

PRODUCT MONOGRAPH

Pr CONDYLIN[®]

Podofilox Topical Solution 0.5%

Antimitotic Agent

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PRODUCT MONOGRAPH

NAME OF DRUG

Pr CONDYLINE®

Podofilox Topical Solution 0.5%

THERAPEUTIC CLASSIFICATION

Antimitotic Agent

ACTIONS

Necrosis of visible tissue is observed following treatment of genital warts with CONDYLINE (Podofilox Topical Solution 0.5%). The exact mechanism of action is unknown.

CONDYLINE (Podofilox Topical solution 0.5%) is believed to exert its antimitotic effect by binding to tubulin, at a site close to but not identical to the binding site of colchicine; it is thought that this antimitotic effect causes necrosis of wart tissue, the observed clinical effect. In addition, podofilox is known to interfere with nucleoside transport which may also contribute to its action (1). Crude podophyllum resin, from which podofilox is extracted, has been shown to produce mitotic arrest and necrosis of wart tissue.

INDICATIONS

CONDYLINE (Podofilox Topical Solution 0.5%) is indicated for the topical treatment of external genital warts (Condylomata acuminata) confined to the penile and vulvar regions. The effectiveness of podofilox in the treatment of perianal or mucous membrane warts has not been established.

CONTRAINDICATIONS

CONDYLINE (Podofilox Topical Solution 0.5%) is contraindicated for patients who develop hypersensitivity to podofilox or intolerance to any component of the formulation. CONDYLINE

should not be applied to open wounds. The consumption of alcoholic beverages for several hours after treatment is to be avoided.

WARNINGS

CONDYLINE (PODOFILOX TOPICAL SOLUTION 0.5%) IS INTENDED FOR TOPICAL USE ONLY.

CONDYLINE IS A POTENT VESICANT AND IS TO BE USED ONLY AS DIRECTED BY A PHYSICIAN. EXTREME CARE SHOULD BE TAKEN TO AVOID CONTACT WITH THE EYE, TONGUE OR ANY MUCOSAL TISSUE OF THE GENITAL AREA (INCLUDING VAGINA, CERVIX, ANUS OR PERIANUS). IF CONTACT WITH THE EYES OCCURS, FLUSH IMMEDIATELY WITH COPIOUS AMOUNTS OF WATER AND SEE A DOCTOR IMMEDIATELY.

PRECAUTIONS

Diagnosis:

Although Condylomata (genital warts) have a characteristic appearance, histopathologic confirmatory tests should be obtained if there is any question of the diagnosis. Differential diagnosis from squamous cell carcinoma (so called "Bowenoid papulosis") is of particular concern. Squamous cell carcinoma may also be associated with human papillomavirus but **should not** be treated with CONDYLINE (Podofilox Topical Solution 0.5%).

General:

CONDYLINE (Podofilox Topical Solution 0.5%) may not prevent either the recurrence of previously resolved warts or the development of new warts at sites remote from the treatment site. The recommended method of application, frequency of application and duration of usage should not be exceeded (See DOSAGE and ADMINISTRATION).

The use of large volumes, greater than 0.25 mL per application or 0.5 mL per day, should be avoided. This can best be accomplished by limiting the treatment area to less than 10 square centimeters and instructing the patient in the proper application of the product.

Genital warts may be contagious and the patient should be instructed to abstain from sexual intercourse. If this is not possible, a latex condom must be used until the infected partner is declared cured by the physician.

The patient should be instructed that if the product is accidentally spilled on undiseased skin, it should be wiped off at once and the exposed skin washed vigorously with warm soapy water and rinsed thoroughly. This product should not be used if growth or surrounding tissue is inflamed or irritated. Self-treatment of genital warts with surface areas greater than 10 square centimeters should not be permitted. The patient should be cautioned against applying the drug to lesions other than warts.

Information for Patients:

The patient should be provided with a Patient Information leaflet when a CONDYLINE prescription is filled.

Long Term Safety:

Reports of lifetime carcinogenicity studies in rodents with podofilox, the drug substance, are not available. In general, podofilox was not shown to be carcinogenic in published animal studies (5, 6, 7, 8, 9). There are published reports that, in the mouse studies, crude podophyllin resin (containing podofilox) applied topically to the cervix produced changes resembling carcinoma *in situ*. These changes were reversible at five weeks after cessation of treatment. In another published study, epidermal carcinoma of the vagina and cervix was found in 1 out of 18 mice following 120 applications of podophyllin, applied twice weekly over a 15-month treatment period.

Podofilox was not mutagenic in the Ames plate reverse mutation assay, either with or without metabolic activation, at concentrations up to 5 mg/plate. There was no evidence of potential oncogenicity in the BALB/3T3 cell transformation assay. Results from the mouse micronucleus *in vivo* assay using podofilox 0.5% solution in concentrations up to 25 mg/kg indicate that podofilox should be considered a potential clastogen (a chemical that induces disruption and breakage of chromosomes).

Daily topical application of CONDYLINE (Podofilox Topical Solution 0.5%) at doses up to the equivalent of 0.2 mg/kg (5 times the recommended maximum human dose) to rats throughout gametogenesis, mating, gestation, parturition and lactation for two generations demonstrated no impairment of fertility.

Use in Pregnancy:

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

Use in Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from podofilox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness in children have not been established.

Use in patients with special diseases and conditions:

CONDYLINE (Podofilox Topical Solution 0.5%) should not be used in diabetics or people with poor blood circulation. Podofilox should not be applied on moles, birthmarks or unusual warts with hair growing from them. Podofilox should not be used on tissue which was recently exposed to laser surgery or cryosurgery.

ADVERSE REACTIONS

In clinical trials (16) the following have been shown to be the most common local adverse events which were reported at some time during treatment:

Inflammation - 67 %

Burning - 62 %

Erosion - 59 %

Pain - 49 %

Other - *e. g.*, bleeding, itching, dizziness, insomnia - 21 %

These reactions may be greater in the occluded prepuce of the uncircumcised male patient.

OVERDOSAGE

TOPICAL - SYMPTOMS AND TREATMENT:

In cases of tingling, burning or extreme tenderness, soak the area in cold water for 10 minutes; repeat as required for the relief of pain. A mild analgesic, eg. acetylsalicylic acid with codeine or acetaminophen with codeine may be beneficial for pain management in some cases. Adjuvant topical anti-inflammatory therapy eg. hydrocortisone acetate, can be advantageous for alleviation of local discomfort.

SYSTEMIC - SYMPTOMS AND TREATMENT:

Topically applied CONDYLINE (Podofilox Topical solution 0.5%) may be absorbed systemically. It may cause systemic toxicity after oral ingestion. Neurotoxic reactions are observed after oral doses exceeding 0.5 mg podofilox per kg body weight. For an adult this dose corresponds to the equivalent of the content of two bottles of 3.5 mL CONDYLINE.

Systemic toxicity may lead to prolonged peripheral neuropathy. Initial symptoms are weakness, drowsiness, dizziness, diarrhoea and general indisposition. A later symptom may be coma with the risk of respiratory failure, ileus, vascular crisis and death. Treatment of overdose is principally symptomatic and supportive therapy.

Hemoperfusion through coal filter and symptomatic treatment may prevent a fatal outcome.

Possible toxic effects of the bone marrow (e.g. leukocytosis, pancytosis) are generally transitory.

DOSAGE AND ADMINISTRATION

Apply twice daily, morning and evening (every 12 hours) for three consecutive days followed by four days without treatment. The use of CONDYLINE (Podofilox Topical Solution 0.5%) twice a day for three days constitutes a treatment cycle. Treatment cycles should be repeated up to four times until there is no visible wart tissue.

If there is incomplete response after four treatment cycles, alternative treatment should be considered.

CONDYLINE is applied to the warts with a cotton tipped applicator supplied with the drug. The wetted applicator should be touched to the wart to be treated, applying the minimum amount of solution necessary to cover the lesion. **Treatment should be limited to less than 10 cm² of wart tissue and to no more than 500 µg (0.5 mL) of the solution per day.**

To ensure that only the genital warts are treated and properly applied, the physician performs the first application for the patient as an office procedure. The patient is shown how to minimize contact with the surrounding healthy tissue and the use of a hand mirror which may help, when he/she applies the solution at home. There is no evidence to suggest that more frequent application will increase efficacy, but this would be expected to increase the rate of local adverse reactions and systemic absorption.

Before applying the medication, the area to be treated should be gently washed with soap and water and gently patted dry. If an area in the occluded prepuce (under the foreskin) is being treated, care should be taken to allow the solution to dry before letting the foreskin return to its normal position. Avoid contact with clothing until the solution has dried. After each treatment, the used applicator should be properly and safely disposed of in a garbage can, out of reach of children, and the patient should wash his/her hands. It is recommended that the **area not be washed following application** of CONDYLINE as is the practice with traditional podophyllum resin preparations.

PHARMACEUTICAL INFORMATION

PROPER NAME OF THE DRUG SUBSTANCE:

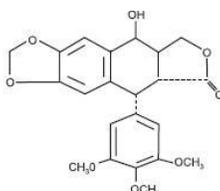
PODOFILOX

CHEMICAL NAME: (5R, 5aR, 8aR, 9R) – 5, 8, 8a, 9 – Tetrahydro – 9 – hydroxy – 5 – (3, 4, 5 – trimethoxyphenyl) – furo [3', 4':6, 7] naphthol - [2, 3-d] – 1, 3 – dioxol – 6 (5aH) – one

MOLECULAR FORMULA: C₂₂H₂₂O₈

MOLECULAR WEIGHT: 414.40

MOLECULAR STRUCTURE:



DESCRIPTION:

A white or almost white crystalline powder with no characteristic odour, freely soluble in acetone and 96% alcohol; soluble in chloroform, toluene, methylene chloride and ethyl acetate; and very slightly soluble in water and hexane.

COMPOSITION:

CONDYLINE (Podofilox Topical Solution 0.5%) is a hydro-alcoholic solution containing 5 mg/mL podofilox; a sodium lactate buffer stabilizes a 1:10 aqueous solution between 2.5 and 4.

STABILITY AND STORAGE RECOMMENDATIONS:

Store at 15-25°C, away from light and heat, in a tightly-closed container.

DOSAGE FORM:

CONDYLINE is available in a 5 mL amber glass bottle with plastic child-resistant cap containing 3.5 mL of 0.5% podofilox. Package includes a sealed bag containing thirty cotton-tipped applicators.

PATIENT INFORMATION LEAFLET

Pr CONDYLINE®

Podofilox Topical Solution 0.5%

NOTICE: TREAT ONLY THE WARTS INDICATED BY THE PHYSICIAN

CONTENTS:

CONDYLINE is a hydro-alcoholic solution containing 5 mg/mL podofilox, with a sodium lactate buffer that stabilizes the 1:10 aqueous solution with a pH between 2.5 and 4.

INDICATIONS:

For the removal of external genital warts located on the penis and vulva.

PRECAUTIONS:

CONDYLINE may not be able to prevent the reappearance of previously healed warts or the development of new warts at a location that was not previously treated.

CONDYLINE is for external use only.

If CONDYLINE is accidentally spilled on healthy skin, wipe off at once and wash vigorously with warm soapy water and rinse well.

If spilled on mucous membranes or the eyes, flush repeatedly with a large amount of water for fifteen minutes. See a physician **immediately**.

Keep this medication safely out of the reach of children.

DO NOT consume alcoholic beverages for several hours after treatment.

DO NOT permit CONDYLINE to contact eyes, tongue or any mucosal tissue of the genital area including vagina, cervix, anus or perianus.

DO NOT use if growth or surrounding tissue is inflamed or irritated.

If you are a diabetic or have poor blood circulation, consult your physician before using this product.

DO NOT use on moles, birthmarks or unusual warts with hair growing from them.

DO NOT use on tissue which was recently exposed to laser surgery or cryosurgery.

DO NOT self-treat genital warts with surface areas greater than 10 square centimetres (approximately the size of a dollar coin).

DO NOT apply the solution to any other warts. Only apply the solution to the genital warts instructed. Always wash hands after using the solution.

WARNINGS:

CONDYLINE SHOULD BE USED ONLY AS DIRECTED BY A PHYSICIAN. KEEP OUT OF THE REACH OF CHILDREN. CAP TIGHTLY AND IMMEDIATELY AFTER USE. EXTREME CARE SHOULD BE TAKEN TO AVOID ALL CONTACT WITH THE EYES.

SIDE EFFECTS:

Local discomfort is inevitable with the topical treatment of genital warts. Topical reactions are common and usually experienced on the second and third day of treatment in association with the beginning of necrosis of the warts. These reactions tend to be mild and well tolerated.

However, a mild analgesic such as acetylsalicylic acid with codeine or acetaminophen with codeine may be taken for pain management in some cases. Erythema (redness) with some pain and/or superficial ulceration of the skin in the treated area are to be expected.

DOSAGE AND ADMINISTRATION:

The first application of CONDYLINE is to be administered by a physician. You will then apply the solution yourself, at home, and only on those warts pointed out by your doctor. Before applying the medication, gently wash the area to be treated with soap and water and gently pat dry. A skin protectant, such as petrolatum jelly, should be applied to the normal skin adjacent to the wart. Using one of the cotton-tipped applicators supplied, carefully apply only as much CONDYLINE as is necessary to cover the warts while taking care to minimize contact with the surrounding healthy skin. **If you have multiple warts, you may need more solution to cover all the warts. In that case, you must take a fresh applicator. Never reuse an applicator or dip a used applicator into the bottle.** The use of a hand mirror may be helpful for proper application. If an area in the occluded prepuce (under the foreskin) is being treated, care should be taken to allow the solution to dry before letting the foreskin return to its normal position. Avoid contact with clothing until the solution has dried. Apply in the morning and evening for three consecutive days. **After each treatment, the used applicator should be properly and safely disposed of in a garbage can, out of the reach of children, and the hands should be properly washed.**

Do not use more than 2 times a day and not more than 3 days in a row.

This treatment procedure may be repeated at one week intervals with a four day time lapse between treatments, until a cure is obtained.

This should not exceed a four week treatment schedule. If excessive burning or irritation occurs, discontinue treatment and consult a physician. Genital warts may be contagious and the patient should abstain from sexual intercourse. If this is not possible, a latex condom must be used by the male patient until the sexual partner receiving the treatment for genital warts is declared cured by a physician. When using a condom, avoid the simultaneous use of petrolatum or other lubricants because it may increase the risk of rupture of the condom during sexual intercourse.

SUPPLIED:

CONDYLINE is available in a 5 mL amber glass bottle with plastic child-resistant cap containing 3.5 mL of 0.5% podofilox. Package includes a sealed bag containing thirty cotton-tipped applicators.

Store at 15-25°C, away from light and heat, in a tightly-closed container.

Product Monograph available to physicians and pharmacists on request.

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CYTOLOGY

In-vitro, podofilox at 0.01 to 5.0 $\mu\text{g}/\text{mL}$ causes reversible and concentration dependent cytostatic and mitotic arresting effects on human leukaemic lymphoblasts (2). At concentrations of 1 to 10 $\mu\text{g}/\text{mL}$, podofilox has been shown to be toxic to leukaemic cells but not to normal lymphocytes (3).

VIROLOGY

Human papillomaviruses (HPV) cause either clinical or subclinical disease, or both. Clinical disease includes Condylomata acuminata of the vulva and vagina, as well as of the cervix, anus and penis. Warts with verrucous surface develop in genital skin that is susceptible to trauma such as the introitus, prepuce and anus. These findings are consistent with the concept that the causative virus, HPV, infects first the lower most basal cells of the squamous epithelium. Indeed, fissures in the genital skin enhance viral entry.

Molecular biology has assisted in the identification and characterisation of 66 different types of HPV's, 23 of which infect the lower genital tract. HPV types 6 and 11 are found in benign Condylomata acuminata, whereas HPV-16, 18, 31, 33, 35, 39 and the 50's and 60's groups are found in genital squamous cell carcinoma, and particularly in their precursor lesions. Among HPV's, the most frequent type in the genital skin is HPV type 16 (1, 14).

Experimentally, when HPV-infected squamous epithelial cells are grafted into immunologically incompetent nude mice, Condylomata develop. HPV DNA was found in fomites such as underwear, various surgical instruments, and the plume of laser smoke.

CLINICAL PHARMACOLOGY

The **systemic absorption** of topical 0.5% podofilox in alcohol has been evaluated in 52 patients (4). Absorption was related to the volume applied to the wart being treated. When 0.05 mL of 0.5% podofilox was applied to wart tissue, the drug was not detected in serum. When volumes of 0.1 to 1.5 mL were applied, peak levels of 1 to 17 ng/mL in serum were detectable at one to two

hours after application. The **half-life** ranged from 1.0 to 4.5 hours. The drug did not accumulate after multiple treatments.

Volumes of less than or equal to 100 μL per application are adequate to treat most cases of genital warts and volumes of less than or equal to 250 μL twice daily for three days is safe. If 100% of the maximum recommended daily dose (0.5 mL) were absorbed, this would correspond to a dose of approximately 0.04 mg/kg in a 70 kg adult.

PHARMACODYNAMICS

The following table demonstrates the total exposure to podofilox within the range of recommended dosing:

0.5 % Drug

<u>Volume (μL)</u>	<u>mg/dose</u>	<u>mg/kg/dose</u>	<u>mg/kg/24 doses*</u>
50	0.25	0.005	0.12
100	0.50	0.010	0.24
200	1.00	0.020	0.48

* Four 3-day treatment cycles of twice daily application and assuming a 50 kg adult.

TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Reports of lifetime carcinogenicity studies in mice are not available. Published animal studies, in general, have shown the drug substance, podofilox to be not carcinogenic (5, 6, 7, 8, 9). There are published reports that, in mouse studies, crude podophyllin resin (containing podofilox) applied topically to the cervix produced changes resembling carcinoma *in situ* (10). These changes were reversible at five weeks after cessation of treatment. In one reported experiment, epidermal carcinoma of the vagina and cervix was found in 1 out of 18 mice after 120 applications of podophyllin (11) (the drug was applied twice weekly over a 15-month period). Podofilox was not mutagenic in the Ames plate incorporation assay when tested at concentration

up to 5 mg/plate, with and without metabolic activation. No cell transformation was observed in BALB/3T3 cells after exposure to podofilox at concentrations up to 0.008 microgram/mL without metabolic activation and 12 microgram/mL podofilox with metabolic activation. Results from the mouse micronucleus *in vivo* assay using podofilox 0.5% solution in concentrations up to 25 mg/kg, indicate that podofilox should be considered a potential clastogen.

Reproduction and fertility

Daily topical application of CONDYLINE (Podofilox Topical Solution 0.5%) at doses up to the equivalent of 0.2 mg/kg (5 times the recommended maximum human dose) to rats throughout gametogenesis, mating, gestation, parturition and lactation for two generations demonstrated no impairment of fertility.

Teratology

Podofilox was not teratogenic in the rabbit following topical application of up to 0.21 mg/kg (5 times the maximum human dose) once daily for 13 days. The scientific literature contains references that podofilox is embryotoxic in rats when administered systemically in a dose approximately 250 times the recommended maximum human dose (12, 13). Teratogenicity and embryotoxicity have not been studied with intravaginal application. Many antimitotic drug products are known to be embryotoxic. There are no adequate and well-controlled studies in pregnant women.

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