health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 5: GYNAECOLOGY
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the gynaecology chapter.

A: NEW SECTIONS(S)/ SUBSECTION(S)

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
5.13	**Medical management of ectopic pregnancy**	Yes	Methotrexate, IM
5.14	**Family planning referrals from primary care**		
5.14.1	**Intra-uterine contraceptive device**	Yes	NSAIDs, e.g. ibuprofen, oral
5.14.2	**Implants**	No	n/a
5.14.3	**Injectable contraception**	Yes	Ethinyl estradiol, oral 50 mcg/COC containing 50 mg ethinyl estradiol.
			NSAIDs, oral
			Tranexamic acid, oral

5.13 MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY

The following new STG was included in the chapter:

General measures
Ruptured or suspected rupture of an ectopic pregnancy should be managed with urgent resuscitation and surgery. There must be certainty that there is no viable intra-uterine pregnancy.
If the initial hCG level is below the discriminatory zone (< 1500IU/L) -to diagnose a pregnancy on ultrasound, and transvaginal ultrasound cannot definitively identify an intrauterine or extra-uterine gestation, then serial b-hCG measurements are necessary to document either a growing, potentially viable, or a nonviable pregnancy.
Repeat the b-hCG in 48 hours. If the level has dropped, conservative management may be appropriate. The minimum rise in b-HCG for a potentially viable pregnancy in women who present with symptoms of pain and/or vaginal bleeding is 53% every 2 days. If the level has increased by more than 50% or is now above the discriminatory zone, a repeat scan should be done to exclude an intra-uterine pregnancy before methotrexate is administered.

Medicine treatment
Methotrexate should be the first-line management for women who are able to return for follow-up and who have the following characteristics:
» haemodynamic stability and no significant pain
» an unruptured ectopic pregnancy with a mass smaller than 35 mm with no visible heartbeat
» low serum b-hCG, ideally less than 1500 iu/l but can be up to 5000 iu/l
» certainty that there is no intrauterine pregnancy
» willingness to attend for follow-up
There are single dose or multiple dose methotrexate protocols available. The single dose protocol is less expensive, requires less intensive monitoring and does not require folinic acid rescue. The single dose protocol is recommended for the medical management of ectopic pregnancy.

Protocol:
Day 1: Do urea, creatinine, AST, full blood count to exclude abnormalities.
- Methotrexate, IM, 50 mg/m^2 of body surface area (BSA).
  - BSA may be calculated based upon height and weight on the day of treatment using the formula BSA = square root ([cm X kg]/3600)

Day 4: Repeat b-hCG.
Day 7: Repeat b-hCG.
<u>If the decrease from day 4 to day 7 is ≥15%:</u>
» Continue with weekly b-hCG until undetectable.

<u>If decrease <15% and patient still fulfil the criteria for medical management:</u>
- Methotrexate, IM, 50 mg/m^2 BSA.

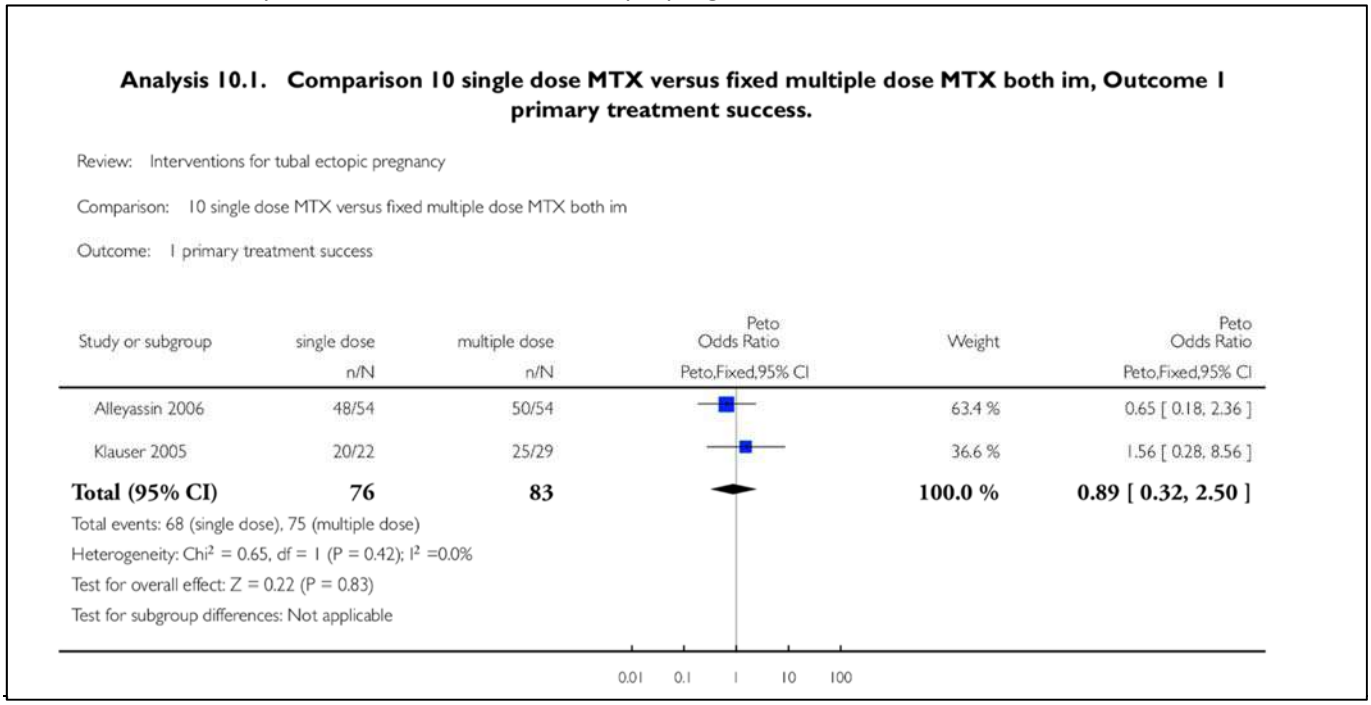
Day 14: Repeat b-hCG.

Referral
After two doses of methotrexate, if the decline in b-hCG is still <15% on day 14, refer for specialist care.

Guidelines: Recommendations are aligned with Royal College of Obstetricians & Gynaecologists (RCOG) guidelines that are developed using AGREE II criteria (Clinical Governance Advice No. 1 – Development of RCOG Green-top Guidelines 4 May 2015). Furthermore, the EML Clinical Guide cellphone application has a BSA tool to assist with dosing of methotrexate. The Adult Hospital Level Committee was of the opinion that as this is a "no brainer", a technical medicine review need not be developed for methotrexate, IM for ectopic pregnancy. Despite uro-gynaecology generally managed at tertiary level of care, it was noted that management may take place at regional level of care and comprehensive guidance was added to the STG, noting that there are no treatment protocols to guide management for tertiary and quaternary essential medicines.
Rationale: Aligned with standard of care and Guidelines.
Level of Evidence: III Guidelines [1] [2]

Methotrexate, IM: *caution box not added*
NEMLC had raised concerns pertaining to precautions related to methotrexate in this specific clinical setting. As a general rule, all contra-indications are not listed for medicines in the STGs and EML (information is sourced from package inserts); and the risk in this setting – a single dose of methotrexate in a healthy young woman was not considered to be very high.
Recommendation: Contraindications for methotrexate not be listed in the STG.
Rationale: The risk of using methotrexate in this setting was not considered to be very high – single dose in a healthy young woman; and generally all contra-indications for EML medicines are not listed in the STGs.
Level of Evidence: III Expert opinion

Protocol: *single dose protocol recommended*
There are two regimens- a 'single dose' and a 'multiple dose' regimen for management of ectopic pregnancies. However, the multiple dose regimen is more complex and not recommended for use at district/regional level. Cochrane review[3] suggests that there is no difference between single- and multiple- dose protocols in terms of the effectiveness and safety of medical treatment of ectopic pregnancies.



Level of Evidence: I Systematic review, Guidelines

[1] Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. National Guideline Clearinghouse [Internet]. [cited 2017 Jun 8]. Available from: https://guideline.gov/summaries/summary/39274/ectopic-pregnancy-and-miscarriage-diagnosis-and-initial-management-in-early-pregnancy-of-ectopic-pregnancy-and-miscarriage?q=ectopic+pregnancy.
Diagnosis and Management of Ectopic Pregnancy [Internet]. Royal College of Obstetricians & Gynaecologists. [cited 2017 Jun 8]. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg21/
[2] Practice Committee of American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy: a committee opinion. Fertil Steril. 2013 Sep;100(3):638-44. https://www.ncbi.nlm.nih.gov/pubmed/23849842
[3] Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD000324. https://www.ncbi.nlm.nih.gov/pubmed/17253448

5.14. FAMILY PLANNING REFERRALS FROM PRIMARY CARE

The following STGs were developed to provide continuum of care for patients who developed excessive bleeding on family planning treatment, despite adequate treatment at primary care.

5.14.1 INTRA-UTERINE CONTRACEPTIVE DEVICE

The following new STG was included in the chapter:

General measures

Where there is excessive bleeding after insertion:

» Exclude perforation of the uterus

Abnormal bleeding for > 3 months:

» Exclude cervical or pelvic infection, partial expulsion, intrauterine or ectopic pregnancy (rare) or other pathology.

If no pathology is detected:

» Counsel.

Medicine treatment

If no pathology is detected:

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly for 5 days.
  - Follow up and if bleeding is unacceptable, offer alternative contraception and remove IUCD.

NSAIDs: Cochrane review[4] (15 RCTs, n=2702) showed that NSAIDs (naproxen, suprofen, mefenamic acid, ibuprofen, indomethacin, flufenamic acid, alclofenac, and diclofenac) were effective in reducing menstrual blood loss associated with IUD use. No important differences emerged in the one trial comparing the effect of different NSAIDs on bleeding.
Recommendation: NSAIDs be recommended for excessive bleeding (without pathological cause) associated with IUCDs.
Rationale: Evidence of efficacy that NSAIDs reduce bleeding associated with IUD use. Authors of Cochrane review suggest that NSAIDs should be considered as first-line therapy; if NSAIDs are ineffective, tranexamic acid may be considered as second-line therapy.
Level of Evidence: I Systematic review

5.14.2 IMPLANTS

The following new STG was included in the chapter:

Failure to locate an implant (in the arm) by palpation:

» Ultrasound guided removal of deep implants must be done by specially trained providers at regional hospitals.

5.14.3 INJECTABLE CONTRACEPTION

The following new STG was included in the chapter:

General measures

Heavy or prolonged bleeding despite adequate treatment with combined oral contraceptives:

» Do thorough gynaecological examination to exclude other pathology.

» Check haemoglobin and prescribe iron if needed. See section 2.2 Anaemia, iron deficiency.

Medicine treatment

[4] Grimes DA, Hubacher D, Lopez LM, Schulz KF. Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006034. https://www.ncbi.nlm.nih.gov/pubmed/17054271

- Ethinylestradiol, oral, 50 mcg daily for 3 months.

OR

COC containing 50 mcg ethinylestradiol, oral, for 3 months.

If no response to high dose ethinylestradiol, replace with:

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal for 5 days.

If no response to NSAID, replace with:

- Tranexamic acid, oral, 500 mg 8 hourly for 4 days.

If there is no response to above-mentioned treatment:

» Change to another method of contraception. See Primary Health Care Standard Treatment Guidelines - Chapter 7: Family planning.

High dose ethinyl estradiol and NSAIDs: Aligned with NDoH National Contraceptive Policy, 2012.
Level of Evidence: III Guidelines

Tranexamic acid, oral: Cochrane review[5] suggests that antifibrinolytic therapy causes a greater reduction in objective measurements of heavy menstrual bleeding when compared to placebo or other medical therapies (NSAIDS, oral luteal phase progestagens and ethamsylate). There was no increase in side effects compared to placebo and other agents. However, no costing studies or data determining risk of thromboembolic events is available.

- *Results of the review:*
  - antifibrinolytic vs placebo; 2 RCTs:
    - reduction in mean blood loss: weighted mean difference (WMD) - 94.0, 95% CI -151.4 to -36.5; I2=0%
    - mean reduction of blood loss: WMD -110.2, -146.5 to -73.8, I2=0%
    - patient perceived improvement in monthly menstrual blood loss RR 2.5, 0.9 to 7.3 (one RCT)
  - antifibrinolytic vs mefenamic acid, norethisterone and ethamsylate:
    - reduction in mean blood loss: WMD -73.0, 95% CI -123.4 to -22.6; WMD -111.0, -178.5 to -43.5; WMD -100, -143.9 to -56.1 respectively
    - tranexamic acid in the participants' perception of an improvement in menstrual blood loss: nonsignificant trend in favour of tranexamic acid.
    - no significant differences in the frequency of reported side effects with tranexamic acid vs other agents.

Note: Findings based mostly on one RCT.
Recommendation: Tranexamic acid recommended for excessive bleeding with injectable progestins, if there has been no response to high dose estrogen and NSAIDs.
Rationale: Limited evidence suggests that tranexamic acid has a greater reduction in heavy menstrual bleeding compared to mefanamic acid and norethisterone. However, the results should be interpreted with caution as findings are based mostly on single underpowered trials. Tranexamic acid, oral[6] is more expensive than NSAIDs[7] and high dose estrogen[8].
Level of Evidence: II Systematic review of low quality RCTs.

[5] Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database Syst Rev. 2000;(4):CD000249. https://www.ncbi.nlm.nih.gov/pubmed/11034679
[6] 60% of SEP price (SEP database, 27 May 2017): TXA, oral 500 mg 8 hrly x4d (12 tab @ average weighted price of R3.33) = R 39.96
[7] Contract circular price (HP09-2016SD): Ibuprofen, oral 400 mg 8 hrly x 5d (15 tabs) = R3.82
[8] Contract circular price (RT283-2017): Estradiol, oral, 50 mcg daily (28 tabs) = R36.47

B: AMENDMENTS TO MEDICINE TREATMENT

SECTION	MEDICINE	ADDED/DELETED/AMENDED
5.2 Uterine bleeding, abnormal	LNG-IUS	Not added (but added to T&Q EML)
	Tranexamic acid, oral	Retained
5.3 Pelvic inflammatory disease (PID) - Stage II-IV	Amoxicillin/clavulanic acid, IV	Not added
	Ceftriaxone, IV	Retained
	Metronidazle, IV	Retained
5.7 Infertility	Clomifene, oral	Retained
	Letrozole, oral	Added
	Anastrazole, oral	Not added
	Aromatase inhibitors, oral	Not added as a therapeutic class
- Investigations	Prolactin level	Deleted as routine investigation
5.8.2 Incomplete miscarriage in the first trimester: Medical evacuation	Misoprostol	Protocol amended
5.8.3 Midtrimester miscarriage (from 13–22 weeks gestation)		
- If no cervical dilation	Misoprostol	Protocol amended
- Previous Caeserean-section:	Misoprostol	Indication extended
5.9 Termination of pregnancy (TOP)	Misoprostol	Retained
5.9.1 Management for pregnancies of less than 14 weeks of gestation		
Manual vacuum aspiration		
- Routine analgesia for vacuum aspiration:	Pethidine, IM	Deleted
	Morphine, IM	Retained
- Paracervical block:	Lidocaine 1% injection	Added
Medical TOP	Mifepristone, oral	Retained
	Misoprostol	Directions for use amended
	Mifepristone/misoprostol	Protocol amended
5.9.2 From the thirteenth week (12 weeks and 1 day) up to the twentieth week (19 weeks and 6 days)		
	Mifepristone, oral	Retained and dose not amended
	Misoprostol	Protocol amended
	Time interval between mifepristone and misoprostol	Not amended
	Medical TOP	Management amended to guide on inpatient management
- Analgesia	Pethidine, IM	Deleted
	Morphine, IM	Retained
	Contraception	Guidance provided on counselling
5.10 Sexual assault	Levonorgestrel 1.5 mg, oral	Dose amended for obese women
	Metclopramide, oral	Added
5.12 Menopause and perimenopausal syndrome	Hormone replacement therapy, oral	Retained and caution updated
- HT is contra-indicated, poorly tolerated or ineffective	Venlafaxine, oral	Not added
	Fluoxetine, oral	Added as first line option
	Citalopram, oral	Added for women on concomitant tamoxifen.

5.2 UTERINE BLEEDING, ABNORMAL

LNG-IUS: *not added (but, added to the T&Q EML)*
Tranexamic acid, oral: *retained*

LNG-IUS

In the previous review cycle of the Adult Hospital Level STGs and EML (2015), despite evidence of efficacy suggesting that LNG-IUS provides a clinically relevant reduction in menstrual blood loss due to HMB, with greater patient retention at 2 years than with standard of care as recommended in the STG, LNG-IUS was unaffordable and indication creep was a concern. There was also mention of greater cost-effectiveness of LNG-IUS as compared to surgical interventions up to 10 years. Refer to medicine review: LNG-IUS for management of pain associated with endometriosis, May 2015, below, for detailed information:

lng-ius for hmb_adults_medicin

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Thus, a costing model was commissioned to determine the cost effectiveness of LNG-IUS compared to standard of care as recommended in the current STG. Refer to the report, below, for detailed information:

Levonorgestrel-IUS_ Economic Evaluatior

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: LNG-IUS not be included on the Adult Hospital Level EML for abnormal uterine bleeding (AUB), but rather on the Tertiary & Quaternary EML, where there has been treatment failure – prescribed and administered by gynaecologists (However, consumption, uptake and budgetary impact to be monitored to inform whether LNG-IUS for AUB should be accessed universally at secondary level of care, going forward).
Rationale: The feasibility of affordability in the short-term needs consideration. The capital outlay of 800 million warrants proof of concept, despite the cost-effectiveness in the long-term; and it is recommended that a survey, pilot study or qualitative study be considered to determine acceptability and actual uptake of LNG-IUS. There is no local data to determine the acceptability of intrauterine devices, which is reported to be low (utilisation of copper IUCD is reported to be low in public sector). It is also uncertain as to whether acceptability was low amongst patients or healthcare workers. Tertiary level of care may provide a more controlled environment to monitor the use of LNG-IUS – however, Guidelines for use of LNG-IUS at tertiary level of care needs to be developed. Furthermore, it would be the discretion of the Tertiary facility/Provincial Pharmaceutical and Therapeutics Committee to enable access of this intervention at lower levels of care.
Level of Evidence: I Systematic review, Expert opinion

Additional points:

- Gynaecologists were in favour of LNG-IUS for AUB; but scope creep would require careful monitoring.
- The agent is currently on tender as a non-EML item, at a price of R 905.88 per unit[9], and it is recommended that National Department of Health/National Treasury to enter into price negotiation of LNG-IUS with the supplier.
- NEMLC was of the opinion that AUB was probably not adequately managed in clinical practice and women either remain on NSAIDs and hormone therapy or are not treated at all. There is a research opportunity to determine real-world clinical pathways for the management of AUB in public sector, identifying opportunity costs such as hospitalisations and blood transfusions.

NEMLC meeting of the 27 September 2018:
The NEMLC recommended the following:

- LNG-IUS not be included on the Adult Hospital Level EML, but rather on the Tertiary & Quaternary EML for abnormal uterine bleeding, where there has been treatment failure – prescribed and administered by gynaecologists. (However, consumption, uptake and budgetary impact to be monitored to inform whether LNG-IUS for AUB should be accessed universally at secondary level of care, going forward).
- *Rationale:* LNG-IUS for abnormal uterine bleeding has been shown to be cost-effective, but is not affordable for inclusion to the secondary level EML. Tertiary level of care would provide a more controlled environment to monitor the use of LNG-IUS. Furthermore, it would be the discretion of the Tertiary facility/Provincial Pharmaceutics and Therapeutics Committee to enable access of this intervention at lower levels of care.

Level of Evidence: I Health Technology Assessment, Systematic review, Expert opinion

Tranexamic acid, oral
The high price of tranexamic acid (TXA), oral is concerning, and an investigation ensued – see the report below on the consumption and price of TXA, 20 August 2018:

[9] Contract circular RT283-2017, price up to date as of 3 September 2018.

TranexamicAcidTabl
ets-Consumption&F

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

There is a need for in depth market intelligence before and during a tender cycle.

5.3 PELVIC INFLAMMATORY DISEASE (PID)

Stage II–IV

Amoxicillin/clavulanic acid, IV 1.2 g: *not added*
Ceftriaxone, IV 1 g: *retained*
Metronidazle, IV 500 mg: *retained*

Amoxicillin/clavulanic acid, IV 1.2g 8 hourly" is currently more expensive than "Ceftriaxone,IV 1g + Metronidazole, IV 500 mg, 8 hourly[10]" (i.e. 3 day treatment course costs R 180.63 vs. R 69.81, respectively); and was not included in the STG.

5.7 INFERTILITY

Letrozole, oral: *added*
Anastrazole, oral: *not added*
Aromatase inhibitors, oral: *not added as a therapeutic class*
Clomifene, oral: *retained*

Background: Previously NEMLC recommended that the evidence review (June 2017) for letrozole in infertility be forwarded to the Tertiary & Quaternary (T&Q) Committee for consideration for inclusion on the T&Q EML, as the agent was cost-prohibitive for use at secondary level of care[11]. Subsequently the T&Q Committee tabled an updated review (March 2020) at the NEMLC meeting of 19 March 2020, and it was noted that there had been a price decrease for letrozole and that it would probably be affordable for use at secondary level of care[12]. Therefore, the Adult Hospital Committee updated the previous June 2017 review and related STG recommendations.

Refer to the updated evidence review (29 April 2020), below:

Letrozole for
Infertility-AdultReve

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: The Adult Hospital Level Committee recommends that letrozole be considered for inclusion on the Adult Hospital Level EML, for anovulation. It is noted that letrozole is currently not registered with the South African Health Products Regulatory Authority for induction of ovulation.
Rationale: Updated Cochrane review (n=2954) showed a higher clincal pregnancy rate and live birth rate of letrozole compared to clomifene or clomifene+metformin; number needed to treat for an additional beneficial outcome=10; moderate quality evidence.
The rate of miscarriage by pregnancy and multiple pregnancy rate between treatment groups showed little or no difference, but the funnel plot showed mild assymetry suggesting publication bias.
The recent decrease in price of letrozole makes it a cheaper alternative to clomifene.
Level of Evidence: II Meta-analysis of low to moderate quality RCTs[13]

[10] Contract circular RT301-2017 (average weighted prices): Ceftriaxone,IV, 1g: R5.84; Metronidazole, IV 500mg: R5.81; Co-amoxyclav, IV, 1.2g: R20.07
[11] Minutes of the NEMLC meeting of 14 December 2017
[12] Minutes of the NEMLC meeting of 19 March 2020
[13] Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2018 May 24;5:CD010287. https://www.ncbi.nlm.nih.gov/pubmed/29797697

NEMLC had also recommended[14] that the evidence for a class effect (aromatase inhibitors) be reviewed for use in infertility, as anastrozole previously on tender, was reasonably priced[15].

Evidence review for anastrazole:
Ovulation induction success rates with clomifene are poor (±30%). However, no available RCT evidence could be retrieved for anastrozole – studies have mostly been done with letrozole. As the management of infertility cases resistant to clomifene would take place at tertiary level of care – the Adult Hospital Level Expert Review Committee (ERC) recommended that medicine review be forwarded to Tertiary and Quaternary (T&Q) Committee for consideration for inclusion on the T& Q EML.
Recommendation: The Adult Hospital Level Committee recommends that aromatase inhibitors not be considered for inclusion on the Adult Hospital level EML. The Committee recommends that consideration be made for possible use at Tertiary and Quaternary level where there has been no response to clomifene. Clomifene is included in the secondary level EML for infertility.
Rationale: Evidence showed a higher clinical pregnancy rate and live birth rate of letrozole vs. clomifene or clomifene+metformin. Furthermore, there is a paucity of RCT evidence for anastrozole and therefore aromatase inhibitors cannot be considered as a therapeutic class for use in infertility. Infertility cases that are resistant to clomifene would require further management at sub specialist facilities.
Level of Evidence: II Meta-analysis of low to moderate quality RCTs[16], Expert opinion

Investigations
Prolactin level: *deleted as routine investigation*
An external comment was received recommending the deletion of prolactin levels as an investigative test, as it is not a routine investigation and an expensive assay.
Recommendation: Prolactin levels be deleted as a diagnostic test for the management of infertility in the STG.
Rationale: Aligned with guidelines[17] that recommends that, '*Women who are concerned about their fertility should not be offered a blood test to measure prolactin. This test should only be offered to women who have an ovulatory disorder, galactorrhoea or a pituitary tumour'.*
Level of Evidence: III Guidelines

Additional amendments
Following the review of the evidence, the text of the STG was updated as follows:

Medicine treatment **Note:** Women should be counselled on the risk of multiple births with medicines inducing ovulation.

5.8.2 INCOMPLETE MISCARRIAGE IN THE FIRST TRIMESTER

Medical evacuation
Misoprostol: *protocol amended*
Recommendations aligned with the updated FIGO[18] Guidelines, as follows:
From:

• ~~Misoprostol, oral/PV, 600 mcg as a single dose.~~ o ~~Repeat after 24 hours if necessary.~~

To:

• Misoprostol, PV, 800 mcg every 3 hours for 2 doses. o Repeat after 24 hours if necessary.

[14] Minutes of the NEMLC meeting of 12 April 2018.
[15] Contract circular HP04-2016ONC: Anastrozole 1 mg 30 tabs = R 34.29.
[16] Franik S, Kremer JAM, Nelen WLDM, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014 Feb 24;(2):CD010287
[17] National Collaborating Centre for Women's and Children's Health (UK). Fertility: Assessment and Treatment for People with Fertility Problems. London: Royal College of Obstetricians & Gynaecologists; 2013 Feb. https://www.ncbi.nlm.nih.gov/pubmed/25340218
[18] Morris JL, Winikoff B, Dabash R, Weeks A, Faundes A, Gemzell-Danielsson K, Kapp N, Castleman L, Kim C, Ho PC, Visser GHA. FIGO's updated recommendations for misoprostol used alone in gynecology and obstetrics. Int J Gynaecol Obstet. 2017 Sep;138(3):363-366. https://www.ncbi.nlm.nih.gov/pubmed/28643396

OR

- Misoprostol, SL, 600 mcg every 3 hours for 2 doses
  - Repeat after 24 hours if necessary.

Level of Evidence: III Guidelines

5.8.3 MIDTRIMESTER MISCARRIAGE (FROM 13–22 WEEKS GESTATION)

If no cervical dilation

Misoprostol: *protocol amended*

Recommendations aligned with the updated FIGO[19] Guidelines, as follows:

From:

- ~~Misoprostol, PV, 400 mcg immediately.~~

  ~~Follow with:~~
- ~~Misoprostol, oral, 400 mcg every 4 hours until expulsion of the products ofconception.~~
  - ~~Duration of treatment must not exceed 24 hours.~~

To:

- Misoprostol, PV/SL/buccal, 200 mcg every 4–6 hours until expulsion of the products of conception.
  - Duration of treatment must not exceed 5 doses over 24 hours.

Level of Evidence: III Guidelines

Previous Caeserean-section:

Misoprostol: *indication extended*

Although there are concerns about an increased risk of uterine rupture; FIGO Guidelines reported that a Cochrane meta-analysis[20] was inconclusive as data were insufficient to assess the occurrence of uterine rupture. It was likewise reported that "there is insufficient evidence overall of superiority of one dose or schedule of misoprostol over another for use in pregnancies at or over 13 weeks' gestation"; however, lowest possible dose was recommended to reduce adverse effects.

The following text was added to the STG:

Previous Caeserean-section:

- Misoprostol, PV/SL/buccal 100 mcg every 4–6 hours until expulsion of the products of conception.
  - Duration of treatment must not exceed 5 doses over 24 hours.

Level of Evidence: II Systematic review of low quality evidence, Guidelines

5.9 TERMINATION OF PREGNANCY (TOP)

Legal requirements as per the Choice of Termination of Pregnancy Act are described in section 5.9: Termination of pregnancy (TOP); whilst the subsections (sections 5.9.1 and 5.9.2) describe clinical management of TOP for the various trimesters of pregnancy to guide the clinician.

The updated text of the STG follows, below:

The legal criteria for TOP follow below. The clinical management for pregnancies up to 14 weeks is the same (outpatient procedures). From 14 weeks onwards, TOP should be done in a medical facility. Note that the gestational ages used for clinical management differs from the legal cut-offs, e.g. a patient at 12 weeks and 1 day will need the legal requirements as described in the act for TOP after 12 weeks, but the clinical management is the same as for a pregnancy from day one up to 14 weeks (see below).

Summary of Choice of Termination of Pregnancy Act

Women eligibility

Up to 12 weeks and 0 days: On request.

[19] Morris JL, Winikoff B, Dabash R, Weeks A, Faundes A, Gemzell-Danielsson K, Kapp N, Castleman L, Kim C, Ho PC, Visser GHA. FIGO's updated recommendations for misoprostol used alone in gynecology and obstetrics. Int J Gynaecol Obstet. 2017 Sep;138(3):363-366. https://www.ncbi.nlm.nih.gov/pubmed/28643396

[20] Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Cochrane Database Syst Rev. 2010 Apr 14;(4):CD004901. https://www.ncbi.nlm.nih.gov/pubmed/20393941

From the thirteenth week (12 weeks and 1 day) up to the twentieth week (19 weeks and 6 days): If doctor is satisfied that pregnancy was from rape or incest, or there is risk of fetal abnormality or risk to mother's physical or mental health or social or economic circumstances.
More than 20 weeks (≥ 20 weeks 1 day): Doctor and second doctor or registered midwives are satisfied that there is danger to the mother's life, a lethal or severe fetal malformation or fetal death.

Venue
An accredited facility with staff trained in performing TOP, designated by the Member of Executive Council at provincial level.

Practitioner
Up to 12 weeks and 0 days: Doctor, midwife or registered nurse with appropriate training.
From the thirteenth week (12 weeks and 1 day) up to the twentieth week (19 weeks and 6 days): Doctor responsible for decision and prescription of medication; registered nurse/midwife may administer medication according to prescription.

Misoprostol: *retained*
An external comment was received from Pfizer Laboratories advising of the off-label use of TOP and that Pfizer would not take responsibility for any litigation cases, arising from recommendations in the TOP STG. Despite Pfizer withdrawing misoprostol from the market in France, due to litigation in a TOP case, the market authorisation had not been terminated. Pfizer South Africa confirmed that the product would not be withdrawn from the South African market.
Recommendation: Misoprostol be retained for TOP in the STGs, and a statement be including in the preface of the STGs and EML advising that some recommendations may not be aligned with the SAHPRA/MCC registered label/package insert; but are guided by health needs assessment and the best available scientific evidence.
Rationale: Misoprostol was required for TOP, and an average of 25000 TOPs were reported per annum. There is no other product available for medical TOP and the STGs recommends mifeprostol/mifepristone protocol for TOP.

5.9.1 MANAGEMENT FOR PREGNANCIES OF LESS THAN 14 WEEKS OF GESTATION

Manual vacuum aspiration:

Routine analgesia for vacuum aspiration:
Pethidine, IM: *deleted*
Morphine, IM: *retained*
Aligned with the PHC STGs and EML, 2018:

At the NEMLC meeting of 14 December 2017, NEMLC accepted the PHC Committee's recommendation:

PHC NEMLC report of 14 December 2017 – Chapter 6: Obstetrics & gynaecology
6.5 Intrapartum care
Pethidine, IM: deleted
Morphine, IM: added
Paracetamol, oral: added
Ibuprofen, oral: added

Analgesia:
Recommendation: *Morphine, IM replaces pethidine, IM as analgesia during first stage of labour with cervical dilatation < 10 cm.*
Rationale: Regulation 31 replaces regulation 47 of the Medicines and related substances Act 101 of 1965 i.e. access to pethidine is replaced by access to access to schedule 5 and 6 medicines in order to provide intrapartum care. In addition, there are safety concerns regarding pethidine's active metabolite, normeperidine that is potentially neurotoxic.
Level of Evidence: III Regulations[21], Guidelines[22]

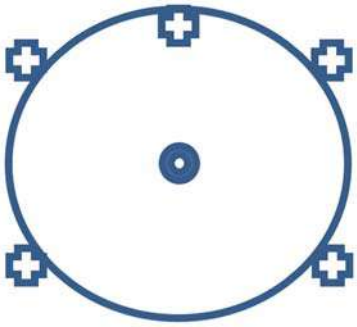
Paracervical block:
Lidocaine 1% injection: *added*
Guidance for paracervical block was added to the STG, based on RCT by Renner et al.[23] The following text was added to the

[21]Regulation 31 of the Medicines and related substances Act 101 of 1965.
[22] SAMF, 2016
[23] Renner RM, Nichols MD, Jensen JT, Li H, Edelman AB. Paracervical block for pain control in first-trimester surgical abortion: a randomized controlled trial. Obstet Gynecol. 2012 May;119(5):1030-7. https://www.ncbi.nlm.nih.gov/pubmed/22525915

STG:

Alternatively, consider a paracervical block:

- Use Lidocaine 1%.
  - Draw up lidocaine 1% in a 20 mL syringe
  - Attach a 20-gauge spinal needle. Inject 2 mL superficially in the cervix at 12h00 and immediately grab the cervix with a tenaculum at 12h00 to stabilise the cervix.
  - Inject remaining 18 mL slowly over 60 ~~minutes~~ seconds into the cervicovaginal junction in four equal doses of 4–5mL at 2, 4, 8, and 10 o'clock (see diagram below).
  - This injection is continuous from superficial to deep (a depth of 3 cm) and again to superficial (injecting with insertion and withdrawal).
  - Manual vacuum aspiration can start after 3 minutes.



Anterior view of the cervix

Level of Evidence: I RCT

Medical TOP: up to 63 days or 9 weeks and 0 days.
Mifepristone, oral: *retained*
Misoprostol: *directions for use amended*
Mifepristone/misoprostol: *protocol amended*

Mifepristone: Retained as part of the TOP treatment regimen for gestation up to 20 weeks. Refer to the updated medicine review and costing analysis, 20 October 2017, for detailed information.

Mifepristone for TOP-Adult Review U

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Misoprostol: An external comment was received advising that misoprostol is self-administered sublingually, rather than per vagina.

The text of the STG was updated as follows:

Up to 63 days or 9 weeks and 0 days:

- Mifepristone, oral, 200 mg, immediately as a single dose.

Followed 24–48 hours later by:

- Misoprostol, ~~PV~~ 800 mcg. sublingually by self-administration.
  - If expulsion has not occurred 4 hours after misoprostol administration, a second dose of misoprostol 400 mcg oral/PV may be given.

Level of Evidence: III Guidelines[24], Expert opinion

Ultrasound: Medical TOP, up to 63 days or 9 weeks and 0 days gestation can be done as an outpatient procedure, and the need for ultrasound on day 7 of the treatment regimen was deleted.
Rationale: Aligned with current practice Guidelines[25] [26].
Level of Evidence: III Guidelines

[24] Royal College of Obstetricians and Gynaecologists. The Care of Women Requesting Induced Abortion. Evidence-based Clinical Guideline Number 7. RCOG Press November 2011. http://www.rcog.org.uk/files/rcog-corp/Abortion%20guideline_web_1.pdf
[25] Royal College of Obstetricians and Gynaecologists. The Care of Women Requesting Induced Abortion. Evidence-based Clinical Guideline Number 7. RCOG Press November 2011. http://www.rcog.org.uk/files/rcog-corp/Abortion%20guideline_web_1.pdf
[26] WHO. Safe abortion: technical and policy guidance for health systems, 2014. http://www.who.int/reproductivehealth/publications/unsafe_abortion/en/

The following note was added to the STG:

Note: Bleeding may persist for up to 1 week. If there is no bleeding after the second dose of misoprostol, the woman must return to the facility as soon as possible as there is a possibility of an incomplete procedure or ectopic pregnancy

5.9.2 FROM THE THIRTEENTH WEEK (12 WEEKS AND 1 DAY) UP TO THE TWENTIETH WEEK (19 WEEKS AND 6 DAYS)

Mifepristone, oral: *retained and dose not amended*
Misoprostol: *protocol amended*
Time interval between mifepristone and misoprostol: *not amended*

Mifepristone:

- *Retained* as part of the TOP treatment regimen for gestation up to 20 weeks. Refer to the updated medicine review and costing analysis, 20 October 2017, for detailed information.
- *Dose:* Pharmacovigilance division of the MCC requested that the mifepristone dose for TOP be reassessed, as it does not align with the package insert and may be suggestive of incomplete abortions reported in a study done in the Western Cape[27]. However, evidence supports the 200 mg dosage of mifepristone[28, 29], which is also aligned with international standard of care[30]. It is noted that the causality of incomplete abortions was not assessed in the Western Cape study.

Level of Evidence: I Systematic review and metaanalyses[31], Guidelines[32]

Misoprostol: Treatment regimen amended and aligned with the most recent Royal College of Obstetricians and Gynaecologists Best practice in comprehensive abortion care, June 2015[33].

The following text was deleted:

~~The dose of misoprostol, PV, decreases with increasing gestational age because of the risk of uterine rupture.~~
~~• Misoprostol, PV, 3 hourly to a maximum of 5 doses~~
~~o 13 to 16+6 weeks: 400 mcg, PV.~~
~~o 17 to 20 weeks: 200 mcg, PV.~~
~~Then, misoprostol, PV, 400 mcg 3 hourly for 5 doses at gestation 13–16+6 weeks.~~
~~**OR**~~
~~Misoprostol, PV, 200 mcg 3hourly for 5 doses at gestation 17–20 weeks.~~
~~.If no response after 24 hours, consider adding mechanical cervical ripening in consultation with a specialist.~~
~~Pass a Foley catheter with 30 mL bulb through cervix with sterile technique. Inflate bulb with 50 mL water or sodium chloride 0.9%.~~
~~Tape catheter to thigh with light traction on catheter.~~
~~Attach sodium chloride 0.9% 1 L with giving set to catheter and infuse at 50 mL/ hour through catheter into uterus.~~
~~**Warning**~~
~~Misoprostol can cause uterine rupture in women with previous Caesarean sections and those of high parity. In these women use 200 mcg of misoprostol or alternative methods such as extra-amniotic saline infusion without misoprostol.~~

And, replaced with the following:

Follow 12-24 hours later with:

- Misoprostol, PV, 800 mcg, vaginally.
  - Then, misoprostol oral/PV, 400 mcg every 3 hours until abortion occurs.

[27] Constant D, de Tolly K, Harries J, Myer L. Assessment of completion of early medical abortion using a text questionnaire on mobile phones compared to a self-administered paper questionnaire among women attending four clinics, Cape Town, South Africa. Reprod Health Matters. 2015 Feb;22(44 Suppl 1):83-93. https://www.ncbi.nlm.nih.gov/pubmed/25702072
[28] Kulier R, Kapp N, Gülmezoglu AM, HofmeyrGJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD002855. https://www.ncbi.nlm.nih.gov/pubmed/22071804
[29] Chen MJ, Creinin MD. Mifepristone With Buccal Misoprostol for MedicalAbortion: A Systematic Review. Obstet Gynecol. 2015 Jul;126(1):12-21. https://www.ncbi.nlm.nih.gov/pubmed/26241251
[30] Royal College of Obstetricians and Gynaecologists. The Care of Women Requesting Induced Abortion. Evidence-based Clinical Guideline Number 7. RCOG Press November 2011. http://www.rcog.org.uk/files/rcog-corp/Abortion%20guideline_web_1.pdf
[31] Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD005216. https://www.ncbi.nlm.nih.gov/pubmed/21249669
[32] Royal College of Obstetricians and Gynaecologists. The Care of Women Requesting Induced Abortion. Evidence-based Clinical Guideline Number 7. RCOG Press November 2011. http://www.rcog.org.uk/files/rcog-corp/Abortion%20guideline_web_1.pdf
[33] The Royal College of Obstetricians and Gynaecologist. Best practice in comprehensive abortion care, June 2015. https://www.rcog.org.uk/globalassets/documents/guidelines/best-practice-papers/best-practice-paper-2.pdf

If after 24 hours abortion does not occur, mifepristone can be repeated 3 hours after the last dose of misoprostol, and 12 hours later misoprostol may be recommenced.

Level of Evidence: III Guidelines

Time interval between mifepristone and misoprostol:
Systematic review by Shaw et al (2013)[34] showed no difference between 12-24 hour versus 24-48 hour intervals between mifepristone and misoprostol administration on safety and efficacy in second-trimester abortion.
Results:

- Induction times (first misoprostol dose to expulsion) were only 1-2 hours longer for a 12- to 24-hour interval compared with a 36-48-hour interval.
- Total abortion times (mifepristone to expulsion) were at least 18 hours longer in the 36- to 48-hour group.
- Induction times varied by misoprostol dosing, with 400-microgram misoprostol protocols resulting in shorter induction times than 200-microgram protocols.

The authors concluded that "Shortening the mifepristone-misoprostol interval, thereby reducing total abortion time, does not compromise the safety or efficacy of second-trimester medication abortion and may be used to accommodate patient or health care provider preference".

Recommendation: Interval between mifepristone and misoprostol for 2nd trimester TOP was retained as 12-24 hours.
Rationale: Shortening the mifepristone-misoprostol interval from 24-48 hours to 12-24 hours, thereby reducing total abortion time, does not compromise the safety or efficacy of second-trimester medication abortion and may be used to accommodate patient or health care provider preference.
Level of Evidence: I Systematic review

Medical TOP: *Management amended to guide on inpatient management*
Text updated as follows, aligned with guidelines:

Medical TOP: From 12 weeks onwards, inpatient care in facilities with 24-hour service and facilities for general anaesthesia, as there is a greater risk for bleeding or a need for surgical completion of the procedure.

Level of Evidence: III Guidelines[35]

Analgesia:
Pethidine, IM: *deleted*
Morphine, IM: *retained*
See discussion above, under **5.9.1 Management for pregnancies of less than 14 weeks of gestation.**

Contraception: *guidance provided on counselling*
Text of the STG was amended to include the following:

Contraception
Counsel all women on effective contraception, especially long-acting reversible methods.
All methods can be given at the time of the procedure, with the exception of the IUCD at a medical TOP.

Level of Evidence: III Guidelines[36]

5.10 SEXUAL ASSAULT

Emergency contraception:
Levonorgestrel 1.5 mg, oral: *dose amended for obese women*
Aligned with the PHC STG (currently under review): Section 7.4 Contraception, emergency.

[34] Shaw KA, Topp NJ, Shaw JG, Blumenthal PD. Mifepristone-misoprostol dosing interval and effect on induction abortion times: a systematic review. Obstet Gynecol. 2013 Jun;121(6):1335-47. https://www.ncbi.nlm.nih.gov/pubmed/23812471
[35] WHO. Safe abortion: technical and policy guidance for health systems, 2012. http://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241548434/en/
[36] WHO. Safe abortion: technical and policy guidance for health systems, 2012. http://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241548434/en/

NEMLC report for PHC Chapter 7: Family planning:

Levonorgestrel, oral: directions for use amended
Double-dose emergency contraception recommended for obese women was considered feasible:
Evidence:

- *Jatlaoui et al, 2016[37]showed that limited data of poor quality suggests that obesity (>80 kg and/or BMI ≥ 30) was associated with an increased risk of pregnancy with emergency contraception. The following analyses were undertaken:*
  - *Secondary analysis using LNG data from meta-analysis of 2 RCTs[38]:*
    - *Between 70 and 80 kg: pregnancy rates rose from2% to 6%.*
    - *Women <75 kg with various BMI's had a low pregnancy rate of< 2%.*
  - *Secondary analysis pooled data from 3 RCTs on LNG ECPs[39] found no increase in pregnancy risk with increasing weight or BMI and found no consistent association betweenpregnancy and both factors when adjusted for other covariates.*
- *Edelman et al, 2016[40]: Small pharmacokinetic study (n=10) concluded that "obesity adversely impacts both the levels of LNG EC and this likely explains its lack of efficacy in obese women. Doubling the dose appears to correct the obesity-related PK changes but additional research is needed to determine if this also improves EC effectiveness in obese women".*
  "The total LNG Cmax for obese subjects following ECx1 (5.57±2.48 ng/mL) was significantly lower than the level observed in normal BMI women (10.30±2.47, p=0.027). Notably, ECx2 increased the Cmax".

Recommendations:

- *Dose of LNG EC be doubled for obese women (> 80 kg with a BMI ≥ 30)*

Rationale: Limited data of poor quality suggests that obese women had an increased risk of pregnancy with LNG EC. PK study showed that doubling the dose increases Cmax.
Level of Evidence: II Systematic review of poor quality RCTs, Pharmacokinetic study

Metclopramide, oral: *added*
Antiemetic added as needed, in this clinical setting where medicines for emergency contraception, HIV post-exposure prophylaxis and STI prophylaxis are concomitantly administered.
Level of Evidence: III Expert opinion

5.12 MENOPAUSE AND PERIMENOPAUSAL SYNDROME

Hormone replacement therapy, oral: *retained and caution updated*
Observational follow up of the Women's Health Initiative Randomized Trials[41] suggests that "among postmenopausal women, hormone therapy with CEE plus MPA for a median of 5.6 years or with CEE alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years".
Level of Evidence: III Observational study

And, the following text included in the STG:

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.

Venlafaxine, oral: *not added*
Refer to the medicine review:

[37]Jatlaoui TC, Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception. 2016 Dec;94(6):605-611.
[38]Glasier A, Cameron ST, Blithe D, Scherrer B, Mathe H, Levy D, Gainer E, UlmannA. Can we identify women at risk of pregnancy despite using emergencycontraception? Data from randomized trials of ulipristal acetate andlevonorgestrel. Contraception. 2011 Oct;84(4):363-
[39]Gemzell-Danielsson K, Kardos L, von Hertzen H. Impact of bodyweight/body mass index on the effectiveness of emergency contraception with levonorgestrel: a pooled-analysis of three randomized controlled trials. Curr Med Res Opin. 2015 Dec;31(12):2241-87.
[40]Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception. 2016 Jul;94(1):52-7.
[41] Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Chlebowski RT, Howard BV, Thomson CA, Margolis KL, Lewis CE, Stefanick ML, Jackson RD, Johnson KC, Martin LW, Shumaker SA, Espeland MA, Wactawski-Wende J; WHI Investigators. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA. 2017 Sep 12;318(10):927-938. https://www.ncbi.nlm.nih.gov/pubmed/28898378

Venlafaxine for Menopause-Adult R

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

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).[42]

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[43, 44, 45]

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)[46]. 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.

HT is contra-indicated, poorly tolerated or ineffective:
Fluoxetine, oral: *added as first line option*
Citalopram, oral: *added for women on concomitant tamoxifen*

A medicine review for SSRIs was developed (see below); but the Adult Expert Review Committee was of the opinion that switching patients from tamoxifen to anastrazole due to the fluoxetine-tamoxifen drug-drug interaction was not an option, as anastrazole should be retained as a second line oncologic option, (in patients not responding to tamoxifen).

Refer to the medicine review: SSRIs for control of menopausal symptoms in women where hormone therapy is contra-indicated, July 2018, for detailed information.

SSRIs for MenopuasalSymtpo

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee reccomends SSRIs for menopausal symptoms, where there is poor response to HT or where HT is contra-indicated. However, citalopram is preferred over fluoxetine, in women taking concomitant tamoxifen.

[42] Cobin RH, Goodman NF. American association of clinical endocrinologists and american college of endocrinology position statement on menopause–2017 update. Endocr Pract. 2017 Jul 1;23(7):869–80.
[43] Rada G, Capurro D, Pantoja T, Corbalán J, Moreno G, Letelier LM, Vera C. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev. 2010 Sep 8;(9):CD004923. https://www.ncbi.nlm.nih.gov/pubmed/20824841
[44] Yamaguchi N, Okajima Y, Fujii T, Natori A, Kobayashi D. The efficacy of nonestrogenic therapy to hot flashes in cancer patients under hormone manipulation therapy: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2013 Oct;139(10):1701-7. https://www.ncbi.nlm.nih.gov/pubmed/23974271
[45] Ramaswami R, Villarreal MD, Pitta DM, Carpenter JS, Stebbing J, Kalesan B. Venlafaxine in management of hot flashes in women with breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2015 Jul;152(2):231-7. https://www.ncbi.nlm.nih.gov/pubmed/26067931
[46] Li L, Xu L, Wu J, Dong L, Zhao S, Zheng Q. Comparative efficacy of nonhormonal drugs on menopausal hot flashes. Eur J Clin Pharmacol. 2016 Sep;72(9):1051-8.

Rationale: Evidence of effficacy for SSRI and the need for an alternative for HT, in women where HT is contra-indicated, is poorly tolerated or not effective. SSRIs/SNRIs has generally been shown to be more effective than placebo at reducing vasomotor symptoms and menopause in the short-term, but their long-term benefits (or harms) are largely unknown. Citalopram is preferred over fluoxetine, as there is more data for citalopram, though of low methodological quality and the drug-drug interaction of fluoxetine with tamoxifen should be considered.
Level of Evidence: III RCT with disease-oriented outcomes[47]

NEMLC MEETING OF 27 SEPTEMBER 2018:
NEMLC accepted the medicine review, and recommended that where hormone therapy for menopausal symptoms, is contra-indicated, poorly tolerated or ineffective that:

- Fluoxetine, oral is recommended as first line therapy in this cohort of patients.
- Citalopram, oral, be recommended with concomitant tamoxifen.

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note:*** *Information sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[47] Davari-Tanha F, Soleymani-Farsani M, Asadi M, Shariat M, Shirazi M, Hadizadeh H. Comparison of citalopram and venlafaxine's role in treating sleep disturbances in menopausal women, a randomized, double-blind, placebo-controlled trial. Arch Gynecol Obstet. 2016 May;293(5):1007–13. https://www.ncbi.nlm.nih.gov/pubmed/26437957