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

MEDICINE REVIEW:

1. Executive Summary

Date: May 2018
Medicine (INN): Trichloroacetic acid (TCA) or imiquimod, topical.
Medicine (ATC): n/a
Indication (ICD10 code): Treatment of anogenital warts (A63.0/B07)
Patient population: Adults
Prevalence of condition: Overall (females and males combined) reported annual incidence (including new and recurrent) ranges from 160 to 289 per 100,000, with a median of 194.5 per 100,000. [Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. *BMC Infectious Diseases*. 2013;13:39. doi:10.1186/1471-2334-13-39]
Level of Care: Hospital Level, adults
Prescriber Level: Medical officer
Current standard of Care: Podophyllin 20% Tinct. Benz.Co., topical
Efficacy estimates: (preferably NNT) *Thurgar et al:*
i) Complete clearance at end of treatment:

- Imiquimod 5% cream (12/16 weeks) - patient applied vs podophyllin 20–25% (clinician applied): OR 1.07 (0.15 to 3.45), not statistically significant.
- TCA vs podophyllin 20–25% (clinician applied): OR 1.23 (0.30 to 3.56), not statistically significant.

ii) Surgical excision more effective than podophyllin 20–25% at reducing recurrence at ≥ 6 months (OR 0.14, 0.02 to 0.50).
Motivator/reviewer name(s): Dr R Griesel/ Dr H Dawood (assisted by Ms TD Leong) & Prof K Cohen
PTC affiliation: Dr Dawood: KZN Provincial PTC ; Prof Kohen: WC Provincial PTC

2. **Name of motivator(s)/ author(s):** Motivator: Dr R Griesel; Primary reviewer: Dr H Dawood (assisted by Ms TD Leong); Second reviewer: Prof K Cohen

3. **Author affiliation and conflict of interest details:**
   i. *Dr H Dawood:* Greys hospital, KZN Department of health; Caprisa, UKZN; Adult Hospital Level Committee (2017-2020); *Conflict of interest declared:* MSD: ECMID 2018 - Conference attendance; ACTA study - DSMB member (crypto meningitis); Adcock Ingram - HIV discussion with general practitioners.
   ii. *Ms TD Leong:* NDoH Essential Drugs Programme; Secretariat to the Adult Hospital Level Committee; no conflicts of interest declared.
   iii. *Prof K Cohen:* University of Cape Town - Division of Clinical Pharmacology, Department of Medicine; Primary Health Care Expert Review Committee (2016-2018) and National Essential Medicines List Committee (2016-2020); no conflicts of interest declared.

4. Introduction/ Background

Ano-genital warts (AGW) or condylomata acuminata (CA) is usually secondary to sexually acquired human papilloma virus infection (HPV). Treatment options can be divided into patient-applied and clinician-administered therapies. First-line patient-applied therapies include imiquimod, podophyllotoxin and sinecatechins whilst first line clinician-administered therapies include cryotherapy, trichloroacetic acid (TCA), surgical excision, electro-surgery, and carbon dioxide laser therapy. Analysis by mixed treatment analysis indicates that ablative techniques were typically more effective than topical interventions at completely clearing AGWs at the end of treatment. (Thurgar E, et al. Health Technol Assess 2016; 20(24)).

However, ablative techniques require resources in terms of skill and equipment and therefore not readily available at all levels of care. As a result, topical treatments are the preferred first line treatment for AGWs and podophyllin 20% Tinct. Benz.Co., topical is currently on the Essential Medicines List (EML). There are manufacturer supply issues of podophyllin 20% in South Africa currently and hence alternative topical agents are needed.

Podophyllin (current standard of care)

The current standard of care is podophyllin 20% in compound bezoin tincture for the treatment of external moist warts in the anogential region. Use of podophyllin is contra-indicated in pregnancy and areas of application may ulcerate and become painful. Current EML guidance is for podophyllin to be applied by a health care worker

Podophyllum is a plant extract that blocks cell division at metaphase and leads to cell death. The availability of podophyllin is therefore limited by the scarcity of the plant and lack of organised cultivation of the plant.

Ready-made formulations containing podophyllotoxin, an active ingredient found in podophyllum are available on the global market.

Trichloroacetic acid (TCA)

Trichloroacetic acid (TCA) is an alternative for the management of external genital warts. The product is a white crystalline mass which can be prepared with sterile water solution. TCA is a caustic acid that destroys the wart tissue via chemical coagulation of tissue proteins. TCA must be applied by a health care provider. It can be used on the vulva and vagina, and during pregnancy and is a relatively inexpensive caustic agent. The agent is contra-indicated for use in urethral meatus warts. TCA should be applied carefully because excessive application can lead to damage to adjacent tissues and long term scarring may result. A transient burning sensation may occur at the site of application. If severe pain is experienced following application of TCA, the agent may be neutralised with soap or sodium bicarbonate. There is limited evidence for efficacy and safety of TCA.

Like podophyllin, a barrier of petroleum jelly may help protect unaffected surrounding areas. TCA is applied once weekly for three to four weeks or every two weeks for 8 to 10 weeks, with a maximum of 6 treatments. TCA may be used in pregnancy and side effects are similar to podopyllin.

Disadvantages of TCA are:

1. need for application by a health care worker. (This is the recommendation for podophyllin as well in current EML).
2. TCA like podophyllin requires multiple treatment sessions.
3. There is no MCC/SAHPRA registered product currently available on the South African market
4. The preparation requires compounding, which is complex and requires a fume cupboard and protective clothing
5. Sourcing the raw material is challenging and as this product is very toxic

Imiquimod

Imiquimod is an immunomodulator that modifies the immune response (specifically innate immune system). Imiquimod binds to toll-like receptor 7 and triggers the cellular release of cytokines. Treatment with imiquimod leads to increases in interferon-alpha, interleukin-1beta, interleukin-6 and tumour necrosis factor-alpha. This enables blocking of

multiplication of invading pathogens, including viruses. Due to the effect on the immune system, caution is advised when using imiquimod in the treatment of people who are receiving immunosuppressive treatments.

Imiquimod 5% cream (12.5 mg of imiquimod in 250 mg of cream) is applied topically three times per week on non-consecutive days (e.g. Monday, Wednesday and Friday or Tuesday, Thursday and Saturday) before bedtime for 16 weeks. The cream should be left in place for 6–10 hours and the treated area should be washed with mild soap and water after the treatment period. A local site reaction may occur if excess cream is applied or if contact is prolonged. This includes erythema (61%), erosion (30%), excoriation/flaking/scaling (23%) and oedema (14%)
Systemic adverse events include headache, nausea and myalgia.

Imiquimod is contraindicated in people who are hypersensitive to imiquimod or to any of the excipients in the formulation. As imiquimod elicits an effect through stimulating the immune system, caution is advised when using imiquimod in the treatment of people who are receiving immunosuppressive treatments.

5. Purpose/Objective i.e. PICO

Do trichloroacetic acid (TCA) and imiquimod have similar efficacy and safety to podophyllin (20%) for the treatment of viral and/or ano-genital warts (AGWs)?

- **P** *(patient/population):* Adults ≥ 16 years with clinically diagnosed AGWs (with or without biopsy confirmation).
- **I** *(intervention):* Topical treatments evaluated: podophyllotoxin (0.5%), imiquimod or trichloroacetic acid (TCA)
- **C** *(comparator):* Podophyllin 20% Tinct. Benz.Co., topical
- **O** *(outcome)*: AGW clearance at completion of treatment (which may be up to 16 weeks for imiquimod).

6. Methods:

a. Data sources*: Medline, Scopus (EMBASE), Pubmed,Cochrane and Web of Sciences .*

b. Search strategy:

We used the following search terms: anogenital warts or genital warts or podophyllin (20%,30%,0.5%) or trichloroacetic acid.

We included systematic reviews for the treatment of AGWs, randomised controlled trials (RCT) of topical treatment for AGWs and guidelines for the treatment of AGWs.

c. Evidence synthesis

We found two randomised trials (RCTs) comparing podophyllin to TCA:

An open label RCT of 120 patients with genital warts found no difference (93.3% in each arm) in “completely treated” genital warts between podophyllin(20%) and TCA(30%). A recurrence of 6.6% was reported in the podophyllin group only at 6 months. The study did not clearly state the primary outcome and duration of treatment, nor was any statistical analysis undertaken. (Tabari et al ,2010).

A second open label RCTof 100 patients followed up for three months reports a clearance of 78% (38/47) and 81% (39/48) in podophyllin and TCA respectively. Recurrence was 30 % in the podophyllin group and 13% in the TCA group. However, no statistical analysis is reported. (Nath et al,1990). Overall local pain was reported in 8.5% of cases overall with no distinction of adverse events by intervention.

Two studies compared imiquimod with podophyllin. In the first study (Padhiar 2006, Indian J Sex Transmit Dis 2006; 27:67–9), the initial treatment period was 16 weeks with imiquimod 5 % (n=30) vs. 6 weeks with podophyllin 20%) (n=30) followed by a 6-month follow-up period after clearance of AGWs in a sexually transmitted disease (STD) clinic. Those with clinically diagnosed external AGWs with at least two but no more than 50 AGWs at baseline were included.HIV infected individuals were excluded. AGW clearance at end of treatment was 16/30(53%) (imiquimod) 14/30(47%)(podophyllin), no p value was reported.

In a systemic review by Thurgar et al (2016):

ii) Podophyllotoxin 0.5% solution was associated with statistically significant improvements in complete clearance at end of treatment compared with:

- podophyllotoxin 0.5% cream (OR 0.30, 95% CI 0.04 to 0.99; OR < 1 favours podophyllotoxin 0.5% solution)
- podophyllotoxin 0.3% cream (OR 0.19, 95% CI 0.007 to 0.874; OR < 1 favours podophyllotoxin 0.5% solution)
- TCA (OR 0.17, 95% CI 0.02 to 0.63; OR < 1 favours podophyllotoxin 0.5% solution).

Overall podophyllotoxin 0.5% solution had a 92.6% (95% CI 81.8% to 98.4%) probability of completely clearing lesions compared with 56.1% (95% CI 20.3% to 85.0%) for imiquimod 5% cream. The confidence intervals are wide, suggesting uncertainty associated with the results.

Conclusion: Overall, there is a lack of data with respect to comparative effectiveness of the three interventions and the potential advantages and disadvantages of each intervention is unclear. Furthermore, the RCTs are small, lack statistical analysis, clear reporting of outcomes with limited effect size reporting and the ability to discern bias in reporting of the current RCTs limits the quality of the studies. No study assessed the effectiveness of the three treatments in a head-to-head comparison. A RCT comparing each intervention in terms of effectiveness is needed.

Furthermore, there is uncertainty around effectiveness in recurrent episodes of AGWs, and whether the type of AGW affects treatment effectiveness. Most studies did not stratify by previous treatment and AGW type and this may influence treatment efficacy.

Author, date	*Type of study*	N	Population	Comparators	Primary outcome	Effect sizes	Comments
Tabari et al (2010)	Open label RCT	120	Iran	Podophyllin and TCA	Not stated	No difference in "completely treated" 56/60 vs 56/60	No statistical analysis Pregnant women excluded
Nath et al (1990)	Open label RCT	100	India	Podophyllin and TCA	Clearance rate	38/47 vs 39/48	No statistical analysis Pregnant : TCA only
Komericki (2011)	RCT	51	Austria	Imiquimod 5% vs podophyllin 0.5% solution	Clearance rate	15/20 vs18/25, p=1	4 weeks podophyllin vs 16 weeks imiquimod
Padhiar(2006)	RCT	60	India	Imiquimod 5% vs podophyllin 20%(clinican applied)	Clearance rate	16/30 vs 14/30, p not reported	6 weeks podophyllin vs 16 weeks imiquimod

d. Evidence quality:

Low overall quality of evidence: Two open label RCTs for TCA with no statistical analysis and two RCTs comparing imiqumod with podophyllin.

Overall the studies do not report key characteristics such size, number and location of lesions and whether lesions where keratinised or non-keratinised. The treatment of warts in the setting of HIV infection was lacking as only one study reported on the outcomes with imiqumod (Gilson RJ, AIDS 1999;13:2397–404.)

7. Alternative agents:

First-line patient-applied therapies include imiquimod, podophyllotoxin and sinecatechins whilst clinician-administered therapies include cryotherapy, trichloroacetic acid (TCA), surgical excision and electro-surgery.

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 [X]	Efficacy in clearance of warts – evidence reviewed above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	Genital warts are not life-threatening, but cause discomfort, significant psychosocial harm, including low self-esteem, negative self-perception, embarrassment and anxiety. Furthermore, there is a risk of onward transmission if not treated.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [x] No [ ] *List the members of the group:* First-line patient-applied therapies include imiquimod, podophyllotoxin and sinecatechins whilst clinician-administered therapies include cryotherapy, trichloroacetic acid (TCA), surgical excision and electro-surgery. *List specific exclusion from the group:* Imiquimod, cryotherapy, surgical excision, electro-surgery.	*Rationale for therapeutic alternatives included:* Health Technology Asssesment reviewed efficacy, safety and cost-effectiveness of various treatment options. *Reference:* Lacey CJ et al (2012) *Rationale for exclusion from the group:* • imiquimod: cost • cryotherapy, surgical excision, electro-surgery, limited skills and equipment.
VALUES & PREFERENCES / ACCEPTABILITY	**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]	

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
		x

Cost of medicines/ treatment course:

Medicine	**Cost (ZAR)**
Podophyllin 20% in Tinct Benzoin Co BP, 15 ml	**See Appendix II** 1357.30
Imiquimod 12.5 mg sachet 3xwk x12wks, 36 sachets	819.70 to 1639.39*
Imiquimod 12.5 mg sachet 3xwk x12wks, 36 sachets AND initial GP consultation at level 1 facility**	1026.70 to 1846.39
Imiquimod 12.5 mg sachet 3xwk x16wks, 48 sachets	1092.93 to 2185.85*
Imiquimod 12.5 mg sachet 3xwk x16wks, 48 sachets AND initial GP consultation at level 1 facility**	1299.93 to 2392.85
Podophyllotoxin 0.5%, 3 ml	93.66 to 187.33*

*30 to 60% of SEP – SEP database 6June2018

** UPFS, 2018 (R 207.00)

Note:

- Need for pharmacy assistance and training of clinicians.

- Limited evidence showing that imiquimod (patient applied) may be as effective as podophyllin 20% in Tinct Benzoin Co (clinician applied) for complete clearance at the end of treatment, not statistically significant and wide CI: OR 1.07, 95% CI 0.15 to 3.45. (Thurgar et al)

Additional resources:

i) MSH International Products Price Guide, 2015:

- Podophyllin 25% solution (15ml) – CRSS(DDU): $40.65 = approximately R 500.00

References:

http://mshpriceguide.org/en/home/

https://www.oanda.com/currency/average (Average $ exchange rate: R12.175)

ii) *Thurgar et al:* HTA showed that:

-Podophyllotoxin 0.5% solution is cost-effective – however, product not available on South African market

- Podophyllin preparations are not as cost-effective, due to lower rate of clearance; higher rate of recurrence – though preparation costs are low. Extemporaneous preparation is possible at secondary level of care.

- CO2 laser therapy or surgical excision are likely to represent a cost-effective treatment option at second line.

- There is uncertainty around the cost-effectiveness of treatment with imiquimod, TCA and cryotherapy at second line. These agents not found to be cost-effective because of their relatively lower rates of complete clearance vs. CO2 laser therapy and surgical excision. (There is uncertainty around treatment effects and rates of recurrence).

EQUITY

Would there be an impact on health inequity?

Yes	No	Uncertain
		X

FEASIBILITY	Is the implementation of this recommendation feasible? Yes ☐ No ☐ Uncertain ☒ x	Uncertain as dependent on clinician expertise

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 low quality of evidence for products other than podophyllin, the Adult Hospital Level Committee recommends podophyllotoxin 0.5% for clearance of ano-genital warts. However, due to limited availability of this product, the current recommendation of the extemporaneous preparation of podophyllin 20% in compound benzoin tincture BP be retained in the STG and EML.

Rationale: Limited evidence of efficacy suggesting that podophyllotoxin 0.5% is the most effective medicinal intervention for clearing ano-genital warts. However, as access is limited, the current recommendation, podophyllin 20% in compound benzoin tincture BP, be retained in the national EML as an extemporaneous preparation (see appendix I).

Level of Evidence: II Health Technology Assesment of low quality evidence, Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X		

VEN status:

Vital	Essential	Necessary
	X	

NEMLC Minutes of 27 September 2018:
NEMLC accepted the above-mentioned recommendation and recommended that on final ratification of the dermatology chapter that a circular be disseminated advising that podophyllotoxin and podophyllum are superior agents for clearance of ano-genital warts.

Monitoring and evaluation considerations: Monitoring for adverse events.

Research priorities: The available evidence on the clinical effectiveness and cost-effectiveness of treatments used in anal genital warts is limited. A RCT that compares each intervention in a head-to-head study in terms of effectiveness is needed.

References:

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APPENDIX I

Extemporaneous preparations should be compounded by a pharmacist or under pharmacist supervision. Labelling should contain batch number, date of preparation and expiry date; and all relevant labelling specific to the preparation in accordance with the "General regulations made in terms of the Medicines and Related Substances Act, 1965(Act NO. 101 of 1965), as amended".

- Podophyllin 20% in compound benzoin tincture BP, 100 mL.

  Ingredients:

Podophyllin resin BP	20 g	
Compound benzoin tincture	BP	to 100 mL

  Method:

1. Weigh out the podophyllin resin, and place in 100 mL amber glass bottle (previously dried out with a few drops of 70% alcohol).
2. Add compound benzoin tincture to 100 mL and mix well.
3. Decant 10 mL in an amber glass bottle for a treatment course and label appropriately.