**DESCRIPTION**

Veregen® is a topical drug product for topical use. The drug substance in Veregen® is ointment, which is a partially purified fraction of the water-soluble part of green teas from Camellia sinensis (L.) Kuntze, if 2 to 3 leaves, and is a mixture of catechins and other green tea components. Catechins constitute 65 to 85% by weight of the total drug substance, which includes more than 5% of (-)-Epigallocatechin gallate (EGCG), other catechin-based substances such as (-)-Gallocatechin gallate, (-)-Epigallocatechin (EGC), (-)-Gallocatechin (GC), and (-)-Epicatechin (EC). In addition to its leaves, catechin-based components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2 to 3% of the drug substance. The remaining amount of the drug substance contains undescribed botanical constituents derived from green tea leaves.

The structural formulae of catechins are shown below.

**General Structure of Catechins**

**Components**

- (-)-Epigallocatechin (EGC) (5,7,4'-trihydroxy-3',5'-dimethoxy-3-(3,4-dihydroxyphenyl)-6-(3,4-dihydroxyphenyl)-2-pyridone)
- (-)-Epigallocatechin gallate (EGCG) (5,7,4'-trihydroxy-3',5'-dimethoxy-3-(3,4-dihydroxyphenyl)-6-(3,4-dihydroxyphenyl)-2-pyridone)
- (-)-Epicatechin (EC) (3,4-dihydroxy-5-(3,4-dihydroxyphenyl)-2-pyridone)
- (-)-Gallocatechin (GC) (5,7-dihydroxy-3',5'-dimethoxy-3-(3,4-dihydroxyphenyl)-2-pyridone)
- (-)-Catechin (C) (5,7-dihydroxy-3-(3,4-dihydroxyphenyl)-2-pyridone)

Each gram of the ointment contains 120 mg of catechins in a water-free base consisting of isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

**Pharmacology**

**Pharmacodynamics**

Veregen® is indicated for the topical treatment of external genital and perianal warts (Condylomata acuminata) in immunocompetent patients 18 years of age and older with external genital and perianal warts (baseline and new) by week 16, presented in Tables 1 and 2 for all randomized subjects dispensed medication.

**Pharmacokinetics**

The mode of action of Veregen® is not known. Catechins constitute 85 to 95% (by weight) of the total drug substance, which includes more than 5% of (-)-Epigallocatechin gallate (EGCG), other catechin-based substances such as (-)-Gallocatechin gallate, (-)-Epigallocatechin (EGC), (-)-Gallocatechin (GC), and (-)-Epicatechin (EC). In addition to its leaves, catechin-based components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2 to 3% of the drug substance. The remaining amount of the drug substance contains undescribed botanical constituents derived from green tea leaves.

**Clinical Pharmacology**

**Pharmacodynamics**

The pharmacodynamics of topically applied Veregen® have not been sufficiently characterized at this time. However, data suggest that patients experience greater clearance of warts after repeated topical application of Veregen® than 15% to 18% with the use of a single inert vehicle at 40 to 60 times the dose.

**Pharmacokinetics**

In an oral (gavage) carcinogenicity study, sinecatechins was administered daily for 2 years at 0.25, 0.50 and 1.0 mg/kg/day (87-fold MRHD in rats; 173-fold MRHD in rabbits) to male and female rabbits. Female rabbits were dosed from Day 4 of gestation through lactation. At 0.25 mg/kg/day, no treatment-related effects on pre- and post-natal development, growth, or survival were observed. At 0.50 mg/kg/day, female rabbits had reductions in litter size and postnatal body weights of up to 40%. Fetal body weights were also reduced at 1.0 mg/kg/day. Administration of sinecatechins was associated with reduced fetal body weights and delays in fetal development at doses of up to 1,200 mg/kg/day (86-fold MRHD in rats; 173-fold MRHD in rabbits) and no evidence of teratogenicity or any of the differences observed in the mouse study.

A combined fertility and early-fetal development study using orally administered sinecatechins revealed no evidence of a teratogenic effect in pregnant rats. No evidence of adverse effects on pre- and post-natal development were observed. Administration of sinecatechins from Day 4 of gestation through parturition and lactation. The high and intermediate dose levels (0.05, 0.10 and 0.15 mL/rat/day) increased in a concentration-related manner the incidence of stillbirths and resorptions. The high dose level of 0.15 mL/rat/day also resulted in an increased incidence of amniotic fluid. These results were not related to early fetal death but did cause adverse effects on the development and function of the placenta, reproduction and fertility at any dose tested.

There are adequate and well-controlled studies in pregnant women. Veregen® is an ointment that is likely to be excreted into milk. The safety and efficacy of Veregen® in lactating woman are unknown.

**INDICATION AND USAGE**

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

**CONTRAINDICATIONS**

Veregen® is contraindicated in patients with a history of sensitivity reactions to any of the components of the ointment. In case of hypersensitivity, treatment should be discontinued.

**WARNINGS**

Veregen® has not been evaluated for the treatment of condyloma, intra-venous, rectal and perianal papillomatous lesions, and should not be used for the treatment of these conditions.

**PRECAUTIONS**

**General**

Use of Veregen® open wounds should be avoided. For topical dermatologic use only.

Safety and efficacy have not been established for Veregen® in the treatment of dendritic skin lesions, molluscum contagiosum, or in the treatment of non-papillomatous lesions of the skin.

Patients should be advised to wear eye protection of the genital and perianal area to avoid ocular irritation.

**Information for Patients**

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

1. This medication is only to be used as directed by a physician. It is not for external use on lesions of the eyelid or oral mucosal areas as an application to the skin is not intended.

2. It is not necessary to shave off warts prior to the next application. When the treatment area is washed or a bath is taken, the treatment area should be applied with the ointment.

3. It is common for patients to experience local skin reactions such as erythema, pruritus, burning, dryness, and skin irritation. Local skin reactions such as erythema can occur and should be promptly reported to the healthcare provider.

4. The treatment area should be cleansed and patted dry before applying the ointment. If the tampon is changed while the ointment is on the skin, the ointment should be washed off prior to its use. Veregen® may weaken condoms and vaginal diaphragms. Therefore, Veregen® should be used in combination with birth control in women is not recommended.

5. Female patients using contraceptive agents should consider insertion the tampons before applying the ointment. If the tampon is changed while the ointment is on the skin, the accidental exposure of the genital area to Veregen® should be promptly reported to the healthcare provider.

6. Sexual intercourse or oral contact should be avoided until the ointment on the skin, or the ointment should be washed off prior to its use. Veregen® may weaken condoms and vaginal diaphragms. Therefore, Veregen® should be used in combination with birth control in women is not recommended.

7. It is common for patients to experience local skin reactions such as erythema, pruritus, burning, dryness, and skin irritation. Local skin reactions such as erythema can occur and should be promptly reported to the healthcare provider.

8. Veregen® may cause eye irritation and conjunctivitis. Therefore, Veregen® should be used in combination with birth control in women is not recommended.

9. Local skin reactions in the form of a lesion is not related to a lesion of the skin under consideration.

10. 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 warts should be treated with Veregen®.

11. The treatment area should not be handled or otherwise covered or concealed as ointment is applied.

12. Uncircumcised males treating warts under the foreskin should retract the foreskin.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

The Microtest (Recombinant Human Dose) of Veregen® Ointment, 15% was not assayed for carcinogenic potential in long-term studies. The highest dose of 123.5 mg sinecatechins for the maximal multiple of human exposure calculations per day, based on these data, was 0.2% of the human exposure dose (HED).

**CLINICAL STUDIES**

Two Phase 3 randomized, double-blind, vehicle-controlled studies were performed to evaluate the safety and efficacy of Veregen® Ointment in the treatment of immunocompromised patients 15 years of age and older with external genital and perianal warts. The study subjects applied the ointment 3 times daily for 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment). Both studies met the median baseline area was 15 mm$^2$ range 12 to 506 mm$^2$), the median baseline number of warts was 3 (range 1 to 32).

The primary efficacy outcome was the response rate defined as the proportion of patients with complete clinical clearance of all external genital and perianal warts and new warts occurring during week 16. Both studies reported a complete clearance in 11.1% (3) of the 27 patients at baseline. The response rate observed in the clinical trials of a drug cannot be directly compared to rates in different populations. Veregen® Ointment, 15% was not evaluated in a similar study in children. Veregen® Ointment, 15% is not recommended for use in children.

**Pediatric Use**

Veregen® Ointment, 15% has not been studied under these circumstances. Veregen® Ointment, 15% is not recommended for use in children.

**ADVERSE REACTIONS**

**Local Skin Reactions**

In the phase 3 clinical trials, a total of 172 subjects received Veregen® Ointment, 15% through week 16. There were no other treatment-related effects on pre- and post-natal development, growth, or survival were observed. The safety and efficacy of Veregen® in lactating woman are unknown.

**Pediatric Use**

Veregen® Ointment, 15% has not been tested under these circumstances. Veregen® Ointment, 15% is not recommended for use in children.

Side effects that were observed in the clinical trials include erythema, dryness, and pruritus. There were no other treatment-related effects on pre- and post-natal development, growth, or survival were observed. The safety and efficacy of Veregen® in lactating woman are unknown.
**Patient Information**

**VEREGEN (sinecatechins) Ointment, 15% Rx Only**

Read this leaflet carefully before you start using Veregen® Ointment, 15%, and each time you use your ointment. There may be new information on this leaflet. What should I tell my doctor before taking veregen®?

- **Uncircumcised men** treating warts under the foreskin should retract the foreskin
- **Women using tampons**: Insert the tampon before applying the ointment. If you
- **Avoid** contact with your eyes, nostrils and mouth while ointment is on your
- **Avoid sexual contact (genital, anal or oral)** when Veregen
- **As it is not known if Veregen

**How should I use veregen®?**

- **Do not apply Veregen
- **Do not** cover the treated area. Loose-fitting underwear can be worn after
- **Take your doctor before taking Veregen®. Tell your doctor about all your health conditions and all the medicines you take includ-
- **Regional Lymphadenitis**

<table>
<thead>
<tr>
<th>Local and Regional Adverse Reactions During Treatment (as % of Subjects)</th>
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<tbody>
<tr>
<td><strong>Reaction</strong></td>
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<td>-----------------</td>
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<td>Burning</td>
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<td>Pruritus</td>
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<td>Erythema</td>
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<td>Discharge</td>
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<td>Reaction</td>
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**What is veregen®? Veregen® Ointment, 15% is a medicine for skin only. It is used for the treatment of genital, anal and perianal warts and is usually applied to the skin for 16 weeks. 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®?**

- **Pregnant or planning to become pregnant, or breastfeeding.**
- **Avoid** sexual contact (genital, anal or oral) when Veregen
- **Applying** Veregen® Ointment, 15% three times per day — in the morning, at
- **Regional Lymphadenitis**

**How should I use veregen®? Veregen® Ointment, 15% only on the area affected as prescribed by your doctor.

- **Avoid** contact with your eyes, nostrils and mouth while ointment is on your
- **Avoid** sexual contact (genital, anal or oral) when Veregen
- **Do not** apply Veregen

**What are the ingredients in veregen®?**

- **Inactive ingredients**: Water, Isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmito...