South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Family planning

MEDICINE REVIEW:

1. Executive Summary

Date: 26 August 2020 (Update of August 2019 review)
Medicine (INN): Transdermal contraceptive patch with progestin and estrogen
Medicine (ATC): G03AA progestins and estrogens, fixed combinations
Indication (ICD10 code): Contraceptive management (Z30.0/Z30.4/Z30.8)
Patient population: Women of childbearing potential (WOCP)
Prevalence of condition: n/a - This is for prevention of pregnancy
Level of Care: Primary health care
Prescriber Level: Primary health care nursing prescriber
Current standard of Care: Oral contraception containing progestin and estrogen
Efficacy estimates: (preferably NNT): n/a
Motivator/reviewer name(s): GS Gebhardt, E Bera
PTC affiliation: *GS Gebhardt:* Tygerberg Hospital, Western Cape

2. **Name of author(s)/motivator(s):** Prof GS Gebhardt, E Bera; supported by Trudy D Leong for comparative costing analysis.

3. **Author affiliation and conflict of interest details:**

Primary reviewer – GS Gebhardt

Stellenbosch University and Tygerberg Hospital; Adult Hospital Level Committee member (2017-2020); No Conflicts of interest to declare.

Secondary reviewer – E Bera

Department of Obstetrics & Gynaecology, University of the Witwatersrand; Adult Hospital Level Committee member (2017-2020); No conflicts of interest to declare.

Support – TD Leong

Essential Drugs Programme, National Department of Health; Secretariat to the Primary Health Care and Adult Hospital Level Expert Review Committees; No conflicts of interest to declare.

4. Introduction/ Background:

The currently available contraceptive patch is a 20 cm^2 adhesive patch that contains 600 µg ethinyl estradiol (EE) and 6 mg norelgestromin (NGMN), releasing 33.9 µg EE and 203 µg NGMN per day. The previous version contained 750 µg EE and 6 mg NGMN, and released 35µg ethinyl estradiol and 150 µg NGMN per day. Most of the studies reported below was done on the higher dose patch. NGMN is an active metabolite of norgestimate, the same progestin in some combined oral contraceptive (COC) formulations (1).

Steady state concentration is reached within 2 weeks of patch use, though pregnancy prevention is achieved after 1 week.

The contraceptive patch has some advantages over the OC pill:

- There is less variability in plasma concentrations of estrogen, which may decrease estrogen-related side effects such as nausea
- Improved adherence (compared to a daily COC pill) as it is only applied once a week
- Age does not affect adherence (perfect use range from 88% to 91% across different age groups, compared to 67,7% to 85% for COC and with the lowest rates in <20 year old females).(2)

The contra-indications are similar to COC, although there may be a modest increase in risk for venous thrombo-embolism than with COC, unadjusted Odds Ratio (OR) 1.23; 95% CI 0.86 to 1.77 compared to OR of 1.0 for the reference - norgestimate/EE COC. (3) Note that this study was industry sponsored. Due to concerns over increased risk of thrombotic events, a black box warning was released by the US Food and Drug Administration (FDA) in 2004 for the higher dose 750 µg EE/6 mg NGMN formulation and updated again most recently in 2011. (1)

The patch is removed after one week of use and replaced with another at that time, such that the user will have three consecutive weeks where they are wearing the patch. After three weeks, there is a patch free week during which patients can expect to have a withdrawal bleed. The efficacy of the patch is similar to other methods of combined hormonal contraception (see below), though patients weighing more than 90kg or with a body mass index >30kg/m^2 have a higher risk of unintended pregnancies.(4)

The literature search evaluated the efficacy, tolerability and compliance of the combined contraceptive patch compared to combined oral hormonal contraceptives. It is obvious that none of the studies would be able to reduce bias using blinding given the characteristics of the intervention (oral administration of a daily contraceptive or a weekly transdermal skin patch).

Population	Women of reproductive age
Intervention	Hormonal contraceptive transdermal patch containing progestin and estrogen
Comparison	Oral contraception containing progestin and estrogen
Outcomes	Efficacy – prevention of pregnancy Safety – weight gain, bleeding patterns, endometriosis, HIV acquisition, other adverse events

5. Methods:

a. **Data sources: PubMed, ScienceDirect and EMBASE**

b. **Search strategy;** ("administration, cutaneous"[MeSH Terms] OR ("administration"[All Fields] AND "cutaneous"[All Fields]) OR "cutaneous administration"[All Fields] OR "transdermal"[All Fields]) AND ("contraception"[MeSH Terms] OR "contraception"[All Fields]) AND ("adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "teenagers"[All Fields]) AND adherence[All Fields] AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("contraception"[MeSH Terms] OR "contraception"[All Fields])

c. **Evidence synthesis**

1. A 2015 systematic review in the Cochrane library by Krashin et al (*Hormonal and intrauterine methods for contraception for women aged 25 years and younger*) includes a single study comparing COC versus transdermal patch- there was no difference in pregnancy rates after 6 months (OR of 1.0, 95% CI 0.05 to 18.57) nor in the continuation rates (OR 0.38, 95%CI 0.05 to 2.77). The review concludes that current evidence was insufficient to

compare efficacy and continuation rates for hormonal and intrauterine contraceptive methods in women aged 25 years and younger.(5)

2. A second Cochrane systematic review (Lopez et al) reviewed *Skin patch and vaginal ring versus combined oral contraceptives for contraception*. There are 18 trials included (5 multicenter trials dealing with the combination ethinyl estradiol and norelgestromin patch) and was updated in 2013(6). The main findings related to the patch are:
    a. No difference in efficacy as compared to COC (the odds ratio of pregnancy for the patch versus the COC were similar)
    b. More patch users discontinued early from the trials reporting those data than women assigned to use the COC (pooled OR 1.59, 95% CI 1.26 to 2).
    c. Patch users were more likely to discontinue due adverse events than COC users (pooled OR 2.28, (95% CI 1.61 to 3.25).
    d. Patch users showed better compliance to the regimen per cycle than COC users (OR for compliance 2.05 (95% CI 1.38 to 2.29).
    e. In one trial, there were less breakthrough bleeding and spotting on the patch, for the rest of the trials there were no difference.
    f. Patch users more often reported breast discomfort or pain compared to the COC group in three trials (OR vary between 2.98 and 9, all significant).

There are no other systematic reviews identified.

There are no further randomized trials on the norelgestromin/ethinyl estradiol 6/0.6mg patch compared to COC identified since 2013. It appears as if worldwide use has decreased since 2010. There are a few randomized trials on a newer patch containing gestodene, these are all phase 3 studies.

In summary, the patch is an alternative method for women who require combined contraception, with similar efficacy, better compliance than combined oral contraceptives; but slightly higher side-effect profile (i.e. associated venous thromboembolism).

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?
Confident [ ] Not confident [x] Uncertain [ ]</td><td>Limited data – see above</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [x]</td><td>Benefits outweigh potential harms</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [x] No [ ]

List the members of the group.
All other available contraceptive modalities, as women’s choice is a prerogative.
List specific exclusion from the group: n/a</td><td>Rationale for therapeutic alternatives included: All other available contraceptive modalities, as women’s choice is a prerogative.
References: n/a

Rationale for exclusion from the group: n/a

References: n/a</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 [ ] No [ ] Uncertain [x]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [x] Less intensive [ ] Uncertain [ ]</td><td>Price of family planning agents/ month (28 days):
<table>
<tr><th>Family planning agent</th><th>Pack size Price (ZAR)</th><th>Price/ 28 days (ZAR)</th></tr>
<tr><td>Norelgestromin/ethinyl estradiol 6/0.6mg, 3 patches (100% of SEP*)</td><td>159.37</td><td>159.37</td></tr>
<tr><td>Norelgestromin/ethinyl estradiol 6/0.6mg, 3 patches (60% of SEP*)</td><td>95.62</td><td>95.62</td></tr>
<tr><td>Copper IUCD</td><td>159,99**</td><td>2,45</td></tr>
<tr><td>Levonorgestrel/ethinyl estradiol, triphasic tablets</td><td>6,28**</td><td>6,28</td></tr>
<tr><td>Levonorgestrel tablets</td><td>3,03**</td><td>3,03</td></tr>
<tr><td>Levonorgestrel/ethinyl estradiol, monophasic tablets</td><td>2,90**</td><td>2,90</td></tr>
<tr><td>Norethisterone enanthate injectionl</td><td>24,01**</td><td>12,01</td></tr>
<tr><td>Etonogestrel implant</td><td>224,58**</td><td>5,74</td></tr>
<tr><td>DMPA injection</td><td>15.40**</td><td>5,13</td></tr>
</table>
* SEP database, March 2020, https://mpr.code4sa.org/
**Contract circulars RT283-2017, HP03-2017CHM/01
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [ ] Uncertain [x]</td><td>Dependant on availability on other modalities and patient preference</td></tr>
</table>

FEASIBILITY	Is the implementation of this recommendation feasible? Yes [x] No [ ] Uncertain [ ]	

Type of recommendation	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
	[X]	☐	☐	☐	☐

Recommendation: Based on the evidence reviewed, the Adult Hospital Level Committee does not recommend inclusion of norelgestromin/ethinyl estradiol 6/0.6mg patches on the national Essential Medicine List. Contraceptive patches containing other progestins are being investigated in clinical trials and further assesment of this contraceptive modality is reccomended for review, pending SAHPRA registeration and product is locally accesible.
Rationale: Risk benefit assesment favours combined oral contraceptive (containing the same progestin) in terms of associated veno-thromboembolic events. More clear data of the risk of VTE for the difeferent progestins, on adherence and acceptability of the contraceptive patch in local context and a more affordable price would further contribute to decision-making. (Authors of a systematic review concluded that there is limited evidence of low to moderate quality that showed conflicting results of VTE risk associated with patch or ring compared to COCs (7).
Level of Evidence: II Moderate quality clinical trials and a Systematic Review (for safety)

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[X]	[X]

VEN status: n/a

Vital	Essential	Necessary
[ ]	[ ]	[ ]

NEMLC MEETING OF 26 SEPTEMBER 2019:
NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, above.

NEMLC MEETING OF 17 SEPTEMBER 2020:
NEMLC accepted the updated medicine review that now includes comparative pricing.

Monitoring and evaluation considerations

Research priorities

- Feasibility of self administration
- Long term safety profile
- Local acceptability studies

References

1. Galzote RM, Rafie S, Teal R, Mody SK. Transdermal delivery of combined hormonal contraception: a review of the current literature. Int J Womens Health. 2017 May 15;9:315–21.
2. Archer DF, Cullins V, Creasy GW, Fisher AC. The impact of improved compliance with a weekly contraceptive transdermal system (Ortho Evra®) on contraceptive efficacy. Contraception. 2004 Mar;69(3):189–95.
3. Jick SS, Hagberg KW, Kaye JA. ORTHO EVRA® and venous thromboembolism: an update. Contraception. 2010 May;81(5):452–3.
4. Dragoman MV, Simmons KB, Paulen ME, Curtis KM. Combined hormonal contraceptive (CHC) use among obese women and contraceptive effectiveness: a systematic review. Contraception. 2017 Feb 1;95(2):117–29.
5. Krashin J, Tang JH, Mody S, Lopez LM. Hormonal and intrauterine methods for contraception for women aged 25 years and younger. Cochrane Database Syst Rev [Internet]. 2015 [cited 2019 Aug 15];(8). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009805.pub3/full?highlightAbstract=withdrawn%7Cintrauterine%7Csystem%7Cintrauterin
6. Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev [Internet]. 2013 [cited 2019 Aug 15];(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003552.pub4/full?highlightAbstract=patch%7Cwithdrawn%7Ccontracept%7Ccontraceptive%7Ccontraceptiv
7. Tepper NK, Dragoman MV, Gaffield ME, Curtis KM. Nonoral combined hormonal contraceptives and thromboembolism: a systematic review. Contraception. 2017 Feb;95(2):130-139.

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