APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

VEREGEN™ 10 % ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of the ointment contains 100 mg of sinecatechins extract (as dry extract, refined) from Camellia sinensis (L.) O. Kuntze, folium (green tea leaf) (24-56:1), corresponding to: 55-72 mg of (-)-epigallocatechingallate.

First extraction solvent: water

Excipient(s) with known effect:

1 g of ointment contains:

50 mg Propylene glycol monopalmitostearate

350 mg Isopropyl myristate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ointment

Brown, smooth ointment, free from gritty particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VEREGEN™ is indicated for the cutaneous treatment of external genital and perianal warts (*condylomataacuminata*) in immunocompetent patients from the age of 18 years.

4.2 Posology and method of administration

Posology for adults

Up to 250 mg **VEREGEN** ointment as total single dose, corresponding to about 0.5 cm of ointment strand, to be applied three times per day to all external genital and perianal warts (750 mg total daily dose).

Duration of use

Treatment with **VEREGEN** should be continued until complete clearance of all warts, however, no longer than 16 weeks, even if new warts develop during the treatment period.

Paediatric population

The safety and efficacy of **VEREGEN** in children and adolescents below the age of 18 years have not been investigated. No data are available.

Older people

An insufficient number of older people were treated with **VEREGEN** ointment to determine whether they respond differently from younger subjects.

Patients with hepatic impairment

Patients with severe liver dysfunction (e.g. clinically relevant elevation of liver enzymes, increase of bilirubin, increase of INR) should not use **VEREGEN** due to insufficient safety data. (see sections 4.4 and 4.8).

Method of administration

A small amount of **VEREGEN** should be applied to each wart using the fingers, dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts (max. 250 mg in total for all warts/ per single dose).
Only apply to affected areas; any application into the vagina, urethra or anus must be avoided.
Do not apply to mucous membranes.
For cutaneous use only.

If a dose is missed, the patient should continue with the normal treatment regimen.

It is recommended to wash the 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** should be washed off the treated area before sexual activity.

Female patients using tampons should insert the tampon before applying **VEREGEN**.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Avoid contact with the eyes, nostrils, lips and mouth.

VEREGEN should not be applied to open wounds, broken or inflamed skin.

Therapy with **VEREGEN** is not recommended until the skin has completely healed from any previous surgical or drug treatment.

VEREGEN has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal or intra-anal warts and must not be used for the treatment of these conditions.

Female patients with genital warts in the vulvar region should use the ointment with caution as treatment in this area is associated more often with severe local adverse reactions (see section 4.8). Accidental application into the vagina must be avoided. In case of accidental application into the vagina immediately wash off the ointment with warm water and mild soap.

Uncircumcised male patients treating warts under the foreskin should retract the foreskin and clean the area daily to prevent phimosis. When early signs of

stricture occur (e.g. ulceration, induration or increasing difficulty in retracting the foreskin) the treatment should be stopped.

New warts may develop during treatment.

Condoms should be used until complete clearance of all warts as **VEREGEN** does not eliminate the HPV-virus and does not prevent transmission of the disease.

VEREGEN may weaken condoms and vaginal diaphragms. Therefore, the ointment should be washed off the treated area before the use of condoms and sexual contact. Additional methods of contraception should be considered.

If the sexual partner of the patient is infected, treatment of the partner is advisable to prevent re-infection of the patient.

Do not expose the treated area to sunlight or UV irradiation, as **VEREGEN** has not been tested under these conditions.

The use of an occlusive dressing should be avoided (see section 4.8).

VEREGEN stains clothing and bedding.

Mild local skin reactions such as erythema, pruritus, irritation (mostly burning), pain and oedema at the site of application are very common and should not lead to discontinuation. They should decrease after the first weeks of treatment (see section 4.8).

An interruption of the treatment may be indicated in case of more intense local skin reaction causing unacceptable discomfort or increase in severity or associated with a lymph node reaction. The treatment with **VEREGEN** can be resumed after the skin reaction has diminished.

In case a vesicular local reaction occurs, the patient should be advised to consult a doctor to exclude a genital herpes infection.

The effectiveness and safety in patients taking immunomodulatory medicines have not been investigated. Those patients should not use **VEREGEN** ointment.

The safety and effectiveness for treatment beyond 16 weeks or for multiple treatment courses have not been investigated.

Patients with severe liver dysfunction (e.g. clinically relevant elevation of liver enzymes, increase of bilirubin, increase of INR) should not use **VEREGEN** due to insufficient safety data. (see section 4.8).

VEREGEN contains propylene glycol monopalmitostearate which may cause skin irritations and isopropyl myristate which may cause irritation and sensitization of the skin.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

Concomitant use of other local treatments in the wart area should be avoided (even like sitz baths, topically applied zinc or vitamin E etc.).

Concomitant intake of high-dosed oral green tea extract preparations (food supplements) should be avoided (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of **VEREGEN** in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of **VEREGEN** during pregnancy, although systemic exposure to epigallocatechingallate is expected to be low following dermal application of **VEREGEN**.

Breastfeeding

It is unknown whether **VEREGEN** or its metabolites are excreted in human milk.

A risk to the suckling child cannot be excluded.

No effects on the breastfed newborn / infant are anticipated since systemic exposure to epigallocatechingallate is expected to be low following dermal application of **VEREGEN**.

Fertility

There is no evidence of an effect on the fertility in the rat following dermal (male) and vaginal (female) application, respectively (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, it is unlikely that **VEREGEN** will have an effect on the ability to drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The safety of **VEREGEN** was assessed in pivotal clinical studies and post-marketing surveillance. The most frequently reported adverse drug reactions were local skin and application site reactions at the wart treatment site.

Most commonly erythema, pruritus, irritation (mostly burning), pain, oedema, ulcer, indurations and vesicles were observed.

Mild local skin reactions are related to the mode of action and should not lead to discontinuation.

Female patients with warts in the vulva had a higher incidence of local skin and application site reactions.

Hypersensitivity was observed. In case of hypersensitivity to **VEREGEN** treatment should be discontinued.

b. Tabulated summary of adverse reactions

Adverse reactions are presented below by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and Infestations	Uncommon	Application site infection, application site pustules, genital herpes infection, staphylococcal infection, urethritis, vaginal candidiasis, vulvovaginitis
Blood and lymphatic system disorders	Common	Inguinal lymphadenitis/ lymphadenopathy
Skin and subcutaneous tissue disorders	Uncommon	Rash and papullar rash
Renal and urinary disorders	Uncommon	Dysuria, micturition urgency, pollakisuria
Reproductive system and breast disorders	Common	Phimosis
	Uncommon	Balanitis, dyspareunia
General disorders and administration site conditions	Very common	Local reactions at the application site like erythema, pruritus, irritation/burning, pain, ulcer, oedema, induration and vesicles

	Common	Local reactions at the application site like exfoliation, discharge, bleeding and swelling.
	Uncommon	Local reactions at the application site like discolouration, discomfort, dryness, erosion, fissure, hyperaesthesia, anaesthesia, scar, nodule, dermatitis, hypersensitivity, local necrosis, papules, and eczema

Adverse effects occur with a higher incidence under occlusive conditions (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity.

No case of overdose has been reported. In case of accidental oral intake symptomatic treatment is indicated. There is no specific antidote for Veregen.

No experience with oral intake of the product is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Chemotherapeutics for topical use, antivirals

ATC code: D06BB12.

Mechanism of action and pharmacodynamic effects

The Mechanism of action of the extract from green tea leaves is not known. As shown in non-clinical studies, the extract from green tea leaves acts by inhibiting the growth of activated keratinocytes and by anti-oxidative effects at the site of application. The clinical significance of these findings is unknown.

Clinical efficacy and safety

The results from two independent pivotal Phase 3 efficacy and safety studies in immunocompetent patients 18 years of age or older showed that treatment with **VEREGEN** 3 times daily for up to 16 weeks was significantly more effective than placebo as determined by complete visual clearance of all external genital and perianal warts (i.e. warts that were pre-existing prior to treatment and warts that emerged during treatment).

Over both studies the median baseline wart area was 48.5 mm^2 (range 12 to 585 mm2), and the median baseline number of warts was 6 (range 2 to 30).

The medium used dosage was 456.1 mg/day (range from 23.8 to 1,283 mg/day).

In 401 **VEREGEN** Ointment-treated patients, the complete clearance rate of all warts was 52.4% for both gender as compared to 35.3% in 207 placebo-treated patients (odds ratio: 2.0 [95% confidence interval 1.4 to 2.9]; $p<0.001$).(ITT-analysis; Last observation carried forward, patients missing values set to “no complete clearance”).

For female patients, the complete clearance rate of all warts was 60.8% as compared to 43.8% of placebo-treated female patients ($p=0.001$).

For male patients, the complete clearance rate of all warts was 44.8% as compared to 28.8% of placebo-treated male patients (p=0.005).

For **VEREGEN** treated patients who completed the studies, the clearance rate of all warts was 60.7% [210/346] (both genders) compared to 44.2% [73/165] in placebo treated patients.

For patients treated with **VEREGEN**, the median time to complete clearance of all warts was 16 weeks. The incidence of visual recurrence of warts after treatment during a 3-month follow-up period in patients with complete clearance was 6.5% (13/201) in the **VEREGEN** 10% treated and 5.8% (4/69) in placebo treated patients.

For the safety profile see sections 4.8 and 5.3.

5.2 Pharmacokinetic properties

Based on consistent data obtained in exposure studies (topical application of Veregen 15% and green tea beverage) it can be expected that systemic exposure of catechines following dermal application of **VEREGEN** does not exceed systemic exposure evident from oral green tea consumption. After dermal application of 750 mg Veregen 15% (containing 72 mg of epigallocatechingallate (EGCg), the major catechin of Veregen) the C_{max} lies in the area of 7 ng/ml for EGCg in plasma, with 7.34 ng/ml as highest value measured. This finding was restricted to single patients only. Therefore there seems no indication for systematic systemic exposure of catechines after topically applied **VEREGEN** that would exceed systemic exposure evident from oral green tea consumption established as worldwide consumed beverage. The C_{max} reported for EGCg in the literature following oral administration of green tea beverages are all consistently well above the sporadic concentrations measured in patients in the exposure studies (based on intake EGCg> 50 mg: 1 cup of tea ca. 50 – 200 mg EGCg).

5.3 Preclinical safety data

Preclinical safety data were gained with the extract from green tea leaves or the higher strength Veregen 15% Ointment. No special hazard for humans was revealed concerning safety pharmacology, genotoxicity and carcinogenic potential (herbal preparation). In conventional studies of repeated dose toxicity, no effects beside the local effects could be seen using the Veregen 15% Ointment. Results are fully applicable for the lower strength **VEREGEN** 10% Ointment.

Adverse effects after dermal application were restricted to the site of application and consisted of dermal irritation including erythema, oedema and inflammatory reactions. The severity of these local signs decreased over time under continued treatment. Direct application of Veregen 15% Ointment into the vagina that was tested as a possible inadvertent route in humans resulted in severe transient local inflammatory responses. Studies in animals conducted with Veregen 15% Ointment indicated a potential for skin sensitisation.

No effects on fertility were observed in male rats after dermal and in female rats after vaginal application. Embryofoetal development was not affected after vaginal application in rats. Following subcutaneous injection in the rabbit, there was materno-toxicity characterised by marked local irritation followed by decreased body weight and food consumption which resulted in corresponding influences on foetal development (reduced foetal weight and retarded ossification). No evidence of teratogenicity was found.

After oral administration (no kinetic data available), specific cephalic abnormalities (hydrocephaly, enlarged left ventricle and/or dilatation of the choroid plexus) were noted in single foetuses of all treated groups of both species, but not among control groups. The clinical relevance is not known.

In a pre- and postnatal development study in rats using vaginal administration of Veregen 15% adverse effects (maternotoxicity including stillbirths) were observed. As based on toxicokinetic data available for the studies with vaginal and subcutaneous administration the effects seen on reproductive toxicity occurred at significantly higher systemic concentrations, as compared to those expected in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

white soft paraffin (contains all-rac-α-tocopherol), white beeswax, isopropyl myristate, oleyl alcohol, propylene glycol monopalmitostearate.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

After first opening, use within 6 weeks.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the cap tightly closed to protect from moisture.

6.5 Nature and contents of container

White aluminium tube with white HDPE cap and sealed orifice.

One tube contains 15 g or 30 g of ointment.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand

8 REGISTRATION NUMBER

52/20.2.8/0312

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2021

10 DATE OF REVISION OF THE TEXT

25 May 2021