

CONTENTS

- ▶ External Genital and Perianal Warts: Disease Characteristics
- ▶ Sinecatechins Ointment, 15%: A Novel Treatment Option for External Genital and Perianal Warts
- ▶ Choosing the Most Appropriate Treatment Modality for External Genital and Perianal Warts: Expert Panel Commentary on Incorporating CDC Treatment Guidelines Into Current Clinical Practice

This roundtable meeting and supplement were supported by PharmaDerm, A Division of Nycomed US Inc.

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DECEMBER 2011

Management of External Genital and Perianal Warts (EGW): Proceedings of an Expert Panel Meeting

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INTRODUCTION

External genital and perianal warts (EGW) are a common clinical manifestation of human papillomavirus (HPV) infection. In January 2011, a roundtable of experts was convened to discuss current treatment standards and identify best treatment practices in light of new 2010 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases (STDs) Treatment Guidelines, including its newest recommended treatment option, sinecatechins ointment, 15% (Veregen®, PharmaDerm, Melville, NY, USA). Discussions were led by J. Thomas Cox, MD, Past-President of the American Society for Colposcopy and Cervical Pathology (ASCCP), and recently retired Director, Women's Clinic, Student Health

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continued on page 2

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The most common adverse reactions are local skin and application site reactions including (incidence ≥ 20%) erythema, pruritus, burning, pain/discomfort, erosion/ulceration, edema, induration, and vesicular rash.

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The goal of the roundtable was to discuss the practical integration of new STD treatment guidelines and therapies for EGW into current clinical practice. Discussions centered on 3

main topics: 1) EGW disease characteristics, 2) sinecatechins ointment, 15% as a novel treatment option, and 3) therapy selection in light of updated CDC treatment guidelines.

The 3 articles in this supplement summarize these discussions. ■

External Genital and Perianal Warts: Disease Characteristics

Key Points

- External genital and perianal warts (EGW) are diagnosed in more than 1 million new patients in the United States each year, and may be associated with substantial individual and societal burden
- EGW are caused by sexually transmitted human papillomavirus (HPV) types, with HPV 6 and 11 being responsible for about 90% of EGW
- The time between exposure to HPV and the development of EGW varies, with some cases occurring within 2 to 3 weeks of exposure and others only after several months or years
- EGW have high rates of spontaneous viral clearance and disease regression; however, the time to clearance varies greatly and most individuals with EGW prefer to treat them to hasten resolution

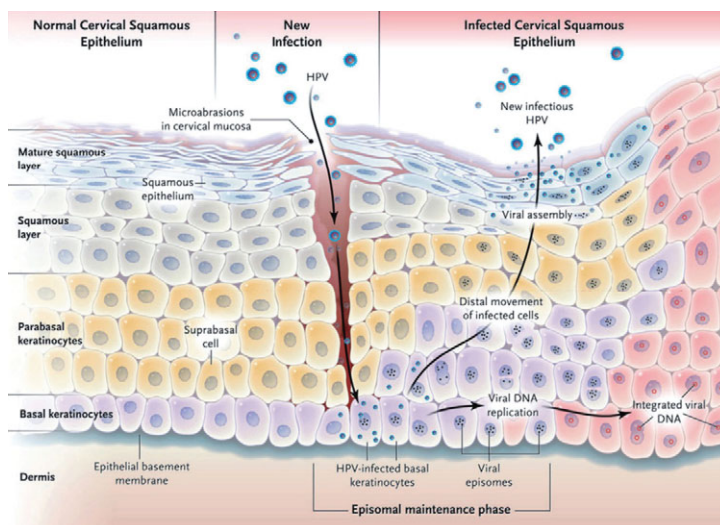
INTRODUCTION

External genital and perianal warts (EGW) are increasingly common in the United States, with more than 1 million new cases diagnosed each year, predominantly among women.^{1,2} The impact of EGW may be substantial for the individuals who contract the disease and for society. For individuals, particularly women, a diagnosis of EGW may provoke psychological and emotional distress.^{3,4} The impact to society may be considerable, with associated costs of new cases estimated to be \$171 million annually.⁵

External genital and perianal warts are a major clinical consequence of one of the most commonly acquired sexually transmitted diseases (STDs): human papillomavirus (HPV) infection.¹ An estimated prevalence in the US population indicates that 15% of adults are currently infected with HPV.⁶ In the year 2000, there were an estimated 6.2 million new HPV infections in the United States, with the majority (74% [4.6 million]) occurring among young Americans (15- to 24-year-olds).⁷ The rise in the number of patients identified with HPV disease may be attributed to increased awareness of the various manifestations of HPV disease and the increased use of HPV DNA testing.⁸ Whereas more than 150 HPV types have been characterized,⁹ 90% of genital and perianal warts are associated with HPV types 6 and 11.¹⁰⁻¹²

The process by which HPV infects and replicates is summarized in **Figure 1**.^{11,13} Briefly, HPV typically gains entry into the epithelium through sites of microabrasion from trauma, or areas naturally thin, such as the transformation zones of the cervix and anus, and infects basal keratinocytes. After a period of latency, viral DNA replication occurs in differentiating cells. As the keratinocytes mature in the upper layers of the epithelium, viral assembly of a protein capsule surrounding the DNA core creates an infective unit; the shedding of this rekindles the process of transmission and release. Because HPV does not kill its host cell, lysis of HPV-infected epithelial cells and release of viral antigen to be detected by the immune system do not typically occur in the

FIGURE 1 Transmission and life cycle of HPV^{11,13}



HPV, human papillomavirus.

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absence of trauma or treatment. Throughout this entire process, HPV remains sequestered within the epithelium. HPV is cleared via a cell-mediated immune response, allowing it to evade the host's natural immune system and limiting the innate immune response.

The time between exposure to HPV and the development of EGW varies, with some cases occurring within 2 to 3 weeks of exposure and others only after many more months or years (median 2.9 months).¹⁴ Many HPV infections are mild and transient and, with an effective immune response, will eventually resolve or regress spontaneously.⁶ However, even with treatment, the median time to resolution is 5.9 months from beginning therapy.¹⁴

A number of risk factors for HPV infectivity has been identified and includes recent change in sex partner(s), a high number of sexual partners, previous infection with herpes simplex, past history of genital warts, early age at first sexual intercourse, compromised immune status, and young age (<25 years).^{6,10} A recent study demonstrated that the incidence of high-risk HPV infection dramatically increases with the number of current and concurrent sex partners.¹⁵

CLINICAL PRESENTATION AND DIAGNOSIS

External genital and perianal warts are generally asymptomatic, but may be uncomfortable or slightly pruritic.^{2,10,16} They manifest as solitary or clustered keratotic plaques and papules on well-keratinized skin, such as the vulva, perianus, and penis, or minimally keratinized lesions on modified mucosa, such as the introitus.^{1,10,16} They are often exophytic and cauliflower-shaped, but may also be flat, papular, keratotic, or frond-like, and the color may vary (flesh-colored, white, gray, or pigmented). Many EGW are visible to the naked eye; therefore, diagnosis is made by visual inspection⁶; however, for smaller lesions, the diagnosis may be aided by bright light and magnification.¹ External genital and perianal warts, especially in younger patients, have high rates of viral clearance and disease regression—as many as 30% over 4 months and approximately 90% will clear within 2 years.^{11,17} The rate of long-term regression is currently unknown.¹⁷

SUMMARY

External genital and perianal warts are a common consequence of HPV infection that impacts individuals and society. Clinical presentation may vary; however, most EGW are visible to the naked eye and can be diagnosed by visual inspection. Although some EGW may clear spontaneously, the time to clearance varies greatly and most individuals with EGW prefer to treat them to hasten clearance. Certainly, persistent disease may require treatment. ■

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continued on page 4

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Safety and efficacy of VEREGEN® have not been established in immunosuppressed patients or patients under 18 years of age, or for the treatment of external genital and perianal warts beyond 16 weeks or for multiple treatment courses.

The most common adverse reactions are local skin and application site reactions including (incidence ≥ 20%) erythema, pruritus, burning, pain/discomfort, erosion/ulceration, edema, induration, and vesicular rash.

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Sinecatechins Ointment, 15%: A Novel Treatment Option for External Genital and Perianal Warts

Key Points

- Sinecatechins ointment, 15% is the newest therapeutic option added to the Centers for Disease Control and Prevention sexually transmitted disease treatment guidelines for treatment of external genital and perianal warts (EGW)
- Sinecatechins ointment, 15% a patient-applied prescription botanical ointment, is composed mainly of a proprietary mixture of catechins derived from leaves of the green tea plant, *Camellia sinensis* (L.) O. Kuntze
- Pooled data from 2 pivotal phase III, randomized, double-blind, placebo-controlled clinical trials demonstrated that sinecatechins ointment, 15% was associated with significantly higher rates of complete clearance of baseline and newly emerging warts, early onset of action, low recurrence rates at 12 weeks post-treatment (among those patients who experienced complete clearance), and shorter time to complete clearance of EGW compared with vehicle treatment
- Sinecatechins ointment, 15% is an effective first-line therapy for EGW

INTRODUCTION

The panel discussed sinecatechins ointment, 15% (Veregen®, PharmaDerm, Melville, NY, USA) because it is the newest therapeutic option added to the Centers for Disease Control and Prevention (CDC) sexually transmitted disease (STD) treatment guidelines for treatment of genital warts. Veregen is a topical ointment indicated for the treatment of external genital and perianal warts ([EGW] *Condylomata acuminata*) in immunocompetent patients 18 years of age or older.¹ It contains a proprietary, quantified mixture of catechins (85% to 95% by weight) and other components derived from green tea leaves (*Camellia sinensis* [L.] O. Kuntze). The main catechin in sinecatechins ointment, 15% is epigallocatechin gallate (EGCg), which comprises more than 55% of the total catechin content.¹

Catechins are an interesting group of compounds, which have

been evaluated for a wide variety of potential health benefits.^{2–4} Most notably, they have demonstrated antioxidant,^{2,3} antiviral,^{2,3} and immune-stimulatory activity.² The mechanism of action of sinecatechins ointment in the clearance of EGW is currently unknown. In vitro, sinecatechins had antioxidative activity, though the clinical significance of this finding is unknown.¹

PHARMACOKINETICS

Topically applied sinecatechins ointment is not systemically absorbed to a clinically relevant extent. Data obtained from pharmacokinetic studies show that there is minimal systemic uptake, with only 1 catechin detected; EGCg was detected in the serum in a very small number of subjects after local application of the ointment.⁵

EFFICACY

Data from 2 phase III randomized, double-blind, vehicle-controlled clinical studies support the efficacy and safety of sinecatechins ointment, 15%.^{6–8} Both studies enrolled patients 18 years of age or older with EGW. A total of 502 patients were randomized to therapy with sinecatechins ointment, 15%, sinecatechins ointment, 10%, or vehicle in Study 1⁷ and 503 patients were randomized to 1 of these 3 treatments in Study 2.⁸ Overall, 397 received sinecatechins ointment, 15% and 207 received vehicle in the combined studies.⁶ Baseline demographic and clinical characteristics were similar in the treatment groups (Table 1).⁶ Nearly half the patients randomized to sinecatechins ointment, 15% or vehicle were women (46.5%), and the mean ± SD age in both treatment groups was 31 ± 12 years. Mean ± SD baseline wart number and area were also similar in both groups (8.4 ± 6.2 vs 7.6 ± 5.0, respectively, and 98.9 ± 138.0 mm² vs 90.9 ± 97.9 mm², respectively). In both groups, ointment was applied 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts).

Pooled data analysis demonstrated that sinecatechins ointment, 15% resulted in complete clearance of baseline and newly emerging warts in 53.6% of patients ($P < .001$ vs vehicle), including 60.4% of women ($P = .010$ vs vehicle) and 47.3% of men ($P = .001$ vs vehicle) (Figure 1).^{1,9} The lower

clearance rate observed in men compared with women, also seen in studies on other topical treatments for EGW, is likely attributed to the greater skin keratinization of the penile shaft, the most common site of EGW in men, which probably affects drug penetration.^{7,8} It is noteworthy that these studies on sinecatechins ointment, 15% used a stringent/rigorous endpoint for EGW (clearance of all warts [baseline and new] vs clearance of baseline warts only). It is also important to recognize that there was a relatively high rate of complete clearance demonstrated in the vehicle group, possibly due to spontaneous disease regression.

Pooled data also demonstrated a shorter time to complete clearance with sinecatechins ointment, 15% than with vehicle treatment (Figure 2, page 6).⁹ Statistically significant differences between active and vehicle treatment groups were evident as early as Week 6 and maintained for the remainder of the treatment period. Timely wart clearance is most certainly desirable for the patient, and also may limit the duration of therapy and number of office visits.

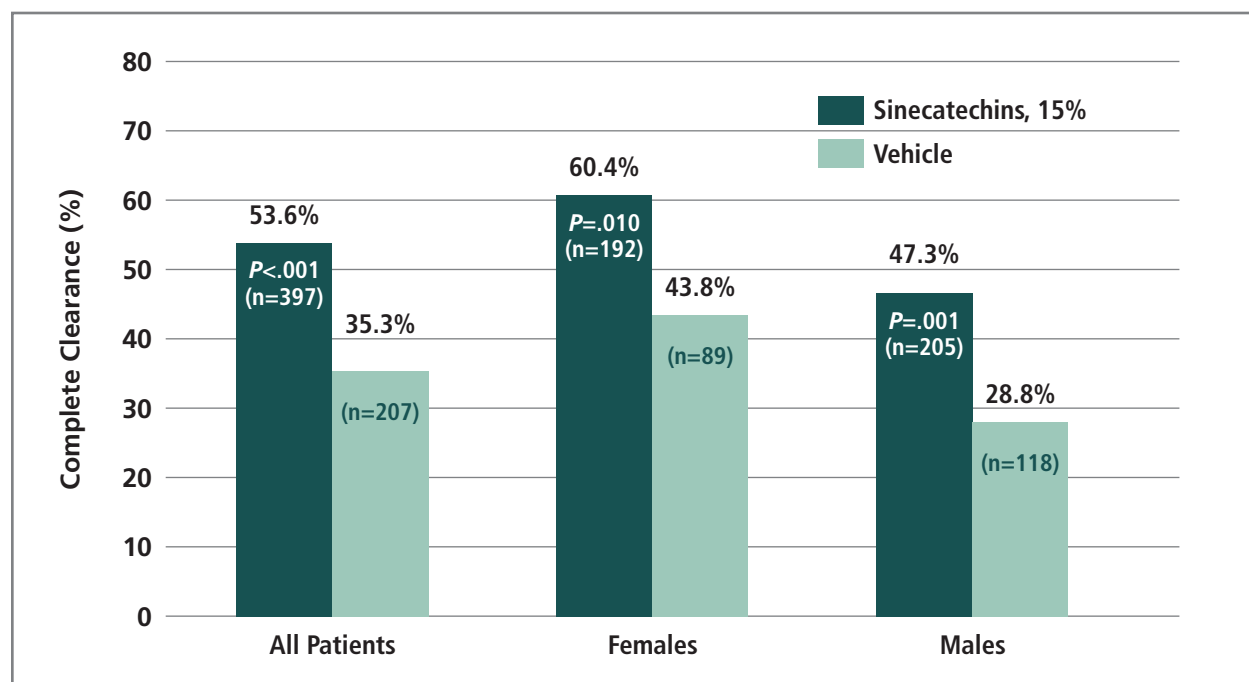
Finally, recurrence rates 12 weeks post-treatment were low in the sinecatechins ointment, 15% group. Only 6.8% of the
continued on page 7

TABLE 1 Demographic and baseline clinical characteristics of patients with EGW in sinecatechins ointment, 15% clinical trials⁶

Characteristic	Vehicle (n=207)	Sinecatechins ointment, 15% (n=397)
Mean (SD) age, years	31 (12)	31 (12)
Gender, n		
Male	118	205
Female	89	192
Race/Ethnicity, n		
Caucasian	126	248
Hispanic	72	135
African	6	11
Asian	1	1
Other	2	2
Childbearing potential (among females), n		
Yes	77	161
No	12	31
Mean (SD) total wart number	7.6 (5.0)	8.4 (6.2)
Mean (SD) total wart area, mm ²	90.9 (97.9)	98.9 (138.0)

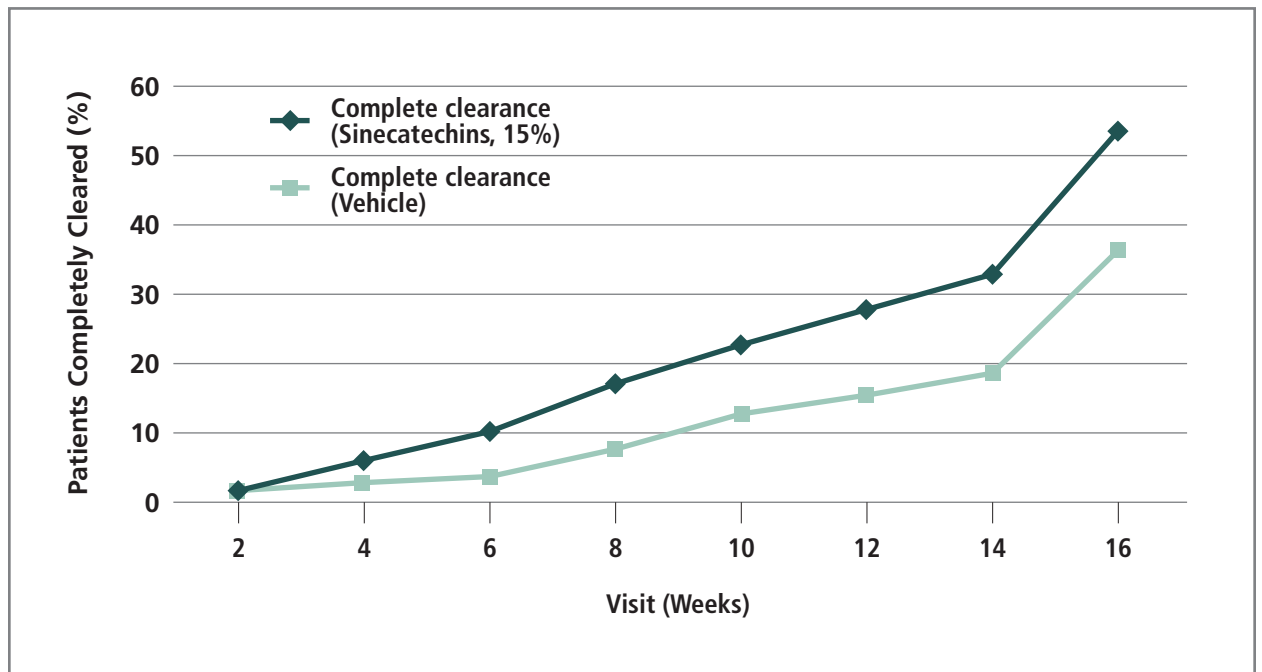
EGW, external genital and perianal warts; SD, standard deviation.

FIGURE 1 Complete clearance of baseline and newly emerging warts with sinecatechins ointment, 15% versus vehicle (full ITT analysis)^{1,9}



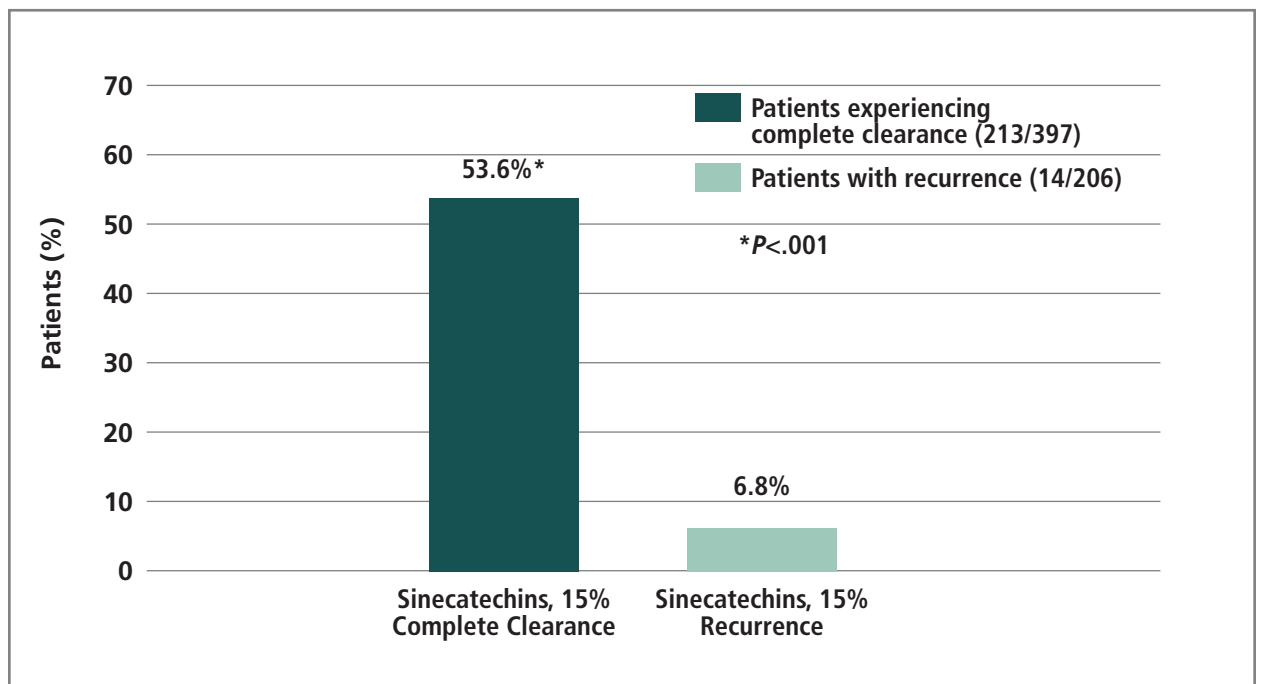
ITT, intent to treat.

FIGURE 2 Percentage of patients wart free at each visit (pooled analysis of data from 2 randomized, double-blind, vehicle-controlled studies)⁹



Complete clearance was significantly greater with sinecatechins, 15% vs vehicle beginning at Week 6 and at all subsequent visits ($P \leq .002$).

FIGURE 3 Recurrence 12 weeks post-treatment in patients with complete clearance of all warts (pooled analysis of data from 2 randomized, double-blind, vehicle-controlled studies)^{1,9}



patients who achieved complete clearance in the sinecatechins-treated group experienced recurrence 12 weeks post-treatment (Figure 3, page 6).⁶

SAFETY

Sinecatechins ointment, 15% was well tolerated in these studies.⁶ Local and regional adverse reactions are summarized in Table 2.¹ Overall, the incidence of adverse events was similar across treatment groups. Treatment with sinecatechins ointment, 15% was, however, associated with a higher incidence of any local skin reaction than those receiving the vehicle only, as would be expected (85.9% vs 60.4%, respectively).⁶ The incidence of these events peaked early during therapy and subsided during the treatment course.⁵ In order to promote patient compliance, patients should be made aware of the potential for sinecatechins ointment, 15% to induce local reactions. The most common adverse reactions were local skin and application site reactions. During clinical trials, only 2.3% of subjects discontinued therapy due to adverse events, and only 2.6% required treatment interruption or dose reduction for any period of time due to irritation.⁹

DOSAGE AND ADMINISTRATION

Sinecatechins ointment, 15% is to be applied 3 times daily to all EGW until complete clearance of all warts or for a period of up to 16 weeks.¹ Patients should be instructed to wash their hands before and after application. They should also be informed that it is not necessary to wash off the ointment from the treated area prior to the next application. Counseling should further include discussion of the potential for the ointment to weaken condoms and vaginal diaphragms.

SUMMARY

Sinecatechins ointment, 15% is an effective and generally well-tolerated patient-applied botanical alternative for EGW treatment. The studies reviewed herein dem-

TABLE 2 Local and regional adverse events in sinecatechins ointment, 15% phase III clinical trials¹

Event, %	Sinecatechins ointment, 15% (n=397)	Vehicle (n=207)
Erythema	70	32
Pruritus	69	45
Burning	67	31
Pain/discomfort	56	14
Erosion/ulceration	49	10
Edema	45	11
Induration	35	11
Vesicular rash	20	6
Regional lymphadenitis	3	1
Desquamation	5	<1
Discharge	3	<1
Bleeding	2	<1
Reaction	2	0
Scar	1	0
Irritation	1	0
Rash	1	0

onstrate that, relative to vehicle, sinecatechins ointment, 15% induces high rates of complete clearance, statistically significant early onset of action, and low rates of recurrence. We conclude that sinecatechins ointment, 15% is an effective first-line therapy for EGW. ■

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The most common adverse reactions are local skin and application site reactions including (incidence ≥ 20%) erythema, pruritus, burning, pain/discomfort, erosion/ulceration, edema, induration, and vesicular rash.

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Choosing the Most Appropriate Treatment Modality for External Genital and Perianal Warts: Expert Panel Commentary on Incorporating CDC Treatment Guidelines Into Current Clinical Practice

Key Points

- The 2010 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines include updated external genital and perianal warts (EGW) treatment recommendations, notably the addition of sinecatechins ointment, 15% as a recommended option for patient-applied EGW treatment
- Therapy selection for EGW can be influenced by a number of factors, including the number and size of warts; the anatomic site of the wart(s); wart morphology; treatment costs, effectiveness, side effects, and convenience; patient preference; and provider experience with various therapies
- According to the roundtable expert panel, the selection of appropriate EGW therapy for individual patients should be made following careful consideration of patient type and clinical presentation

INTRODUCTION

Multiple factors can influence treatment selection for patients with external genital and perianal warts (EGW). The number and size of warts; the anatomic site of the wart(s); wart morphology; treatment costs, effectiveness, side effects, and convenience;

patient preference; and provider experience with various therapies should all be considered when selecting appropriate therapy for individual patients.^{1,2} The 2010 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases (STDs) Treatment Guidelines include updated EGW treatment recommendations, most notably the addition of sinecatechins ointment, 15% as a recommended option for patient-applied treatment of EGW. Additionally, the 2010 CDC STD treatment guidelines include updated and specific recommendations for appropriate patient counseling on HPV disease and genital warts.¹ The objective of this paper is to briefly summarize the roundtable’s approach to the practical integration of the new CDC guidelines into current clinical practice.

THE GUIDELINES: A BRIEF SUMMARY

The new CDC STD treatment guidelines indicate that treatment of EGW may consist of a single treatment or a complete treatment course.¹ Recommended patient-applied therapies include podofilox gel or solution, 0.5%, imiquimod cream, 5%, and sinecatechins ointment, 15% and recommended provider-administered therapies include cryotherapy; podophyllin resin, 10%–25%; trichloroacetic acid (TCA) or bichloroacetic acid (BCA), 80%–90%; and surgery (Table 1).¹

At the time of publication of the guidelines, imiquimod cream, 3.75%, was not available; however, it is now approved by the US Food and Drug Administration and available for EGW treatment. Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir.¹

Ownership of treatment is important for many patients, and patient-applied therapies can play an important role in providing patients with a sense of control over the disease. As regimens for available patient-applied therapies vary considerably,¹ factors that could potentially facilitate or interfere

TABLE 1 Therapeutic options for the treatment of external genital and perianal warts (EGW)¹

Patient-Applied	Provider-Administered
Podofilox gel/solution	Cryotherapy
Imiquimod cream	Podophyllin resin
Sinecatechins ointment	Trichloroacetic acid or bichloroacetic acid
	Surgical removal

with compliance should be considered when selecting therapy for individual patients. Podofilox solution or gel, 0.5%, and imiquimod cream, 5%, both require intermittent application. Podofilox is applied twice daily for 3 days followed by no therapy for 4 days—a cycle that can be repeated up to 4 times. Imiquimod is applied 3 times per week (at bedtime) for up to 16 weeks, typically Monday-Wednesday-Friday or Tuesday-Thursday-Saturday. Sinecatechins ointment, 15% is applied 3 times daily for up to 16 weeks.

Goals of therapy as described in the CDC guidelines include the amelioration of symptoms and removal of warts.¹ Immune containment of the disease and reduced infectiousness are also desirable outcomes.

Specific guidelines for counseling are beyond the scope of this paper; however, the importance of educating patients and their partners about the disease and its treatment should not be overlooked. Recommendations for counseling patients with EGW in the 2010 CDC guidelines include messages regarding prognosis and transmission, with an emphasis on the prevention of spread.¹ Setting patient expectations for treatment (eg, likely length of treatment, potential for side effects/evidence of treatment effects) may also facilitate compliance with prescribed regimen.

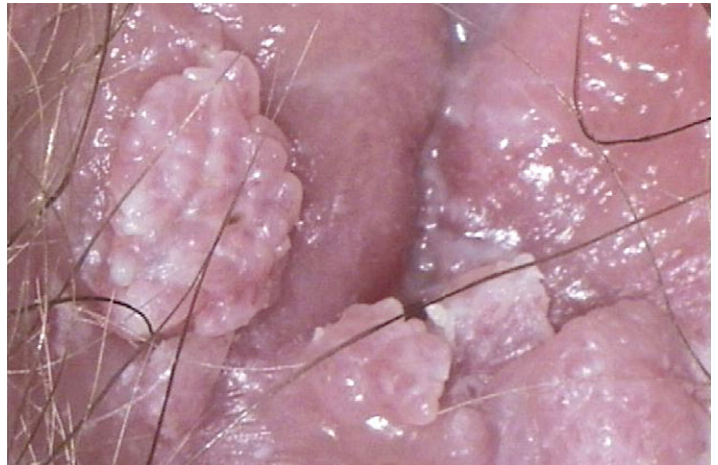
PRACTICAL APPROACH SUGGESTED BY THE ROUNDTABLE: INDIVIDUALIZED THERAPY BASED ON PATIENT TYPE AND CLINICAL PRESENTATION

Treatment-naive patients

Condyloma acuminata (Figure 1) is the most common genital wart morphology noted in treatment-naive patients; however, papules, flat warts, and other presentations are also seen. Primary treatment considerations in this population include the number and location of lesions; patient preference for in-office provider-administered treatment vs patient-applied treatments in the home setting; and the potential benefits of monotherapy versus

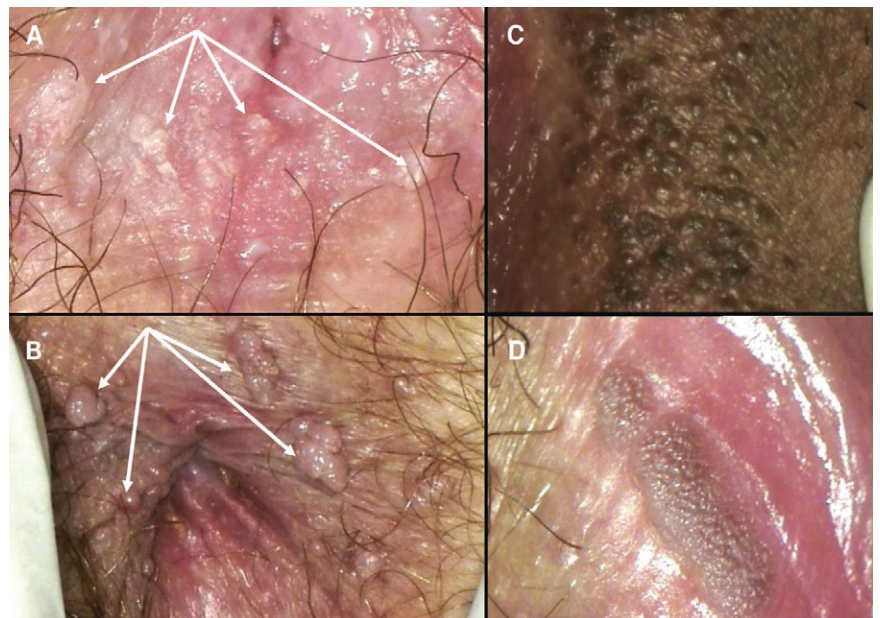
another therapeutic approach. It is best to start the treatment of a small number of warts (ie, 1–3 warts) with a provider-

FIGURE 1 *Condyloma acuminata* in a treatment-naive woman



Reprinted with permission from Medscape Education from Cox JT. Genital warts: best practices for diagnosis and management. Medscape Ob/Gyn Web site. <http://www.medscape.com/viewprogram/6385>. Published December 15, 2006. Medscape Ob/Gyn & Women's Health © 2006.

FIGURE 2 Common morphologic changes observed in patients with EGW: (A) keratinized spiky warts, (B) genital papillomas, (C) pigmented papules, and (D) flat genital warts



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FIGURE 3 Solitary lesion



Cincinnati STD/HIV Prevention Training Center. At: <http://www.stdptc.uc.edu/>. Accessed April 6, 2011. No longer accessible.

FIGURE 4 Multiple/coalescent lesions



Genital Warts Advisor Web site: <http://www.genitalwartsadvisor.com/genital-warts>. Accessed April 6, 2011.

administered therapy and switch to a patient-applied therapy if unresolved after 1 to 2 treatments. However, a large number of external lesions may be an indication for topical therapy first. A change of treatment modality is warranted in patients who have not demonstrated substantial improvement after completion of a specific course of treatment.¹ Patient-applied

therapies may also provide patients with a sense of ownership and control over the disease. The phase III clinical trials provided evidence that sinecatechins ointment, 15% is an effective first-line patient-applied treatment option.

Patients with a prior history of EGW

Patients with a prior history of EGW have often demonstrated difficulty in clearing the warts, whether by spontaneous immune suppression, or by failure to respond to previous treatments. Commonly, EGW present for a longer duration and/or failed previous therapy are more keratinized, thicker, and sometimes larger. Morphologic changes observed in patients with EGW include keratinized spiky warts, genital papillomas, flat genital warts, and pigmented papules (Figure 2, page 9). Treatment considerations for this population extend beyond number and location of warts to include disease status (persistent vs recurrent), concomitant conditions (eg, vaginal candidiasis, dermatitis), host immune status, and experience with prior treatments. Topical therapy is appropriate in cases of high-volume widely scattered lesions; however, patient-applied podofilox is not appropriate when application to an extensive area (>10 cm²) is required.¹ With this in consideration, sinecatechins ointment, 15% is a reasonable patient-applied therapy option in patients with EGW. Of course, as with treatment-naive patients, patient preference should be determined prior to institution of therapy.

Patients with solitary lesions

The primary consideration for treatment of patients with solitary lesions is wart location. Topical patient-applied therapy may be preferable if the wart is on a sensitive area, such as the clitoris (Figure 3). For less sensitive areas, single EGW may be treated with any of the patient-applied or provider-administered therapies, although careful application of TCA, a caustic agent, may potentially accelerate clearance of solitary or small numbers of EGW of various morphologies. Care must be taken to avoid inadvertent application and/or spread to adjacent normal skin, which increases pain and can occasionally result in depigmentation or scarring.

Patients with multiple/coalescent lesions

Patient-applied therapies are often good for initial treatment of multiple/coalescent lesions (Figure 4) to shrink

warts prior to considering provider-administered therapy. However, as mentioned previously, podofilox is not appropriate if the treatment area is extensive ($>10 \text{ cm}^2$).¹ Whereas the CDC treatment guidelines state that follow-up visits are not required for persons using patient-applied therapy, they do suggest that follow-up visits may be useful for assessment of treatment response and as a forum for patients to have questions answered regarding their treatment experience.¹

Biopsy may be appropriate in patients with multiple/coalescent lesions if the diagnosis is uncertain, as when lesions are pigmented or have a cobblestone appearance. Possible indications for biopsy of EGW enumerated in the CDC treatment guidelines are: 1) uncertain diagnosis; 2) failure to respond to therapy; 3) disease worsening during therapy; 4) atypical

FIGURE 5 Vulvar and introital lesions



Cincinnati STD/HIV Prevention Training Center. At: <http://www.stdptc.uc.edu/>. Accessed April 6, 2011. No longer accessible.

FIGURE 6 Perineal/perianal lesions



Reprinted with permission from DermNet Web site: <http://www.dermnet.com/Genital-Warts/picture/8070>. Image: genital-warts-121.jpg

FIGURE 7 Urethral meatal lesions



Reprinted with permission from Medscape Education from Cox JT. Genital warts: best practices for diagnosis and management. Medscape Ob/Gyn Web site. <http://www.medscape.com/viewprogram/6385>. Published December 15, 2006. Medscape Ob/Gyn & Women's Health © 2006.

lesion; 5) compromised immune status; and 6) suspect morphology (pigmented, indurated, fixed, bleeding, or ulcerated).¹ It should be noted that biopsy is also indicated when exophytic cervical warts are present.¹ Additional considerations for biopsy include patient age and Papanicolaou (Pap) test results. However, Pap tests should only be done if it is the appropriate time for the patient to receive her cervical cytology screening or unless screening is otherwise indicated, as EGW is not an indication for screening.¹

Patients with large/massive lesions should be referred

DISCLOSURES

J. Thomas Cox, MD, is a consultant to Gen-Probe and Roche and is a member of the Speakers Bureau for GlaxoSmithKline, PharmaDerm, Graceway Pharmaceuticals, and BD Diagnostics. He has received financial material support from Merck, HPV Vaccine Data and Safety Monitoring Board.

Warner Huh, MD, has received grant/research support from Merck, GlaxoSmithKline, and Roche. He is a consultant for Roche, Helix, BioPharma, Qiagen, Hologic, and Inovio.

E. J. Mayeaux, Jr, MD, is a consultant and serves on the Speakers Bureau for PharmaDerm and Merck.

Michael Randell, MD, is a consultant and serves on the Speakers Bureau for Alaven Pharmaceuticals, Cord Blood Registry, Intuitive Surgical, Merck, Myriad Genetics, OmniGuide, PharmaDerm, Qiagen, Quest Diagnostics, SurgiQuest, Teva Pharmaceuticals, Vermillion, and Watson Pharmaceuticals.

Maida Taylor, MD, is a consultant for Everett Labs, Sempra Labs, ChemoSpain, PharmaDerm, Depomed, and Boehringer Ingelheim.

This roundtable meeting and supplement were supported by PharmaDerm, A Division of Nycomed US Inc.

ACKNOWLEDGMENTS

The authors wish to thank Mary Tom, PharmD, and Malik Cobb, PA-C, for their medical writing and editorial assistance.

for appropriate provider-administered therapy, including surgical removal.

Specific considerations based on wart location

Two anatomic considerations warrant varying treatment options. One already mentioned is the need to consider the sensitivity of the area being treated. Hence, the clitoris and even the introitus may be too sensitive for some women to tolerate cryotherapy or TCA/BCA. In addition, some women who are very hypersensitive to pain may not tolerate any ablative or excisional treatment. In these situations, a patient-applied therapy is often chosen. On the contrary, some women are hypersensitive to one or more of the topical patient-applied therapies and have to abandon such therapy in favor of provider-administered treatments. Each person is individual, and therapy often has to be modified to fit the patient's tolerance issues. Intravaginal use and intra-anal use are the other anatomic considerations for which none of the topical patient-applied therapies are approved.¹

The treatment principles discussed previously essentially apply to all areas of the external genitalia, including the vulva, introitus, perineum, and perianal areas (Figures 5 and 6, page 11). If anal warts are present, cryotherapy with liquid nitrogen, TCA or BCA 80%–90%, or surgical

removal is recommended.¹ Provider-administered therapy should be considered first-line if the lesion is of a type unlikely to respond to patient-applied therapy (eg, significantly keratinized or large cauliflower-type lesions).

According to the CDC STD treatment guidelines, urethral meatal lesions (Figure 7, page 11) should be treated with provider-administered cryotherapy with liquid nitrogen or podophyllin 10%–25% in compound tincture of benzoin.¹ However, if warts are introital, patient-applied therapies may be considered, as discussed previously.

SUMMARY

Major updates to the CDC STD treatment guidelines include the addition of sinecatechins ointment, 15% as a recommended patient-applied therapy option for EGW and new counseling recommendations. These additions are clinically relevant and can be readily incorporated into current clinical practice. ■

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1. Workowski KA, Berman S. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Morb Mortal Wkly Rep.* 2010;59(RR-12):70–74.
2. Scheinfeld N, Lehman DS. An evidence-based review of medical and surgical treatments of genital warts. *Dermatol Online J.* 2006;12(3):5.

The roundtable meeting and this supplement were supported by PharmaDerm, A Division of Nycomed US Inc.

Veregen® (sinecatechins) Ointment, 15% is a topical ointment indicated for the treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years of age or older.

SAFETY INFORMATION

VEREGEN® has not been evaluated to treat urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and should not be used to treat these conditions. Avoid use of VEREGEN® on open wounds.

Avoid exposure of VEREGEN®-treated areas to sun/UV-light because VEREGEN® has not been tested under these circumstances. Safety and efficacy of VEREGEN® have not been established in immunosuppressed patients or patients under 18 years of age, or for the treatment of external genital and perianal warts beyond 16 weeks or for multiple treatment courses.

The most common adverse reactions are local skin and application site reactions including (incidence ≥ 20%) erythema, pruritus, burning, pain/discomfort, erosion/ulceration, edema, induration, and vesicular rash.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Veregen® safely and effectively. See full prescribing information for Veregen®.

Veregen® (sinecatechins) Ointment, 15%

For topical dermatologic use only

Initial U.S. Approval: 2006

INDICATIONS AND USAGE

Veregen® is a topical ointment indicated for the treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older (1.1).

Limitations of Use: Safety and effectiveness of Veregen® have not been established in immunosuppressed patients, in treatment of external genital and perianal warts beyond 16-weeks, or for multiple treatment courses (1.2).

DOSAGE AND ADMINISTRATION

- Veregen® is to be applied three times per day to all external genital and perianal warts (2.1).
- Apply about an 0.5 cm strand of ointment to each wart using the finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts (2.1).
- Veregen® is not for ophthalmic, oral, intra-vaginal, or intra-anal use (2.1).

DOSAGE FORMS AND STRENGTHS

Ointment, 15% (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Veregen® should not be used to treat urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease (5).
- Use of Veregen® on open wounds should be avoided (5).
- Avoid exposure of Veregen® treated areas to sun/UV-light as Veregen® has not been tested under these circumstances (5).

ADVERSE REACTIONS

Most common adverse reactions are local skin and application site reactions including (incidence ≥ 20%) erythema, pruritus, burning, pain/discomfort, erosion/ulceration, edema, induration, and rash vesicular (6).

To report SUSPECTED ADVERSE REACTIONS, contact PharmaDerm®, A division of Nycomed US Inc. at 1-800-929-9300 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Indication
- 1.2 Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Treatment Period

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Instructions for Use
- 17.2 FDA-Approved Patient Labeling

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indication

Veregen® is indicated for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

1.2 Limitations of Use

The safety and effectiveness of Veregen® have not been established for treatment beyond 16-weeks or for multiple treatment courses.

The safety and effectiveness of Veregen® in immunosuppressed patients have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Veregen® is to be applied three times per day to all external genital and perianal warts.

Apply about an 0.5 cm strand of the Veregen® to each wart using the finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts. Patients should wash their hands before and after application of Veregen®.

It is not necessary to wash off the ointment from the treated area prior to the next application.

Veregen® is not for ophthalmic, oral, intravaginal, or intra-anal use.

2.2 Treatment Period

Treatment with Veregen® should be continued until complete clearance of all warts, however no longer than 16 weeks.

Local skin reactions (e.g. erythema) at the treatment site are frequent. Nevertheless, treatment should be continued when the severity of the local skin reaction is acceptable.

3 DOSAGE FORMS AND STRENGTHS

Veregen® is a brown ointment and is supplied in an aluminum tube containing 15 grams (NDC # 10337-450-15) of ointment per tube.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

Veregen® has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and should not be used for the treatment of these conditions.

Use of Veregen® on open wounds should be avoided.

Patients should be advised to avoid exposure of the genital and perianal area to sun/UV-light as Veregen® has not been tested under these circumstances.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In Phase 3 clinical trials, a total of 397 subjects received Veregen® three times per day topical application for the treatment of external genital and perianal warts for up to 16 weeks.

Serious local adverse events of pain and inflammation were reported in two subjects (0.5%), both women.

In clinical trials, the incidence of patients with local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19/397). These included the following events: application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes simplex, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

Local and regional reactions (including adenopathy) occurring at >1% in the treated groups are presented in Table 1.

Table 1: Local and Regional Adverse Reactions During Treatment (% Subjects)

	Veregen® (N = 397)	Vehicle (N = 207)
Erythema	70	32
Pruritus	69	45
Burning	67	31
Pain/discomfort	56	14
Erosion/Ulceration	49	10
Edema	45	11
Induration	35	11
Rash vesicular	20	6
Regional Lymphadenitis	3	1
Desquamation	5	<1
Discharge	3	<1
Bleeding	2	<1
Reaction	2	0
Scar	1	0
Irritation	1	0
Rash	1	0

A total of 266/397 (67%) of subjects in the Veregen® group had either a moderate or a severe reaction that was considered probably related to the drug, of which 120 (30%) subjects had a severe reaction. Severe reactions occurred in 37% (71/192) of women and in 24% (49/205) of men. The percentage of subjects with at least one severe, related adverse event was 26% (86/328) for subjects with genital warts only, 42% (19/45) in subjects with both genital and perianal warts and 48% (11/23) of subjects with perianal warts only. Phimosis occurred in 3% of uncircumcised male subjects (5/174) treated with Veregen® and in 1% (1/99) in vehicle.

The maximum mean severity of erythema, erosion, edema, and induration was observed by week 2 of treatment.

Less common local adverse events included urethritis, perianal infection, pigmentation changes, dryness, eczema, hyperesthesia, necrosis, papules, and discoloration. Other less common adverse events included cervical dysplasia, pelvic pain, cutaneous facial rash, and staphylococemia.

In a dermal sensitization study of Veregen® in healthy volunteers, hypersensitivity (type IV) was observed in 5 out of 209 subjects (2.4%) under occlusive conditions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well controlled studies in pregnant women. Veregen® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The Maximum Recommended Human Dose (MRHD) of Veregen® was set at three times daily topical administration of 250 mg, 750 mg total, containing 112.5 mg sinecatechins for the animal multiple of human exposure calculations presented in this labelling. Dose multiples were calculated based on the human equivalent dose (HED).

Embryo-fetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration, respectively. Oral administration of sinecatechins during the period of organogenesis (gestational Days 6 to 15 in rats or 6 to 18 in rabbits) did not cause treatment related effects on embryo-fetal development or teratogenicity at doses of up to 1,000 mg/kg/day (86-fold MRHD in rats; 173-fold MRHD in rabbits).

In the presence of maternal toxicity (characterized by marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, subcutaneous doses of 12 and 36 mg/kg/day of sinecatechins during the period of organogenesis (gestational Days 6 to 19) resulted in corresponding influences on fetal development including reduced fetal body weights and delays in skeletal ossification. No treatment related effects on embryo-fetal development were noted at 4 mg/kg/day (0.7-fold MRHD). There was no evidence of teratogenic effects at any of the doses evaluated in this study.

A combined fertility/embryo-fetal development study using daily vaginal administration of Veregen® to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not show treatment-related effects on embryo-fetal development or teratogenicity at doses up to 0.15 mL/rat/day (8-fold MRHD).

A pre- and post-natal development study was conducted in rats using vaginal administration of Veregen® at doses of 0.05, 0.10 and 0.15 mL/rat/day from Day 6 of gestation through parturition and lactation. The high and intermediate dose levels of 0.15 (8-fold MRHD) and 0.10 mL/rat/day resulted in an increased mortality of the F₀ dams, associated with indications of parturition complications. The high dose level of 0.15 mL/rat/day also resulted in an increased incidence of stillbirths. There were no other treatment-related effects on pre- and post-natal development, growth, reproduction and fertility at any dose tested.

8.3 Nursing Mothers

It is not known whether topically applied Veregen® is excreted in breast milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

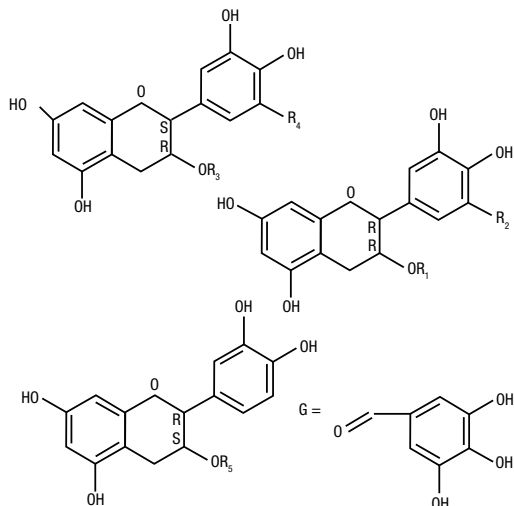
Seven patients (1.4%), older than 65 years of age were treated with Veregen® in clinical studies. This, however, is an insufficient number of subjects to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Veregen® (sinecatechins) Ointment, 15% is a botanical drug product for topical use. The drug substance in Veregen® is sinecatechins, which is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis* (L.) O Kuntze, and is a mixture of catechins and other green tea components. Catechins constitute 85 to 95% (by weight) of the total drug substance which includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg), and some additional minor catechin derivatives i.e. Galocatechin gallate (GCg), Galocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the drug substance contains undefined botanical constituents derived from green tea leaves.

The structural formulae of catechins are shown below.

General Structure of Catechins



Component	Abbrev.	R1	R2	R3	R4	R5
(-)-Epigallocatechin Gallate	(-)-EGCg	G	OH	-	-	-
(-)-Epicatechin Gallate	(-)-ECg	G	H	-	-	-
(-)-Epigallocatechin	(-)-EGC	H	OH	-	-	-
(-)-Epicatechin	(-)-EC	H	H	-	-	-
(-)-Gallocatechin Gallate	(-)-GCg	-	-	G	OH	-
(-)-Gallocatechin	(-)-GC	-	-	H	OH	-
(-)-Catechin Gallate	(-)-Cg	-	-	G	H	-
(+)-Catechin	(+)-C	-	-	-	-	H

Each gram of the ointment contains 150 mg of sin catechins in a water free ointment base consisting of isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mode of action of Veregen® involved in the clearance of genital and perianal warts is unknown. In vitro, sin catechins had anti-oxidative activity; the clinical significance of this finding is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of Veregen® is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of topically applied Veregen® has not been sufficiently characterized at this time. However, data suggest that systemic exposure to catechins after repeated topical application of Veregen® is likely to be less than observed after a single oral intake of 400 mL green tea.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral (gavage) carcinogenicity study, sin catechins was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day (22-fold MRHD; [see Use in Specific Populations (8.1)]). Treatment with sin catechins was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Veregen® has not been evaluated in a dermal carcinogenicity study. Sin catechins was negative in the Ames test, in vivo rat micronucleus assay, UDS test, and transgenic mouse mutation assay, but positive in the mouse lymphoma mutation assay. Daily vaginal administration of Veregen® to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not cause adverse effects on mating performance and fertility at doses up to 0.15 mL/rat/day. This dose corresponds to approximately 150 mg/rat/day (8-fold MRHD).

14 CLINICAL STUDIES

Two randomized, double-blind, vehicle-controlled studies were performed to investigate the safety and efficacy of Veregen® in the treatment of immunocompetent patients 18 years of age and older with external genital and perianal warts. The subjects applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment).

Over both studies the median baseline wart area was 51 mm² (range 12 to 585 mm²), and the median baseline number of warts was 6 (range 2 to 30).

The primary efficacy outcome measure was the response rate defined as the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16, presented in Tables 2 and 3 for all randomized subjects dispensed medication.

Table 2: Efficacy by Region

	Complete Clearance
All Countries (includes the United States)	
Veregen® 15% (N = 397)	213 (53.6%)
Vehicle (N = 207)	73 (35.3%)
United States	
Veregen® 15% (N = 21)	5 (23.8%)
Vehicle (N = 9)	0 (0.0%)

Table 3: Efficacy by Gender

	Complete Clearance
Males	
Veregen® 15% (N = 205)	97 (47.3%)
Vehicle (N = 118)	34 (28.8%)
Females	
Veregen® 15% (N = 192)	116 (60.4%)
Vehicle (N = 89)	39 (43.8%)

Median time to complete wart clearance was 16 weeks and 10 weeks, respectively, in the two phase 3 clinical trials.

The rate of recurrence of external genital and perianal warts 12 weeks after completion of treatment in subjects with complete clearance is 6.8% (14/206) for those treated with Veregen® and 5.8% (4/69) for those treated with vehicle.

16 HOW SUPPLIED/STORAGE AND HANDLING

Veregen® is a brown ointment and is supplied in an aluminum tube containing 15 grams (NDC # 10337-450-15) of ointment per tube.

Prior to dispensing to the patient, store refrigerated 2°C to 8°C (36°F to 46°F). After dispensing, store refrigerated or up to 25°C (77°F). Do not freeze.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (17.2)

17.1 Instructions for Use

Patients using Veregen® should receive the following information and instructions:

- This medication is only to be used as directed by a physician. It is for external use only. Eye contact should be avoided as well as application into the vagina or anus.
- It is not necessary to wash off Veregen® prior to the next application. When the treatment area is washed or a bath is taken, the ointment should be applied afterwards.
- It is common for patients to experience local skin reactions such as erythema, erosion, edema, itching, and burning at the site of application. Severe skin reactions can occur and should be promptly reported to the healthcare provider. Should severe local skin reaction occur, the ointment should be removed by washing the treatment area with mild soap and water, and further doses withheld.
- Sexual (genital, anal or oral) contact should be avoided while the ointment is on the skin, or the ointment should be washed off prior to these activities. Veregen® may weaken condoms and vaginal diaphragms. Therefore, the use in combination with Veregen® is not recommended.
- Female patients using tampons should insert the tampon before applying the ointment. If the tampon is changed while the ointment is on the skin, accidental application of the ointment into the vagina must be avoided.
- Veregen® may stain clothing and bedding.
- Veregen® is not a cure and new warts might develop during or after a course of therapy. If new warts develop during the 16-week treatment period, these should also be treated with Veregen®.
- The effect of Veregen® on the transmission of genital/perianal warts is unknown.
- Patients should be advised to avoid exposure of the genital and perianal area to sun/UV light as Veregen® has not been tested under these circumstances.
- The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
- Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

17.2 FDA-Approved Patient Labeling

PATIENT INFORMATION

Veregen® (sin catechins) Ointment, 15% Rx Only

Read this leaflet carefully before you start using Veregen® Ointment, 15% and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. If you have any questions about Veregen® Ointment, 15% or your condition ask your doctor or pharmacist. Only your doctor can prescribe Veregen® and determine if it is right for you.

What is Veregen® Ointment, 15%?

Veregen® Ointment, 15% is a medicine for skin use only (topical) for the treatment of warts on the outside of the genitals and around the outside of the anus. It is not a treatment for warts in the vagina, cervix, or inside the anus. Your doctor may recommend examination and screening tests (such as a Pap smear) to evaluate these areas.

Who should not use Veregen® Ointment, 15%?

Do not use Veregen® Ointment, 15% if you are **allergic** to an ingredient in Veregen® Ointment, 15%. **The list of ingredients is at the end of this leaflet.**

What should I tell my doctor before using Veregen® Ointment, 15%?

Tell your doctor about all your health conditions and all the medicines you take including prescription, over-the-counter medicine, vitamins, supplements, and herbals. Be sure to tell your doctor if you are:

- **pregnant or planning to become pregnant**, as it is not known if Veregen® Ointment, 15% can harm your unborn baby. Your doctor will determine whether the benefit outweighs the risk.
- **breastfeeding**, as it is not known if Veregen® Ointment, 15% can pass into your milk and if it can harm your baby.
- **using any other type of skin product or have open wounds on the area to be treated**. Veregen® Ointment, 15% should not be used until your skin has healed from other treatments applied to the same area.
- **immunocompromised**. This means that your immune system cannot fight infections as well as it should.

How should I use Veregen® Ointment, 15%?

- Use Veregen® Ointment, 15% only on the area affected **exactly** as prescribed by your doctor.
- **Wash your hands before and after application of Veregen® Ointment, 15%**. A small amount of the ointment should be applied to all warts using your finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts as directed by your doctor.
- **Apply Veregen® Ointment, 15% three times per day—in the morning, at noontime and in the evening**.
- Do not wash off the ointment from the treated area before the next application. When you wash the treatment area or bathe, apply the ointment afterwards.
- Treatment with Veregen® Ointment, 15% should be continued until complete clearance of all warts, however **no longer than 16 weeks**. If your warts do not go away, or if they come back after treatment call your doctor.
- Veregen® Ointment, 15% is not a cure for warts on your genitals or around your anus with certainty. New warts may develop during or after treatment, and may need treatment.

What should I avoid while using Veregen® Ointment, 15%?

- Do not apply Veregen® Ointment, 15% on open wounds or into the vagina or into the anus.
- Genital warts are a sexually transmitted disease, and you may infect your partner.
- Avoid sexual contact (genital, anal or oral) when Veregen® Ointment, 15% is on your genital or perianal skin. If you do choose to have sexual contact, you must wash off the ointment carefully before having protected sexual contact as the ointment may weaken condoms and vaginal diaphragms. Talk to your doctor about safe sex practices.
- Avoid contact with your eyes, nostrils and mouth while ointment is on your finger(s).
- Women using tampons: insert the tampon before applying the ointment. If you need to change your tampon while the ointment is on your skin, avoid getting the ointment into the vagina.
- Uncircumcised men treating warts under the foreskin should retract the foreskin and clean the area daily.
- Do not expose the genital area treated with Veregen® Ointment, 15% to sunlight, sunlamps or tanning beds.
- Do not cover the treated area. Loose-fitting undergarments can be worn after applying Veregen® Ointment, 15%.
- Veregen® Ointment, 15% may stain your light colored clothes and bedding. It is recommended to wear darker colored undergarments while using Veregen® Ointment, 15%.

What are the possible side effects of Veregen® Ointment, 15%?

The most common side effects with Veregen® Ointment, 15% are local skin and application site reactions including:

- redness
- swelling
- sores or blisters
- burning
- itching
- pain

Many patients experience itching, reddening or swelling on or around the application site during the course of treatment. Some of these side effects could be a sign of an allergic reaction. If you experience open sores or other severe reactions at the locations you applied Veregen® Ointment, 15%, stop treatment and call your doctor right away.

You may experience other side effects of Veregen® Ointment, 15%, which are not mentioned here. Ask your doctor or pharmacist for more information.

Patients should be aware that new warts may develop during treatment as Veregen® Ointment, 15% is not a cure.

How should I store Veregen® Ointment, 15%?

- Store Veregen® Ointment, 15% refrigerated or up to 77°F (25°C).
- Do not freeze.
- Make sure the cap on the tube is tightly closed.
- Safely throw away Veregen® Ointment, 15% tubes that are out of date or are empty.

Keep Veregen® Ointment, 15% and all medicines out of the reach of children.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Veregen® Ointment, 15% for a condition for which it was not prescribed. Do not give Veregen® Ointment, 15% to other people, even if they have the same symptoms you have. It may harm them. Do not use Veregen® Ointment, 15% after the expiration date on the tube.

This leaflet summarizes the most important information about Veregen® Ointment, 15%. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Veregen® Ointment, 15% that is written for the doctor.

What are the ingredients in Veregen® Ointment, 15%?

Active ingredient:

A defined green tea extract named sinecatechins.

Inactive ingredients:

Isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

Veregen® is a registered trademark of MediGene AG, D-82152 Planegg/Martinsried, Germany.

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U.S. Patent Nos. 5795911 and 5968973