



Therapeutic Class ReviewSM

Skin – sinecatechins ointment (Veregen[®])

June 2008

New Product for Review:

Sinacatechins ointment
(Veregen[®])[MediGene]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 2, missing PE model and Phase
2 comparative trial data

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Executive Summary

External Genital Warts (EGWs) ^[8,13,14]

- EGWs (condylomata acuminata) are benign skin tumors usually caused by infection with human papillomavirus (HPV) types 6 and 11 that affect approximately 1% of the sexually active population. These virus types are rarely associated with invasive carcinoma.
- Most infections are subclinical (visible warts represent only 1% of infected cases) and transient (less than 2 years duration). Spontaneous regression has been reported to occur within three months in 20 to 30% of cases.
- Principles of treatment
 - The primary goal of treatment is the removal of EGWs.
 - Treatment does not eliminate HPV infection and has an unclear impact on transmission of disease.
 - There is no evidence that the presence of EGWs or their treatment is associated with the development of cervical cancer.
 - If untreated, EGWs might spontaneously resolve, remain unchanged, or increase in size or number.
 - Treatment modality is guided by location of lesions and extent of area involved. Extensive disease is treated with various office-based procedures. Only limited disease can be managed at home by the patient.
 - Clinical practice guidelines and meta-analysis position podofilox and imiquimod as drugs of choice for patient-applied treatment of EGWs. However, these recommendations may be based on trials of uncertain validity.

Sinacatechins (Veregen)

- Sinecatechins ointment (Veregen) is a water extract of green tea leaves containing a mixture of catechins (85-95%) and other green tea components such as gallic acid, caffeine, theophylline and theobromine. It is brown in appearance and contains 150mg of sinecatechins per gram in an ointment base.
- Sinecatechins ointment (Veregen) was approved in October 2006 for the topical treatment of EGWs in immunocompetent adults. Approval was based on pooled results of two clinical trials^[1,6] evaluating the ability of sinecatechins ointment (Veregen) to completely clear EGWs in a significantly higher proportion of subjects compared to placebo.
- Reports of early trials in actinic keratosis and common warts may result in off-label use in these conditions^[5]. Use in common and plantar warts may exceed use in EGWs, based on usage data obtained in late 2002 for a competitor product (Aldara). At the time of report, more than half of Aldara prescriptions are for off-label use in the treatment of common or plantar warts.^[4]

Evidence

- Three randomized, double-blind, placebo-controlled clinical trials conducted in several countries evaluated the efficacy and safety of sinecatechins ointment (Veregen) in a total of 1,246 subjects with EGWs.^[1,6,10]
- All of these trials were critiqued as uncertain or not useful for making healthcare decisions; low trial completion rates, lack of ITT analyses and low compliance with treatment were among the common problems.
- In these trials, a significantly higher proportion of subjects assigned to treatment with the marketed formulation [15% ointment] of sinecatechins ointment (Veregen) experienced complete clearance of EGWs compared to placebo (approximately 56% vs 36%).

Decision

Sinacatechins (Veregen) is non-preferred/non-formulary because:

- There is no reliable evidence of superior safety or efficacy over the current preferred/formulary option.
- There is potential for off-label use in common and plantar warts, for which there is no reliable evidence of safety and efficacy.

Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^{d [4,5]}
Sinacatechins (Veregen)	10/2006	10/2017	Condyloma acuminatum (aka EGW)	Apply topically 3 times daily	Actinic keratosis, common warts, plantar warts
Imiquimod (Aldara)	2/1997	1/2008 (no generic available as of 4/9/2008) ^d	Condyloma acuminatum, actinic keratosis, superficial basal cell carcinoma	Apply topically 3 times per week	Common warts, plantar warts, lentigo maligna, molluscum contagiosum infection
Podofilox (generics)	1/2002	expired	Condyloma acuminatum	Apply topically once or twice daily for 3 days, rest for 4 days, repeat cycle up to 3 more times.	None listed

^a Date applies to approval date for the original brand name medication where there are now generics available.

^c Based on patents listed in Orange Book as of 04/09/2008.

^d As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

References

1. Product dossier: Polyphenon E ointment, 15% [Veregen[®]], MediGene, Planegg/Martinsried, Germany. Data reviewed April 2008.
2. Veregen (kunecatechins) prescribing information. MediGene AG. D-82152 Planegg/Martinsried, Germany, Oct 2006.
3. MediGene AG obtains approval of Polyphenon[®] E ointment in the USA. News release [page on the internet] Available at <http://www.medigene.de/englisch/pressemitteilungen.php?ID=2158> Accessed 1/3/2007.
4. TRG Therapeutic Class Summary, Dermatology Agents: Wart Removal Agents, December 2002.
5. MediGene announces phase 2 trial results of Polyphenon[®] E for treatment of actinic keratosis. News release [page on the internet] Available at <http://www.medigene.de/englisch/pressemitteilungen.php?ID=1905> Accessed 1/3/2007.
6. Stockfleth E, Beti H, Orasan R, Grigorian F, Mescheder A, Tawfik H, Thielert C. Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. *Br J Dermatol* 2008 Mar 20 [epub ahead of print].
7. Yan J, Chen SL, Wang HN, Wu TX. Meta-analysis of 5% imiquimod and 0.5% podophyllotoxin in the treatment of condylomata acuminata. *Dermatology* 2006;213(3):218-23.
8. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR 2006;55(RR-11):1-66.
9. Codner CM, Nasraty S. Management of Genital Warts. *Am Fam Physician*. 2004 Dec 15;70(12):2335-42.
10. Gross G, Meyer K-G, Pres H, Thielert C, Tawfik H, Mescheder A. A randomized, double-blind, four-arm parallel-group, placebo-controlled Phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. *J Eur Acad Dermatol Venereol* 2007 Nov;21(10):1404-12.
11. Drugs@FDA [page on the internet]. Label and approval history for Veregen. Available at: <http://accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetail>. Accessed 1/2/2007.
12. Aldara (imiquimod) prescribing information. Graceway Pharmaceuticals, Bristol, TN, 2007.
13. UpToDate. UpToDate 15.1 [online]. 2007. Available at <http://www.utdol.com>. Accessed February 28, 2007.
14. British Association for Sexual Health and HIV. Sexually Transmitted Infections in Primary Care. London, UK: Royal College of General Practitioners. 2006 March. Available at: http://www.rcgp.org.uk/PDF/clinspec_STI_in_primary_care_NLazaro.pdf. Accessed April 23, 2008.