrane review (Rada et al 2010**(18)**):**
         - *Loprinzi, 2000* (14) n= 191 participants who received three different doses (37.5, 75 and 150 mg) of venlafaxine. The placebo group had a median decrease from baseline of 19% in the frequency of hot flushes at week four (95% CI 14 to 28). The three active arms had greater reductions: 30% for the low dose (95%CI 22 to 53; $p < 0.001$), 46% for the intermediate dose (95% CI36 to 63; $p < 0.001$), and 58% for the highest dose of venlafaxine (95% CI 42 to 67; $p < 0.001$).
         - *Carpenter, 2007* (10) evaluated two doses (37.5 and 75 mg) for 12 weeks. The low-dose (37.5 mg) study included 31 assessable patients. The mean severity of symptoms decreased 7% from baseline in the treatment group and increased 6% with placebo ($p < 0.001$). The 75 mg venlafaxine study included 15 assessable patients. Compared with baseline, the mean severity decreased by 27% from baseline in the treatment group and 5% in the placebo group ($p < 0.001$).

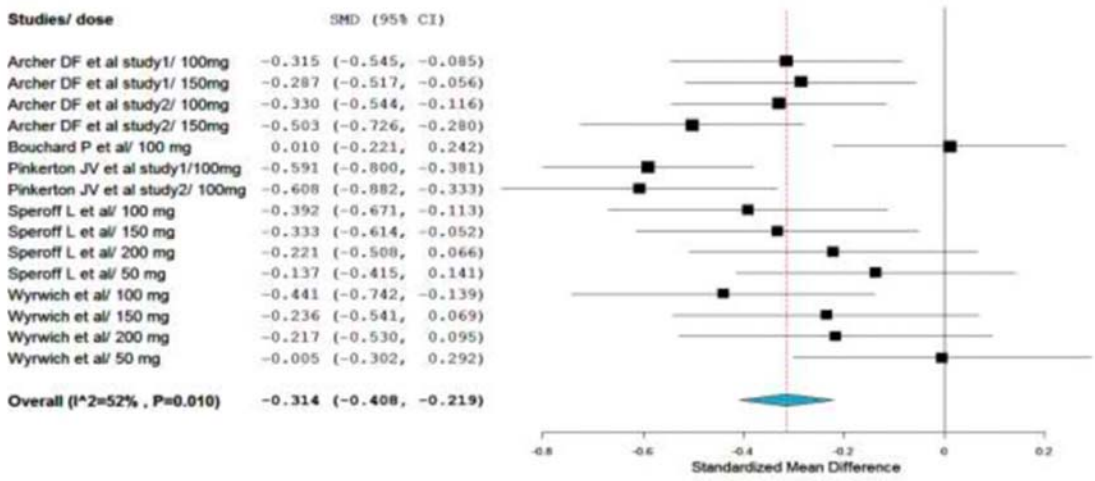
   →no pooled analysis was done and the authors concluded that “…the benefits shown with SSRIs and SNRIs are promising, particularly due to their good safety profile.”

      2. **Yamaguchi et al 2013 (**(20)**:**
         - *Loprinzi, 2000* (14)as above
         - *Loibl, 2006* (13) a double-blind, randomized phase III study in breast cancer survivors with n=31 venlafaxine and n=33 clonidine. Venlafaxine was significantly more effective in reducing the frequency of hot flashes in breast cancer patients than clonidine. (This study was not considered in the Cochrane review.)

- Three further studies which compared gabapentin to placebo or vitamin E. The metaanalysis was conducted on these 5 studies with venlafaxine/gabapentin compared to controls.
- Overall effect was expressed as the standardized mean difference (SMD) and favoured either venlafaxine or gabapentin:

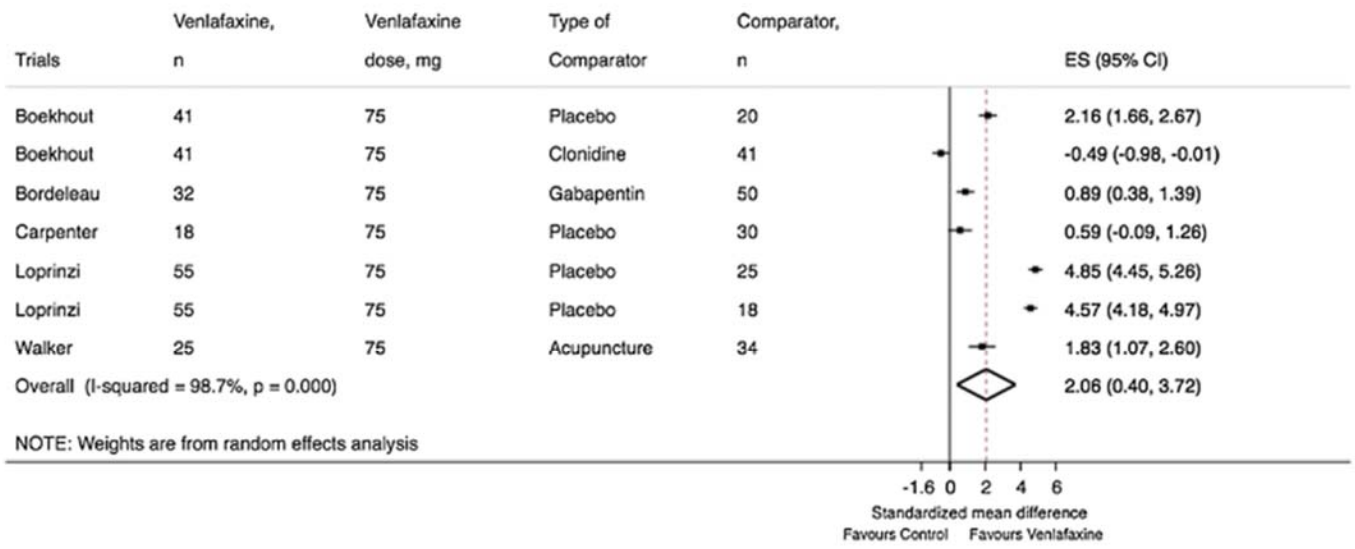


3. *Berhan and Berhan, 2014* (17) conducted a meta-analysis on 7 trials that compared DESVENLAFAXINE(the major active metabolite of venlafaxine that is approved for the treatment of major depressive disorders) and therefore the results (which showed a significant reduction in symptoms compared to controls) may be informative for this review, although the studies included are not for venlafaxine.



4. **Ramaswami et al, 2015** (19): 5 studies
   - *Loprinzi, 2000* (14)(in both Cochrane and Yamaguchi analysis)
   - *Carpenter, 2007* (10) (also in Cochrane review)
   - *Boekhout et al* (5) (double blind, placebo controlled randomized trial with 102 participants comparing venlafaxine to either clonidine or placebo)
   - *Bordeleau et al* (6) (double blind cross-over trial comparing venlafaxine to gabapentin, n=66)
   - *Walker et al* (16) (randomized non-blinded trial comparing n=25 women on venlafaxine with n=25 women receiving acupuncture).

The overall effect again favoured venlafaxine:



The 12 randomised trials identified by the literature search:

1. Boekhout et al (5) (as above)
2. Bordeleau et al (6) (as above)
3. Buijs et al (7) was excluded from the Ramaswami analysis as there was inadequate published information. This was a randomized double-blind cross-over study where 60 breast cancer survivors were given either venlafaxine for 8 weeks followed by a 2-week wash-put period and then 8 weeks' clonidine and vice versa. There was no significant difference in reduction of symptoms between the two drugs.
4. Caan et al, 2015 (8) was a three-arm double-blind, placebo-controlled randomized trial of low-dose oral 17-beta-estradiol 0.5-mg/day or venlafaxine XR 75-mg/day, versus identical placebo. Both drugs reduced menopausal symptoms with no significant difference. Quality of life was measured with the MENQOL, a 29-item self-reported questionnaire. For the venlafaxine group, the mean difference from baseline to 8 week MENQOL between venlafaxine and placebo was −0.2; 95% CI −0.5 to −0.0; p = 0.042.
5. Capriglione et al (9) did a randomized trial with another SSRI (paroxetine) and should therefore be excluded from meta-analysis for venlafaxine, although it is interesting to note that paroxetine significantly reduced hot flashes in weekly frequency and severity and the number of night time awakenings attributed to vasomotor symptoms and increasing sleep duration.
6. Carpenter et al (10)(as above)
7. Davari-Tanha et al, 2016 (11) was a randomized, double-blind, placebo-controlled clinical trial conducted in three groups of 20 postmenopausal women. The patients took venlafaxine75 mg/daily (group I) or citalopram 20 mg/d (group II) or placebo (group III).Severity of hot flashes in both venlafaxine and citalopram was significantly lower in comparison with placebo group(p = 0.02), and there was no significant difference between the two drugs (p = 0.84).

8. Evans et al (12) studied 80 postmenopausal women with more than14 hot flushes per week who were randomized to receive treatment with extended-release venlafaxine or placebo. Subjective assessments at monthly visits of the effects of hot flush symptoms on daily living were significantly improved in the treatment group ($p < 0.001$).
9. Loibl et al (13) see above.
10. Loprinzi et al (14) see above.
11. Simon et al (15) also studied paroxetine.
12. Walker et al (16) see above.

There is therefore scope to update the Ramaswami meta-analysis with the Buijs, Caan,Davari-Tanha and Evans trials as all of these trials showed a superior effect of venlafaxine on menopausal symptoms when compared to controls.

Update of the Ramaswani metaanalysis

The updated analysis was aimed to incorporate the four trials by Buijs, Caan, Davari-Tanha and Evans that were omitted from the Ramaswani metaanalysis (see above).

Summary of Methods: In order to standardize outcome measures between studies (different outcome scales were used), the approach used in the original metaanalysis was applied i.e. Standardized mean differences (SMD) were manually derived for the comparator and venlafaxine arm of each study. However, it was not possible to include the study by Buijs as there was missing hot flash severity data and hence unable to extract and standardize the outcome data. The study by Evans et al also lacked key primary measurements to allow standardization of the outcomes – no confidence intervals are reported for the placebo and venlafaxine groups but rather p-values hence not allowing to compute standard deviations and standardized mean differences. However, as the study reported the summary outcomes on a similar scale (mean differences), the final meta-analysis includes this study. In sensitivity analysis, exclusion of this study did not affect the final effect estimates much. A Random-Effects model was computed as the heterogeneity of the studies in this meta-analysis was high (see results).

Results: Figure 4 below illustrates the effect of venlafaxine and comparator on standardized mean differences in hot flash scores from baseline to completion of treatment. The pooled effect size estimate is 1.68, 95% CI: 0.24 to 3.12. The overall results favour treatment with venlafaxine compared to comparator. The heterogeneity of the studies included in this metaanalysis was significant (I^2=98.8% and p=<0.001).

When the Evans study was excluded, the effect estimates did not change much (1.64, 95% CI: 0.16 to 3.11).

Figure 4a: Effect of venlafaxine and comparator on standardized mean differences in hot flash scores from baseline to completion of treatment.

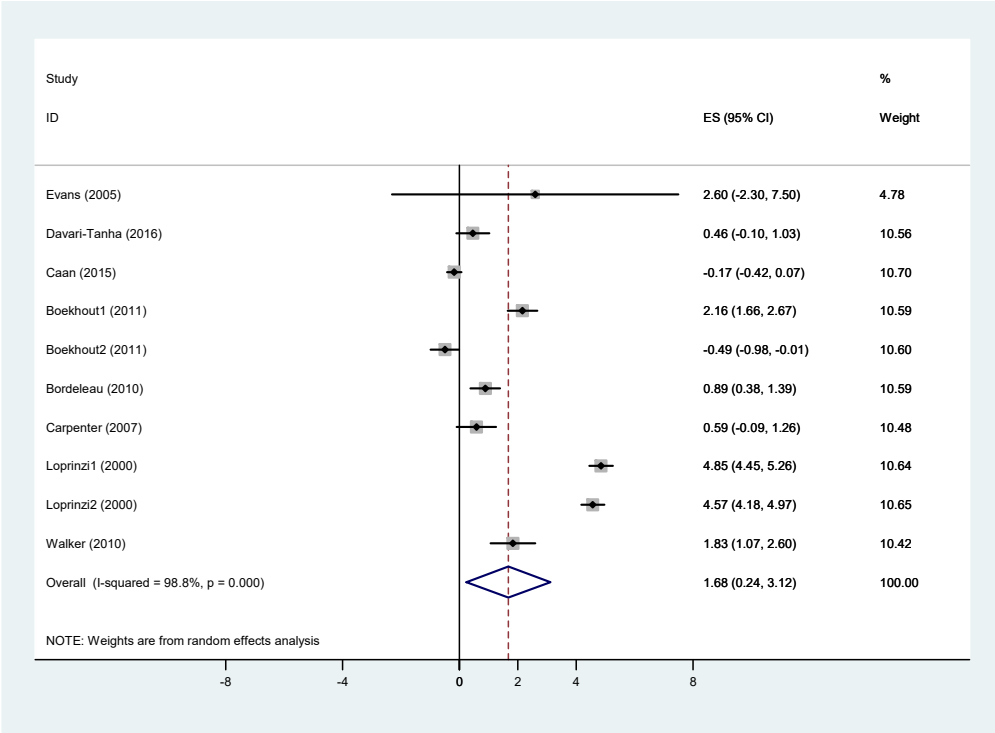
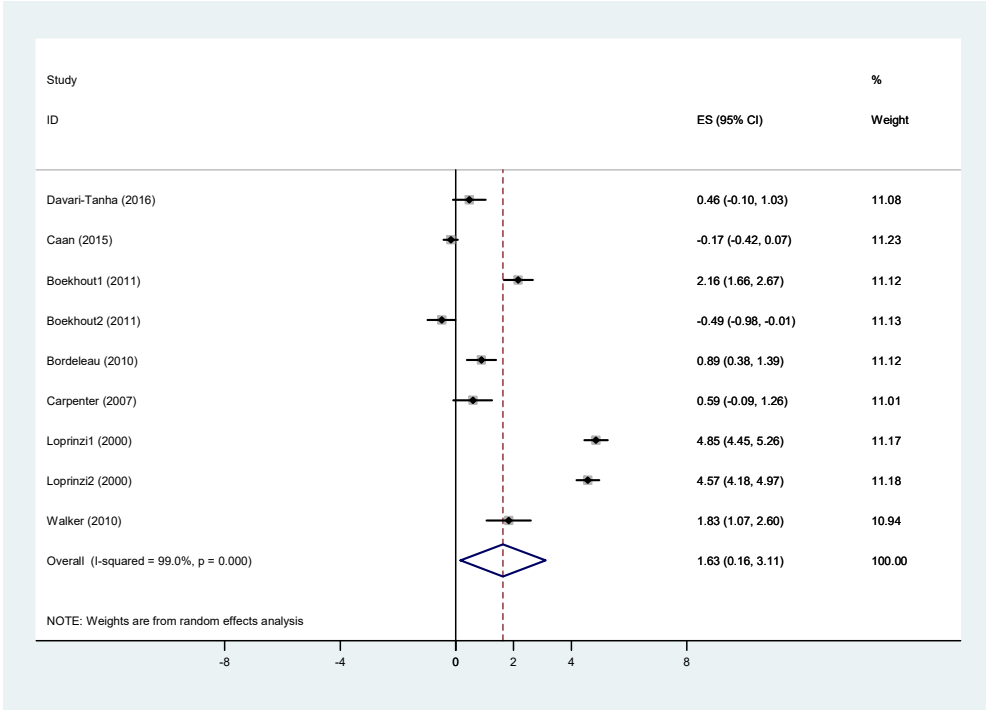


Figure 4b: Effect of venlafaxine and comparator on standardized mean differences in hot flash scores from baseline to completion of treatment (Evans study excluded).

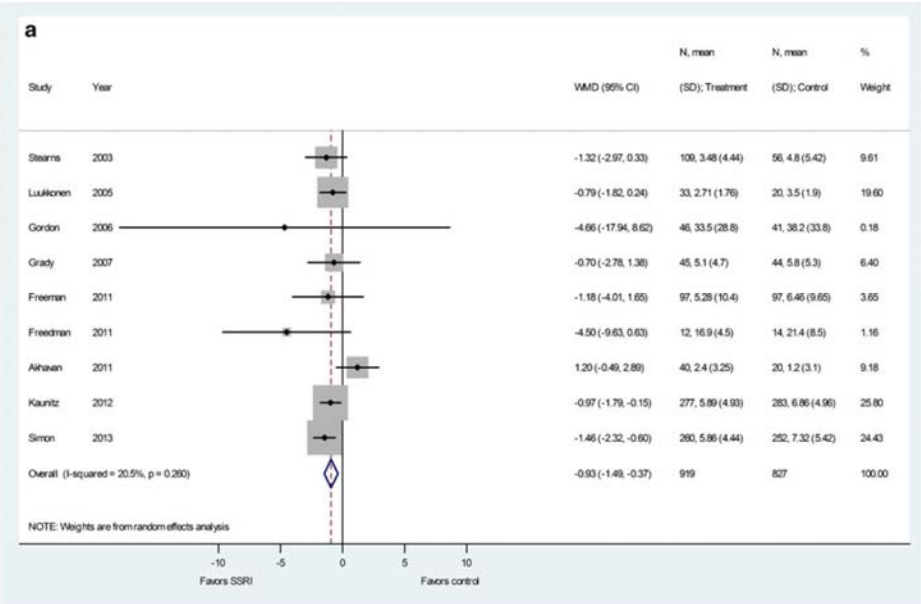


d. Evidence quality: Studies were very heterogeneous (Ramswani meta-analysis: I^2=98.7% and updated meta-analysis: I^2=98.8 to 99.0%) and small; with possible publication bias.

e. Alternative agents:

- Hormone replacement therapy
- SSRI's

SSRIs: A systematic review and meta-analysis of SSRIs for the reduction of hot flashes in post-menopausal women compared to placebo showed an overall modest but statistically significant reduction in hot flash frequency (difference in means -0.93, 95% CI -1.46 to 0.37). This is shown in the forest plot below(33):



The systematic review specifically excluded patients with breast cancer. Fluoxetine and paroxetine should not be used in women with breast cancer, as these agents inhibit the effect of tamoxifen(34). This is due to the inhibition of the activity of the enzyme CYP2D6 that converts tamoxifen to endoxifen (its active metabolite). Venlafaxine is a very weak inhibitor of CYPD26 and can be used in women with breast cancer(35).

There is no head-to-head comparison of SSRIs to SNRIs in the literature for the reduction of menopausal symptoms.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident ☐ Not confident ☐ Uncertain ☐	

<table>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [ ] No [X]</td><td></td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [X] Uncertain [ ]</td><td>Cost of medicines/ month:<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Venlafaxine 37.5 mg daily 28 tabs</td><td>R 36.93*</td></tr><tr><td>Cyproterone/ethinyl estradiol 1mg/2mg 28 tabs</td><td>R 36.22 **</td></tr><tr><td>Estradiol/norethisterone acetate 2mg/1mg 28 tabs</td><td>R 99.09**</td></tr><tr><td>Conjugated estrogens 0.625 mg (28 tabs) + medroxyprogesterone (28 tabs)</td><td>R 123.65** + R 37.82** =R161.47</td></tr></table>* Contract circular HP09-2016SD
** Contract circular RT283-2017
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
☐	☐	☐	☒	☐

Recommendation: Based on this evidence review, the Adult Hospital Committee recommends that venlafaxine be recommended for control of menopausal symptoms with contra-indications to hormone therapy (hormone-dependent cancers, thrombo-embolism, liver disease or unacceptable side-effects to hormone replacement therapy e.g. exacerbation of depression, enlargement of uterine fibroids, exacerbation of endometrioses). The medicine to be prescribed by specialists at regional level of care. SSRIs are not to be recommended for this patient population due to drug-drug interactions of SSRIs (paroxetine and fluoxetine may reduce the efficacy of tamoxifen).
Rationale: Evidence of efficacy and safety of venlafaxine for control of menopausal symptoms. Venlafaxine's price is comparable to current standard of care. There were concerns about SSRI inhibition of enzymes in patients with breast cancer, who would make up a large proportion of this patient population.
Level of Evidence: II Systematic review and metaanalysis of low to moderate quality RCTs

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 14 DECEMBER 2017:
NEMLC acknowledged that, globally, venlafaxine is the standard of care for women with hormone-dependant cancers (i.e. breast cancer, etc)[37]. However, this would be a new medicine for a single indication on the secondary level EML. NEMLC recommended that venlafaxine not be added to the secondary level EML.
Furthermore, as anastrozole is currently on the EML and the tender price is reasonable, NEMLC proposed that the evidence for SSRIs that are currently on the secondary level EML, be reviewed *(refer to the medicine review: SSRIs for menopausal symptoms, July 2018).*

Monitoring and evaluation considerations

Research priorities

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