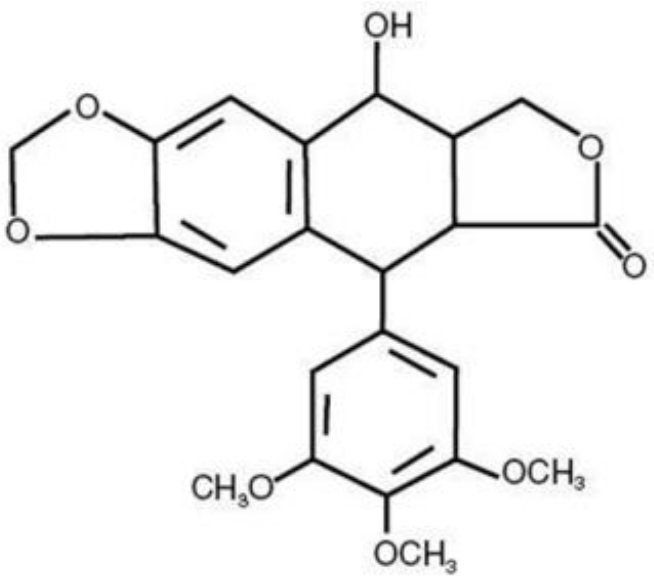
PODOFILOX- podofilox solution
Actavis Pharma, Inc.

Podofilox
0.5% Topical Solution
Rx only
Content Updated: June 2018

DESCRIPTION

Podofilox is an antimitotic drug which can be chemically synthesized or purified from the plant families *Coniferae* and *Berberidaceae* (e.g. species of *Juniperus* and *Podophyllum*). Podofilox 0.5% solution is formulated for topical administration. Each milliliter of solution contains 5 mg of podofilox, in a vehicle containing lactic acid and sodium lactate in alcohol 95%, USP.

Podofilox has a molecular weight of 414.4 daltons, and is soluble in alcohol and sparingly soluble in water. Its chemical name is 5,8,8a,9-Tetrahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)furo[3',4':6,7] naphtho[2,3,d]-1, 3-dioxol-6(5aH)-one. Podofilox has the following structural formula:



CLINICAL PHARMACOLOGY

Mechanism of Action

Treatment of genital warts with podofilox results in necrosis of visible wart tissue. The exact mechanism of action is unknown.

Pharmacokinetics

In systemic absorption studies in 52 patients, topical application of 0.05 mL of 0.5% podofilox solution to external genitalia did not result in detectable serum levels. Applications of 0.1 to 1.5 mL resulted in peak serum levels of 1 to 17 ng/mL 1 to 2 hours after application. The elimination half-life ranged from 1 to 4.5 hours. The drug was not found to accumulate after multiple treatments.

CLINICAL STUDIES

In clinical studies with podofilox 0.5% solution, the test product and its vehicle were applied in a double-blind fashion to comparable patient groups. Patients were treated for 2 to 4 weeks, and reevaluated at a 2-week follow-up examination. Although the number of patients and warts evaluated at each time period varied, the results among investigators were relatively consistent.

The following table represents the responses noted in terms of frequency of response by lesions treated and the overall response by patients. Data are presented for the 2-week follow-up only for those patients evaluated at that time point.

Responses in Treated Patients

	Initially Cleared*	Recurred after Clearing*	Cleared at 2-Week Follow-up*
% Warts (n=524)	79% (412/524)	35% (146/412)	60% (269/449)
% Patients (n=70)	50% (35/70)	60% (21/35)	25% (14/57)

*Cleared and clearing mean no visible wart tissue remained at the treated sites

INDICATIONS AND USAGE

Podofilox 0.5% solution is indicated for the topical treatment of external genital warts (Condyloma acuminatum). This product is *not* indicated in the treatment of perianal or mucous membrane warts (see PRECAUTIONS).

Diagnosis

Although genital warts have a characteristic appearance, histopathologic confirmation should be obtained if there is any doubt of the diagnosis. Differentiating warts 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 podofilox 0.5% solution.

CONTRAINDICATIONS

Podofilox 0.5% solution is contraindicated for patients who develop hypersensitivity or intolerance to any component of the formulation.

WARNINGS

Correct diagnosis of the lesions to be treated is essential. See the "**Diagnosis**" subsection of the **INDICATIONS AND USAGE** statement.

Podofilox 0.5% solution is intended for cutaneous use only. **Avoid contact with the eye. If eye contact occurs, patients should immediately flush the eye with copious quantities of water and seek medical advice.**

PRECAUTIONS

General

Data are not available on the safe and effective use of this product for treatment of warts occurring in the perianal area or on mucous membranes of the genital area (including the urethra, rectum and vagina). The recommended method of application, frequency of application, and duration of usage should not be exceeded (see DOSAGE AND ADMINISTRATION).

Information for Patients

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

Reports of lifetime carcinogenicity studies in mice are not available. Published animal studies, in general, have not shown the drug substance, podofilox, to be carcinogenic.[1,2,3,4,5] There are published reports that, in mouse studies, crude podophyllin resin (containing podofilox) applied topically to the cervix produced changes resembling carcinoma *in situ*.[6] These changes were reversible at 5 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[7] (the drug was applied twice weekly over a 15-month period).

Podofilox was not mutagenic in the Ames plate reverse mutation assay at concentrations up to 5 mg/plate, with and without metabolic activation. No cell transformation related to potential oncogenicity was observed in BALB/3T3 cells after exposure to podofilox at concentrations up to 0.008 mcg/mL without metabolic activation and 12 mcg/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 (a chemical that induces disruption and breakage of chromosomes).

Daily topical application of podofilox 0.5% solution 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.

Pregnancy

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.[8,9] 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. Podofilox should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 pediatric patients have not been established.

ADVERSE REACTIONS

In clinical trials, the following local adverse reactions were reported at some point during treatment.

Adverse Experience	Males	Females
Burning	64%	78%
Pain	50%	72%
Inflammation	71%	63%
Erosion	67%	67%
Itching	50%	65%

Reports of burning and pain were more frequent and of greater severity in women than in men.

Adverse effects reported in less than 5% of the patients included pain with intercourse, insomnia, tingling, bleeding, tenderness, chafing, malodor, dizziness, scarring, vesicle formation, crusting edema, dryness/peeling, foreskin irretraction, hematuria, vomiting and ulceration.

OVERDOSAGE

Topically applied podofilox may be absorbed systemically (see CLINICAL PHARMACOLOGY section). Toxicity reported following systemic administration of podofilox in investigational use for cancer treatment included: nausea, vomiting, fever, diarrhea, bone marrow depression, and oral ulcers. Following 5 to 10 daily intravenous doses of 0.5 to 1 mg/kg/day, significant hematological toxicity occurred but was reversible. Other toxicities occurred at lower doses. Toxicity reported following systemic administration of podophyllum resin included: nausea, vomiting, fever, diarrhea, peripheral neuropathy, altered mental status, lethargy, coma, tachypnea, respiratory

failure, leukocytosis, pancytosis, hematuria, renal failure, and seizures. Treatment of topical overdosage should include washing the skin free of any remaining drug and symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION

In order to ensure that the patient is fully aware of the correct method of therapy and to identify which specific warts should be treated, the technique for initial application of the medication should be demonstrated by the prescriber.

Apply twice daily morning and evening (every 12 hours), for 3 consecutive days, then withhold use for 4 consecutive days. This 1 week cycle of treatment may be repeated up to four times until there is no visible wart tissue. **If there is incomplete response after four treatment weeks, alternative treatment should be considered. Safety and effectiveness of more than four treatment weeks have not been established.**

Podofilox 0.5% solution is applied to the warts with a cotton-tipped applicator supplied with the drug. The drug-dampened 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 cm^2 of wart tissue and to no more than 0.5 mL of the solution per day.** There is no evidence to suggest that more frequent application will increase efficacy, but additional applications would be expected to increase the rate of local adverse reactions and systemic absorption.

Care should be taken to allow the solution to dry before allowing the return of opposing skin surfaces to their normal positions. After each treatment, the used applicator should be carefully disposed of and the patient should wash his or her hands.

HOW SUPPLIED

3.5 mL of podofilox 0.5% solution (NDC 0591-3204-13) is supplied as a clear liquid in amber glass bottles with child-resistant screw caps. Store at 20-25°C (68-77°F). [See USP controlled room temperature.] **Avoid excessive heat. Do not freeze.**

Keep out of reach of children.

Rx only

REFERENCES

1. Berenblum I. The effect of podophyllotoxin on the skin of the mouse, with reference to carcinogenic, cocarcinogenic, and anticarcinogenic action. J Cancer Inst 11:839-841, 1951.

2. Kaminetzky HA, Swerdlow M. Podophyllin and the mouse cervix: assessment of carcinogenic potential. Am J Obst Gyn 95:486-490, 1965.

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formation in the mouse. Brit J Cancer, 9:177-203, 1955.

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8. Didcock K, Jackson D, Robson JM. The action of some nucleotoxic substances on pregnancy. Brit J Pharmacol 11:437-441, 1956.

9. Thiersch JB. Effect of podophyllin (P) and podophylotoxine (PT) on the rat litter in utero. Soc Exptl Biol Med Proc. 113:124-127, 1963.

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Manufactured by:
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San Antonio, TX 78215 USA

Distributed by:
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Parsippany, NJ 07054 USA

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PATIENT INFORMATION

Podofilox 0.5%

Patient Information

Content Updated: August 2014

Rx only

140356 08/14

PODOFILOX 0.5% AND GENITAL WARTS

1. APPLY PODOFILOX ONLY ON THE WARTS POINTED OUT BY YOUR DOCTOR.

2. STOP TREATMENT AND CALL YOUR DOCTOR IF YOU HAVE BLEEDING, SWELLING, OR EXCESSIVE PAIN, BURNING, OR ITCHING.

3. DO NOT USE MORE THAN TWO TIMES A DAY.

4. DO NOT USE FOR MORE THAN THREE DAYS IN A ROW.

5. DO NOT HAVE SEXUAL INTERCOURSE ON THE DAYS YOU ARE APPLYING

PODOFILOX.

6. WASH HANDS AFTER EVERY USE.

INTRODUCTION

Podofilox slowly kills external genital warts. The warts will change from a fleshy skin color to a dry, crusted, dead look, then disappear. Three out of four patients feel some burning or pain after they apply Podofilox. Other side effects may include redness, soreness, tenderness, and small sores. These usually go away within a week after Podofilox is stopped. If pain or other side effects bother you too much, stop applying Podofilox and contact your doctor.

HOW TO USE PODOFILOX

Follow these and your doctor's instructions carefully. Apply Podofilox only on the warts pointed out by your doctor. Do not use it on any other warts on or inside your body, or for any other skin growth.

1 Open the bottle and put it on a flat surface. Hold the bottle and dip the cotton applicator tip into the liquid. Press the applicator tip against the inside edge of the bottle so the applicator is damp with no liquid dripping. Make sure to close the bottle tightly after use.

APPLY PODOFILOX ONLY WHERE YOUR DOCTOR HAS INSTRUCTED YOU

2 Apply Podofilox to the wart. Do not get it on normal skin. If a wart is in a skin fold, spread the skin apart so you can reach the wart. A hand mirror can help sometimes. Let Podofilox dry before letting the skin folds return to their normal position. Wash your hands well with soap and water after you use Podofilox.

3 Apply Podofilox once in the morning and once in the evening for three days in a row. Then stop applying Podofilox and wait four days. Using Podofilox like this is called a treatment week. There is no need to wash Podofilox off the wart area.

DO NOT APPLY PODOFILOX MORE THAN TWICE EACH DAY OR FOR MORE

THAN THREE DAYS IN A ROW. USING PODOFILOX MORE OFTEN WILL NOT MAKE IT WORK BETTER BUT MAY INCREASE SIDE EFFECTS.

4 If the warts do not go away, repeat the Podofilox treatment for another week. You can use Podofilox up to four treatment weeks (REMEMBER: a treatment week is twice a day for three days, then four days with no treatment). Your doctor may ask you to come back for a check-up visit during treatment. If the warts have not gone away after four treatment weeks, stop applying Podofilox and contact your doctor.

IF THE AREA YOU ARE PUTTING PODOFILOX ON IS BLEEDING OR SWOLLEN, OR IF THERE IS EXCESSIVE PAIN, BURNING OR ITCHING, STOP APPLYING PODOFILOX AND CONTACT YOUR DOCTOR.

5 Genital warts can come back. If your warts come back, contact your doctor.

SPECIAL CAUTIONS

- Genital warts are contagious. You can give them to or get them from your sexual partner. Make sure your sexual partner has been checked for genital warts. Condoms can help protect both you and your partner. Do not have sexual intercourse for the three days you are applying Podofilox.
- Women should make sure to use birth control so they will not get pregnant while on Podofilox. The effects on the unborn baby are not known. Women can use Podofilox during their menstrual period.
- Podofilox is prescribed only for your external genital warts. Do not let anyone else use it.

REMEMBER

- Do not use the cotton-tipped applicator more than once. Throw it away so it can not infect anyone else.
- Always wash your hands after using Podofilox.
- Do not get it in your eyes. If you do, immediately flush your eyes with water and contact your doctor.
- Keep the bottle tightly closed and store in an upright position.
- Be sure to keep this and all medications out of the reach of children.
- Store at 20-25°C (68-77°F). [See USP controlled room temperature.]

CONTACT YOUR DOCTOR IF YOU HAVE QUESTIONS ABOUT PODOFILOX.

Keep out of reach of children.

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PRINCIPAL DISPLAY PANEL

Actavis

0.5%

RxOnly

NDC 0591-3204-13

Podofilox Topical Solution 0.5%

For Topical Use Only

3.5 mL

PODOFILOX

podofilox solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0591-3204

Route of Administration	TOPICAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PODOFILOX (UNII: L36H50F353) (PODOFILOX - UNII:L36H50F353)	PODOFILOX	5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
LACTIC ACID (UNII: 33X04XA5AT)	
SODIUM LACTATE (UNII: TU7HW0W0QT)	
ALCOHOL (UNII: 3K9958V90M)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0591-3204-13	3.5 mL in 1 BOTTLE, GLASS; Type 0: Not a Combination Product	12/13/1990	10/31/2024

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA019795	12/13/1990	10/31/2024

Labeler - Actavis Pharma, Inc. (119723554)

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