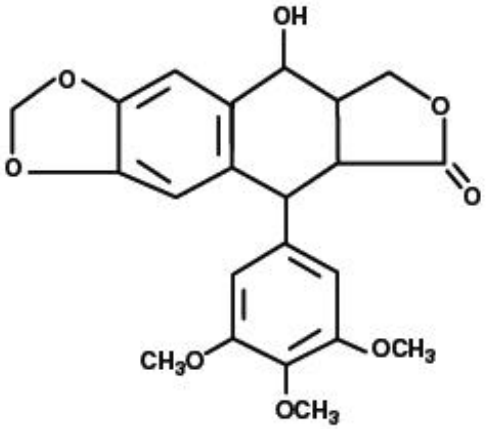
PODOFILOX- podofilox solution
Paddock Laboratories, LLC

Podofilox Topical Solution 0.5%
Rx Only

DESCRIPTION

Podofilox Topical Solution 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 Topical Solution 0.5% 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-trimethoxylphenyl)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 one to two hours after application. The elimination half-life ranged from 1.0 to 4.5 hours. The drug was not found to accumulate after multiple treatments.

CLINICAL STUDIES

In clinical studies with podofilox solution, the test product and its vehicle were applied in a double-blind fashion to comparable patient groups. Patients were treated for two to four weeks, and reevaluated at a two-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.

Response 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 Topical Solution 0.5% 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 Topical Solution 0.5%.

CONTRAINDICATIONS

Podofilox Topical Solution 0.5% 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 Topical Solution 0.5% is intended for cutaneous use only. **Avoid contact with the eye. If eye contact occurs, patient 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 Topical Solution 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 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[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 µg/mL without metabolic activation and 12 µg/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 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.

Pregnancy

Teratogenic Effects:

Pregnancy Category C:

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 during 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.

OVERDOSE

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 one 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 Topical Solution 0.5% is applied to the warts with an 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 Podofilox Topical Solution 0.5% is supplied as a clear liquid in amber glass bottles with child-resistant screw caps. NDC 0574-0611-05. Store at 20° and 25°C (68° to 77°F) [see USP Controlled Room Temperature]. **Avoid excessive heat. Do not freeze.**

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.
3. McGrew EA, Kaminetzky HA. The genesis of experimental cervical epithelial dysplasia. Am J

Clin Path 35:538-545, 1961.
4. Roe FJC, Salaman MH. Further studies on incomplete carcinogenesis: triethylene melamine (T.E.M.) 1,2 benxanthracene and beta-propiolactone as initiators of skin tumor formation in the mouse. Brit J Cancer, 9:177-203, 1955.
5. Taper HS. Induction of the deficient acid DNAase activity in mouse interfollicular epidermis by croton oil as a possible tumor promoting mechanism. Zeitschrift fur Krebsforschung and Klinisch Onkologie (Cancer Research and Clinical Oncology, Berlin). 90:197-210, 1977.
6. Kaminetzky HA, McGrew EA, Phillips RL. Experimental cervical epithelial dysplasia. J Obst Gyn 14:1-10, 1959.
7. Kaminetzky HA, McGrew EA: Podophyllin and mouse cervix: Effect of long term application. Arch Path 73:481-485, 1962.
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.

Manufactured By

Perrigo ®

Minneapolis, MN 55427

2124159

(05-12)

Patient Information

PODOFILOX TOPICAL SOLUTION 0.5% AND GENITAL WARTS

1. APPLY PODOFILOX TOPICAL SOLUTION 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 TOPICAL SOLUTION.
6. WASH HANDS AFTER EVERY USE.

INTRODUCTION

Podofilox Topical Solution 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 Topical Solution. Other side effects may include redness, soreness, tenderness, and small sores. These usually go away within a week after Podofilox Topical Solution is stopped. If pain or other side effects bother you too much, stop applying Podofilox Topical Solution and contact your doctor.

HOW TO USE PODOFILOX TOPICAL SOLUTION

Follow these and your doctor's instructions carefully. Apply Podofilox Topical Solution 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 applicator tip into the liquid. Touch the applicator tip against the inside edge of the bottle so the applicator is wet with no liquid dripping. Make sure to close the bottle tightly after use.

APPLY PODOFILOX TOPICAL SOLUTION ONLY WHERE YOUR DOCTOR HAS INSTRUCTED YOU

2. Apply Podofilox Topical Solution 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 Topical Solution dry before letting the skin folds return to their normal position. Wash your hands well with soap and water after you use Podofilox Topical Solution.
3. Apply Podofilox Topical Solution once in the morning and once in the evening for three days in a row. Then stop applying Podofilox Topical Solution and wait four days. Using Podofilox Topical Solution like this is called a treatment week.There is no need to wash Podofilox Topical Solution off the wart area.

DO NOT APPLY PODOFILOX TOPICAL SOLUTION MORE THAN TWICE EACH DAY OR FOR MORE THAN THREE DAYS IN A ROW. USING PODOFILOX TOPICAL SOLUTION MORE OFTEN WILL NOT MAKE IT WORK BETTER BUT MAY INCREASE SIDE EFFECTS

4. If the warts do not go away, repeat the Podofilox Topical Solution treatment for another week. You can use Podofilox Topical Solution 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 Topical Solution and contact your doctor.

IF THE AREA YOU ARE PUTTING PODOFILOX TOPICAL SOLUTION ON IS BLEEDING OR SWOLLEN, OR IF THERE IS EXCESSIVE PAIN, BURNING OR ITCHING, STOP APPLYING PODOFILOX TOPICAL SOLUTION 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 Topical Solution.
- Women should make sure to use birth control so they will not get pregnant while on Podofilox Topical Solution. The effects on the unborn baby are not known. Women can use Podofilox Topical Solution during their menstrual period.
- Podofilox Topical Solution is prescribed only for your external genital warts. Do not let anyone else use it.

REMEMBER:

- Do not use the applicator more than once. Throw it away so it can not infect anyone else.
- Always wash your hands after using Podofilox Topical Solution.
- 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.

CONTACT YOUR DOCTOR IF YOU HAVE QUESTIONS ABOUT PODOFILOX TOPICAL SOLUTION

Manufactured By

Perrigo®

Minneapolis, MN 55427

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(05-12)

PRINCIPAL DISPLAY PANEL - 3.5 mL Carton

Rx Only

NDC 0574-**0611**-05

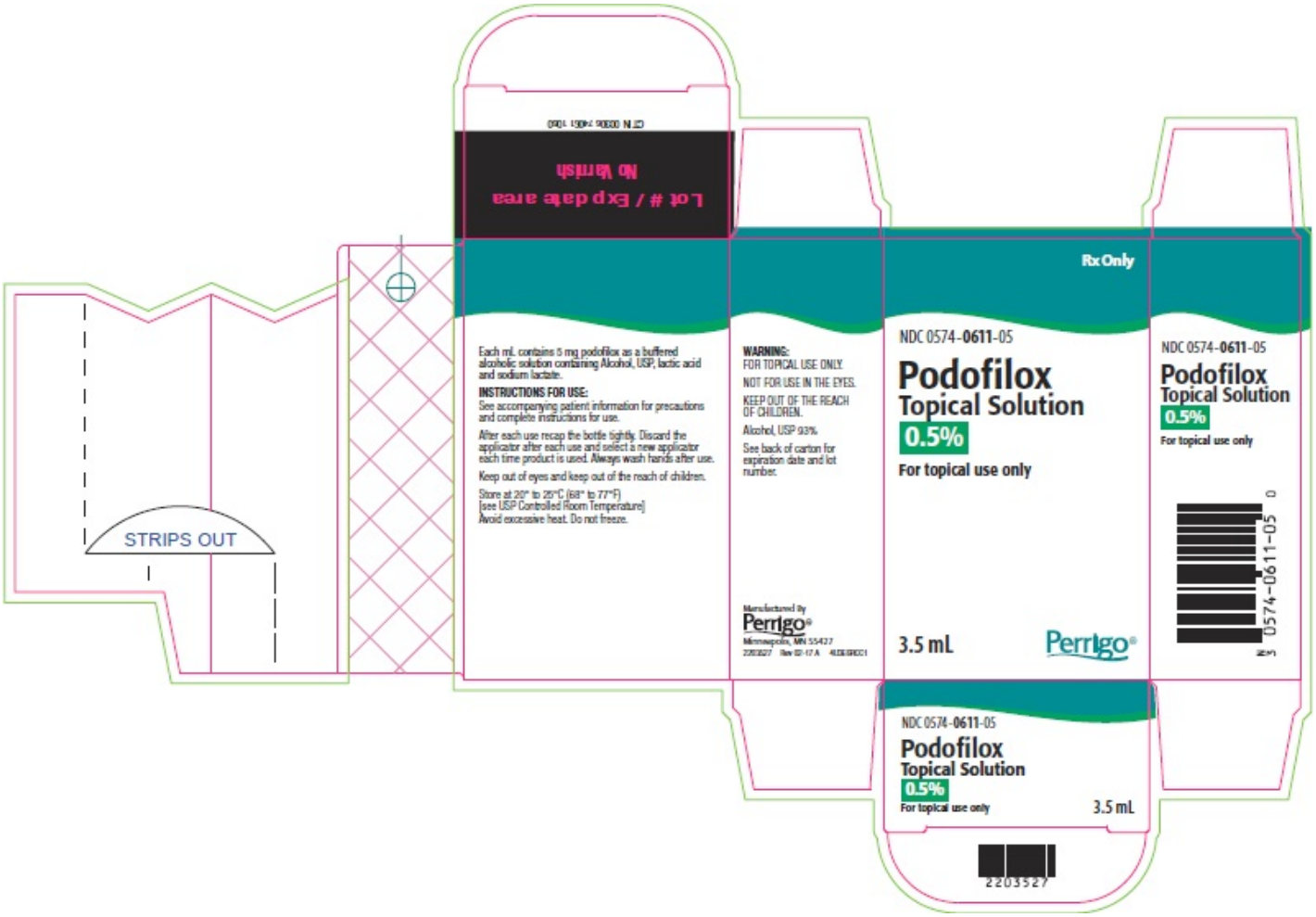
Podofilox

Topical Solution

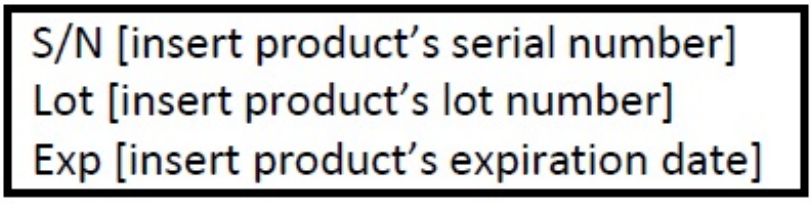
0.5%

For topical use only

3.5 mL



The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.



PODOFILOX

podofilox solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0574-0611
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**
ALCOHOL (UNII: 3K9958V90M)	
LACTIC ACID, DL- (UNII: 3B8D35Y7S4)	
SODIUM LACTATE (UNII: TU7HW0W0QT)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-0611-05	1 in 1 CARTON	01/29/2002	
1		3.5 mL in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075600	01/29/2002	

Labeler - Paddock Laboratories, LLC (967694121)

Revised: 11/2018 Paddock Laboratories, LLC