

Botanical Found Cost Effective for Genital Warts

BY BRUCE JANCIN

WAIKOLOA, HAWAII — Sinecatechins ointment 15%—the first botanical approved by the Food and Drug Administration for prescription use—outperformed imiquimod cream 5% for treatment of external genital warts in a cost-effectiveness analysis.

The analysis by Paul C. Langley, Ph.D., of the University of Minnesota,

Minneapolis, utilized pharmacoeconomic modeling based upon data from the two pivotal phase III, double-blind, vehicle-controlled, randomized trials of sinecatechins ointment 15% (Veregen), along with a systematic review of the published imiquimod (Aldara) literature, Dr. Brian Berman explained at the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation.

As first-line therapy, the botanical was the clear winner with a sustained clearance rate of 51.9%, compared with 40.6% with imiquimod.

The average treatment cost was lower, too, at \$774 compared with \$930. The cost per successful outcome was \$1,492 with sinecatechins ointment and \$2,289 with imiquimod (J. Med. Econ. 2010;13:1-7).

Factoring in the additional cost of

second-line ablative therapy for patients who didn't respond to the initial topical regimen, the average cost of treatment climbed to \$943 in the sinecatechins arm and \$1,138 in the imiquimod group.

"Take this cost-effectiveness analysis with a grain of salt. I find cost-effectiveness analyses are usually paid for by the product that does well, as was the case here," observed Dr. Berman,

ParaGard[®] T 380A[®] intrauterine copper contraceptive

Brief Summary

(See package brochure for full prescribing information)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

ParaGard[®] T 380A Intrauterine Copper Contraceptive should be placed and removed only by healthcare professionals who are experienced with these procedures.

INDICATIONS AND USAGE

ParaGard[®] is indicated for intrauterine contraception for up to 10 years. The pregnancy rate in clinical studies has been less than 1 pregnancy per 100 women each year.

CONTRAINDICATIONS

ParaGard[®] should not be placed when one or more of the following conditions exist:

1. Pregnancy or suspicion of pregnancy
2. Abnormalities of the uterus resulting in distortion of the uterine cavity
3. Acute pelvic inflammatory disease, or current behavior suggesting a high risk for pelvic inflammatory disease
4. Postpartum endometritis or postabortal endometritis in the past 3 months
5. Known or suspected uterine or cervical malignancy
6. Genital bleeding of unknown etiology
7. Mucopurulent cervicitis
8. Wilson's disease
9. Allergy to any component of ParaGard[®]
10. A previously placed IUD that has not been removed

WARNINGS

1. Intrauterine Pregnancy

If intrauterine pregnancy occurs with ParaGard[®] in place and the string is visible, ParaGard[®] should be removed because of the risk of spontaneous abortion, premature delivery, sepsis, septic shock, and, rarely, death. Removal may be followed by pregnancy loss.

If the string is not visible, and the woman decides to continue her pregnancy, check if the ParaGard[®] is in her uterus (for example, by ultrasound). If ParaGard[®] is in her uterus, warn her that there is an increased risk of spontaneous abortion and sepsis, septic shock, and rarely, death. In addition, the risk of premature labor and delivery is increased.

Human data about risk of birth defects from copper exposure are limited. However, studies have not detected a pattern of abnormalities, and published reports do not suggest a risk that is higher than the baseline risk for birth defects.

2. Ectopic Pregnancy

Women who become pregnant while using ParaGard[®] should be evaluated for ectopic pregnancy. A pregnancy that occurs with ParaGard[®] in place is more likely to be ectopic than a pregnancy in the general population. However, because ParaGard[®] prevents most pregnancies, women who use ParaGard[®] have a lower risk of an ectopic pregnancy than sexually active women who do not use any contraception.

3. Pelvic Infection

Although pelvic inflammatory disease (PID) in women using IUDs is uncommon, IUDs may be associated with an increased relative risk of PID compared to other forms of contraception and to no contraception. The highest incidence of PID occurs within 20 days following insertion. Therefore, the visit following the first post-insertion menstrual period is an opportunity to assess the patient for infection, as well as to check that the IUD is in place. Since pelvic infection is most frequently associated with sexually transmitted organisms, IUDs are not recommended for women at high risk for sexual infection. Prophylactic antibiotics at the time of insertion do not appear to lower the incidence of PID.

PID can have serious consequences, such as tubal damage (leading to ectopic pregnancy or infertility), hysterectomy, sepsis, and, rarely, death. It is therefore important to promptly assess and treat any woman who develops signs or symptoms of PID.

Guidelines for treatment of PID are available from the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia at www.cdc.gov or 1-800-311-3435. Antibiotics are the mainstay of therapy. Most healthcare professionals also remove the IUD.

The significance of actinomyces-like organisms on Papanicolaou smear in an asymptomatic IUD-user is unknown, and so this finding alone does not always require IUD removal and treatment. However, because pelvic actinomycosis is a serious infection, a woman who has symptoms of pelvic infection possibly due to actinomyces should be treated and have her IUD removed.

4. Immunocompromise

Women with AIDS should not have IUDs inserted unless they are clinically stable on antiretroviral therapy. Limited data suggest that asymptomatic women infected with human immunodeficiency virus may use intrauterine devices. Little is known about the use of IUDs in women who have illnesses causing serious immunocompromise. Therefore these women should be carefully monitored for infection if they choose to use an IUD. The risk of pregnancy should be weighed against the theoretical risk of infection.

5. Embedment

Partial penetration or embedment of ParaGard[®] in the myometrium can make removal difficult. In some cases, surgical removal may be necessary.

6. Perforation

Partial or total perforation of the uterine wall or cervix may occur rarely during placement, although it may not be detected until later. Spontaneous migration has also been reported. If perforation does occur, remove ParaGard[®] promptly, since the copper can lead to intraperitoneal adhesions. Intestinal penetration, intestinal obstruction, and/or damage to adjacent organs may result if an IUD is left in the peritoneal cavity. Pre-operative imaging followed by laparoscopy or laparotomy is often required to remove an IUD from the peritoneal cavity.

7. Expulsion

Expulsion can occur, usually during the menses and usually in the first few months after insertion. There is an increased risk of expulsion in the nulliparous patient. If unnoticed, an unintended pregnancy could occur.

8. Wilson's Disease

Theoretically, ParaGard[®] can exacerbate Wilson's disease, a rare genetic disease affecting copper excretion.

PRECAUTIONS

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

1. Information for patients

Before inserting ParaGard[®] discuss the Patient Package Insert with the patient, and give her time to read the information. Discuss any questions she may have concerning ParaGard[®] as well as other methods of contraception. Instruct her to promptly report symptoms of infection, pregnancy, or missing strings.

2. Insertion precautions, continuing care, and removal.

(See **Package Brochure for INSTRUCTIONS FOR USE.**)

3. Vaginal bleeding

In the 2 largest clinical trials with ParaGard[®] (see **ADVERSE REACTIONS**, Table 2), menstrual changes were the most common medical reason for discontinuation of ParaGard[®]. Discontinuation rates for pain and bleeding combined are highest in the first year of use and diminish thereafter. The percentage of women who discontinued ParaGard[®] because of bleeding problems or pain during these studies ranged from 11.9% in the first year to 2.2% in year 9. Women complaining of heavy vaginal bleeding should be evaluated and treated, and may need to discontinue ParaGard[®]. (See **ADVERSE REACTIONS.**)

4. Vasovagal reactions, including fainting

Some women have vasovagal reactions immediately after insertion. Hence, patients should remain supine until feeling well and should be cautious when getting up.

5. Expulsion following placement after a birth or abortion

ParaGard[®] has been placed immediately after delivery, although risk of expulsion may be higher than when ParaGard[®] is placed at times unrelated to delivery. However, unless done immediately postpartum, insertion should be delayed to the second postpartum month because insertion during the first postpartum month (except for immediately after delivery) has been associated with increased risk of perforation.

ParaGard[®] can be placed immediately after abortion, although immediate placement has a slightly higher risk of expulsion than placement at other times. Placement after second trimester abortion is associated with a higher risk of expulsion than placement after the first trimester abortion.

6. Magnetic resonance imaging (MRI)

Limited data suggest that MRI at the level of 1.5 Tesla is acceptable in women using ParaGard[®]. One study examined the effect of MRI on the CU-7[®] Intrauterine Copper Contraceptive and Lippes Loop[™] intrauterine devices. Neither device moved under the influence of the magnetic field or heated during the spin-echo sequences usually employed for pelvic imaging. An in vitro study did not detect movement or temperature change when ParaGard[®] was subjected to MRI.

7. Medical diathermy

Theoretically, medical (non-surgical) diathermy (short-wave and microwave heat therapy) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. However, a small study of eight women did not detect a significant elevation of intrauterine temperature when diathermy was performed in the presence of a copper IUD.

8. Pregnancy

ParaGard[®] is contraindicated during pregnancy. (See **CONTRAINDICATIONS** and **WARNINGS.**)

9. Nursing mothers

Nursing mothers may use ParaGard[®]. No difference has been detected in concentration of copper in human milk before and after insertion of copper IUDs. The literature is conflicting, but limited data suggest that there may be an increased risk of perforation and expulsion if a woman is lactating.

10. Pediatric use

ParaGard[®] is not indicated before menarche. Safety and efficacy have been established in women over 16 years old.

ADVERSE REACTIONS

The most serious adverse events associated with intrauterine contraception are discussed in **WARNINGS** and **PRECAUTIONS**. These include:

Intrauterine pregnancy	Pelvic infection
Septic abortion	Perforation
Ectopic pregnancy	Embedment

Table 2 shows discontinuation rates from two clinical studies by adverse event and year.

Table 2. Summary of Rates (No. per 100 Subjects) by Year for Adverse Events Causing Discontinuation

Adverse Event	Year									
	1	2	3	4	5	6	7	8	9	10
Pregnancy	0.7	0.3	0.6	0.2	0.3	0.2	0.0	0.4	0.0	0.0
Expulsion	5.7	2.5	1.6	1.2	0.3	0.0	0.6	1.7	0.2	0.4
Bleeding/Pain	11.9	9.8	7.0	3.5	3.7	2.7	3.0	2.5	2.2	3.7
Other Medical Event	2.5	2.1	1.6	1.7	0.1	0.3	1.0	0.4	0.7	0.3
No. of Women at Start of Year	4932	3149	2018	1121	872	621	563	483	423	325

*Rates were calculated by weighting the annual rates by the number of subjects starting each year for each of the Population Council (3,536 subjects) and the World Health Organization (1,396 subjects) trials.

The following adverse events have also been observed. These are listed alphabetically and not by order of frequency or severity.

Anemia	Menstrual flow, prolonged
Backache	Menstrual spotting
Dysmenorrhea	Pain and cramping
Dyspareunia	Urticarial allergic skin reaction
Expulsion, complete or partial	Vaginitis
Leukorrhea	

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TEVA WOMEN'S HEALTH

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professor of dermatology at the University of Miami.

Sinecatechins ointment 15% is a green tea extract, the chief antioxidant component of which is epigallocatechin gallate.

The systemic exposure following repeated application of the ointment is less than that resulting from drinking 400 mL of green tea.

The botanical is approved as prescription therapy for both external genital and perianal warts.

Dr. Berman highlighted several key findings from the pivotal clinical trials of the botanical, which included more than 1,000 patients.

For one, sinecatechins ointment was significantly more effective in women than in men.

Complete clearance of all warts by week 16—those present at baseline as well as all warts arising during the 16 weeks of treatment—occurred in 60.4% of women and 47.3% of men, Dr. Berman said.

The recurrence rate was remarkably low: just 6.8% during 12 weeks of follow-up after completing the 16 weeks on sinecatechins.

"Most studies of other agents have 20%-50% recurrence rates," the dermatologist noted.

Also noteworthy was the fact that the recurrence rate in the control group was even lower, at 5.9%.

"It turns out there's an irritant in the vehicle.

"Whether that has something to do with the low recurrence rate is not clear," Dr. Berman said.

A disadvantage of the sinecatechins ointment is that it needs to be applied three times daily, while imiquimod calls for application three times per week, he said. ■

Disclosures: Dr. Berman disclosed that he is a consultant to and on the speakers bureaus for 3M, Graceway Pharmaceuticals, and PharmaDerm, which markets Veregen. SDEF and this news organization are owned by Elsevier.