PRODUCT MONOGRAPH

PrWARTEC®

Podofilox topical solution 0.5% w/v

Antimitotic Agent

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PRODUCT MONOGRAPH

PrWARTEC®

Podofilox topical solution 0.5% w/v

THERAPEUTIC CLASSIFICATION

Antimitotic Agent

ACTIONS

Necrosis of visible tissue is observed following treatment of genital warts with Podofilox. The exact mechanism of action is unknown.

Podofilox is a metaphase inhibitor of dividing cells. Podofilox binds to at least one binding site on tubulin. This binding prevents the tubulin polymerisation required for microtubule assembly. At higher concentrations Podofilox also inhibits nucleoside transport through the cell membrane.

The chemotherapeutic action of Podofilox is assumed to be due to inhibition of growth and the ability to invade the tissue of the virus-infected cells. Podofilox prevents cell division in the virus infected cells of the condylomata acuminata.

INDICATIONS

WARTEC® (Podofilox 0.5% topical solution) is indicated for the topical treatment of external genital warts (Condylomata acuminata) confined to the penile and vulvar regions.

CONTRAINDICATIONS

WARTEC® (Podofilox 0.5% topical solution) is contraindicated for patients who develop or have known hypersensitivity to Podofilox or to any component in the formulation (ethanol, phosphoric acid) ***(See Pharmaceutical Information Description section)***.

Open or bleeding wounds should not be treated with **WARTEC®** (Podofilox).

WARNINGS

WARTEC ® (Podofilox TOPICAL SOLUTION 0.5%) IS INTENDED FOR TOPICAL USE ONLY.

PODOFILOX IS A POTENT VESICANT AND IS TO BE USED ONLY AS DIRECTED BY A PHYSICIAN. EXTREME CARE SHOULD BE TAKEN TO AVOID CONTACT WITH EYES, TONGUE OR MUCOSAL TISSUE OF THE GENITAL AREA (INCLUDING THE URETHRA, RECTUM AND VAGINA). IF ACCIDENTAL CONTACT WITH THE EYES OCCURS, BATHE EYES IMMEDIATELY AND THOROUGHLY WITH LARGE AMOUNTS OF WATER AND CONTACT A PHYSICIAN IMMEDIATELY.

PRECAUTIONS

Diagnosis: Although Condylomata (genital warts) have a characteristic appearance, histopathological 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 papillomaviruses but should not be treated with WARTEC®.

General: The recommended method of application, frequency of application and duration of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION). Avoid applying WARTEC® solution to surrounding healthy skin. If WARTEC® is accidentally spilled on healthy skin, wipe off at once and wash vigorously with soap and water and rinse well. The solution should not be applied to any open cuts or abrasions. Where the area of treatment is greater than 4 cm, it is recommended that treatment takes place under the direct supervision of a healthcare professional.

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

Occlusive dressings should not be used on areas treated with WARTEC®.

If severe local skin reactions occur (bleeding, swelling, excessive pain, burning, itching) WARTEC® should be washed immediately from the treatment area with mild soap and water, the treatment discontinued and the patient advised to seek medical advice.

Use in children: Safety and efficacy of topical WARTEC® have not been established in children under the age of 12. Therefore, use in children cannot presently be recommended.

Use in Pregnancy/Lactation:

Pregnancy

There are limited data from the use of WARTEC® in pregnant women.

Although there is very limited systemic absorption from topically applied WARTEC®, antimitotic products such as WARTEC® are known to be embryotoxic. Topical WARTEC® is not recommended during pregnancy or in women of childbearing potential not using contraception.

Nursing Women

WARTEC® is not recommended for use in nursing women.

There is insufficient information on the excretion of topically applied WARTEC® in human milk.

A risk to the newborns/infants cannot be excluded.

Patients with special Diseases and Conditions: Do not use if growth or surrounding tissue is inflamed or irritated. Do not use on moles, birth marks or unusual warts with hair growing from them.

WARTEC®should not be used on tissues which were recently exposed to laser surgery or cryosurgery.

Elderly: There are no specific recommendations for use in the elderly.

Renal and Hepatic impairment: No dosage adjustment is necessary. As there is very limited percutaneous absorption of Podofilox with the recommended dosage, renal impairment is not expected to result in systemic exposure of clinical significance.

Drug Interaction: No interaction with other medications is known.

ADVERSE REACTIONS

Clinical trial data

In clinical trials with WARTEC® 0.5% solution, the following have been shown to be the most common local adverse events which were reported at some time during treatment:

Skin and subcutaneous tissue disorders

Very common (≥1/10) Skin erosion, application site irritation (including erythema, pruritus, skin burning sensation)

Post Marketing Data

Immune system disorders: Application site hypersensitivity

Skin and subcutaneous tissue disorders: Skin ulcer, scab, skin discoloration, blister, dry skin

General disorders and administration site conditions: Application site pain, swelling, application site bleeding

Injury, poisoning and procedural complications: Caustic injury, excoriation, wound secretion

Local irritations might occur on the second or third day of application associated with the start of wart necrosis. In the majority of cases the reactions are mild and they will disappear in a few days.

If severe cases of local irritations occur, this can be treated with local anti-inflammatory drugs. To al1eviate acute pain, analgesics may be used.

OVERDOSAGE, SYMPTOMS AND TREATMENT

Topical

While serious systemic effects have not been reported with the recommended dosage of topical Podofilox , topical overdosage would be expected to increase systemic absorption of the drug and increase the potential for systemic effects, e.g. altered mental state and bone marrow suppression.

If topical overdosage occurs, Podofilox should be washed immediately from the treatment area and symptomatic and supportive therapy initiated.

Systemic

Following oral ingestion, WARTEC® may cause severe gastroenteritis. An excessive oral ingestion of WARTEC® (>0.5 mg/kg, 2 bottles) may cause systemic toxicity. Initial symptoms are general malaise, weakness, drowsiness and dizziness. Later symptoms may be coma with risk of respiratory failure, ileus and vascular crisis.

There is no specific Antidote. Treatment of overdosage is symptomatic and should include supportive care.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Apply an initial application to test for irritation. If after one hour there is no irritation, continue with application as outlined below. The volume of liquid applied should be kept to the minimum, in order to test the irritability.

Apply twice daily, morning and evening (every 12 hours), for 3 consecutive days followed by 4 days without treatment.

Application to the surrounding normal tissue should be avoided.

Occlusive dressings should not be used on areas treated with WARTEC®.

Preferably the physician should perform the first application for the patient as an office procedure.

The affected area should be thoroughly washed with soap and water, and dried prior to application.

Using the applicator provided, the warts should be painted with WARTEC® solution. The treated area should be allowed to 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 or opposing skin surfaces return to its normal position. If residual warts persist, further treatment may be repeated after an interval of 7 days. The treatment may be repeated three times. If there is incomplete response after 4 treatment cycles, alternative treatment should be considered.

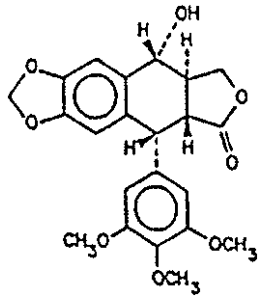
The majority of patients will not require in excess of 30 loops for each application; however, a maximum of 50 loops per application (equivalent to 250 µL of WARTEC® Solution) may be applied. Treatment should be limited to less than 10 cmof wart tissue and to no more than 500 µg (0.5mL) of solution per day.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE: Podofilox (USAN)

CHEMICAL NAME: [5R-(5α,5aβ,8aα,9α)]5,8,8a,9-tetrahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)furo[3',4:6,7] naphto-[2,3-d]-1,3-dioxol-6,(5aH)-one

STRUCTURAL FORMULA:



MOLECULAR FORMULA: $C_{22}H_{22}O_8$

MOLECULAR WEIGHT: 414.4

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:

WARTEC® constitutes a 0.5% (w/v) solution of Podofilox in 70% ethanol, purified water, acidified with phosphoric acid ***(See CONTRAINDICATIONS section)***.

STABILITY AND STORAGE RECOMMENDATIONS:

WARTEC® should be stored at controlled room temperature in light-resistant and tightly closed containers.

DOSAGE FORM:

WARTEC®, 0.5% Podofilox solution for topical application is available in screw capped amber glass bottles. Each pack of WARTEC® consists of a bottle containing 3 mL of WARTEC® solution and a tube of double-ended applicators. The applicators include as loop end for the treatment of separate warts and a spatula end for the treatment of large or fused warts.

PATIENT INFORMATION LEAFLET

PrWARTEC®

Podofilox topical solution 0.5% w/v

NOTICE: TREAT ONLY THE WARTS INDICATED BY THE PHYSICIAN

CONTENTS:

3mL of a clear and colourless ethanolic solution containing Podofilox 5 mg/mL. A set of plastic applicators is provided. WARTEC® also contains purified water, acidified with phosphoric acid.

INDICATIONS:

WARTEC® is to be used for the treatment of external genital warts (condylomata acuminata) located on the penis and vulva by topical application to the affected area.

WARNINGS

WARTEC® should be used only as directed by a physician.

Keep out of reach of children.

Cap tightly and immediately after use.

Extreme care should be taken to avoid all contact with the eyes.

For external use only.

PRECAUTIONS:

WARTEC® is for external use only. The solution should not be applied to any open cuts or abrasions.

Avoid contact with eyes. Should any solution accidentally enter the eye region, flush thoroughly with cold water and contact your doctor immediately.

Avoid contact with the tongue or the inside of the penis, vagina or rectum.

DO NOT use if you are allergic to Podofilox or to any of the ingredients.

DO NOT use on open or bleeding wounds.

NOT FOR use during pregnancy or in nursing women.

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

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

DO NOT apply the solution to any other warts, only the genital warts instructed by your physician.

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

DO NOT put a dressing over the top of an area treated with WARTEC®.

NOT RECOMMENDED in children under the age of 12.

If hypersensitivity to Podofilox develops, discontinue use and consult your physician.

Avoid contact with healthy skin surrounding the wart.

If WARTEC® is accidentally spilled on healthy skin, wipe off at once and wash vigorously with soap and water and rinse well.

Abstain from sexual intercourse while treating warts with WARTEC® and until the skin has healed. If this is not possible, a latex condom must be used until the affected partner is declared cured by the physician.

Wash your hands after using the solution.

DOSAGE AND ADMINISTRATION

Preferably the physician should perform the first application for the patient as an office procedure.

An initial application should be applied to test irritation. If after one hour there is no irritation, continue with application as outlined below. Use only a small amount of WARTEC® solution to test for irritation.

Before treatment, wash all infected areas with soap and water, and dry thoroughly.

Using one of the applicators provided, dip the loop end into the solution.

Apply the solution repeatedly to each wart in turn using the same applicator as directed by your doctor.

Avoid contact with healthy skin surrounding the wart.

Do not use a covering dressing on the treated area.

For larger warts, use the flattened spatula end of the applicator to spread the solution onto the infected area. Allow solution to dry. If an area in the occluded prepuce (under the foreskin or opposing skin surfaces) is being treated, care should be taken to allow the solution to dry before letting the foreskin or opposing skin surfaces return to its normal position.

The treatment described above should be repeated **TWICE A DAY**, morning and evening, for **3 DAYS**, followed by 4 days without treatment. On each occasion the maximum number of loops applied should not be in excess of 50.

If your warts cover an area larger than 4 centimetre squared (approximately the size of a postage stamp); you may need to have this medicine applied by a nurse or doctor in a clinic.

If you still have warts remaining after 7 days, the treatment may be repeated after one week at your doctor's instruction.

OVERDOSE

If you apply a large amount of WARTEC®, wash it off immediately and contact your doctor.

The ingredients of WARTEC® may be harmful if swallowed. If you do accidentally get WARTEC® in your mouth, rinse at once with water. If you accidentally swallow WARTEC® contact your doctor immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

STORAGE

WARTEC® should be stored at controlled room temperature in light-resistant containers.

SIDE-EFFECTS

Like all medicines, WARTEC® can cause side effects, but not everybody gets them.

Some smarting may occur immediately following application but this normally subsides. Should itching or soreness continue to cause discomfort, consult your doctor.

Other side effects may occur:

Very common side effects

- Skin erosion, application site irritation including redness, itching, burning sensation

Rare side effects

The following side effects have been reported **at the site of application**:

- allergic reaction, pain, swelling, bleeding, caustic injury, damage to or loss of the top layer of skin, wound secretion (weeping), skin ulcer, scab, skin discoloration, dry skin, blister

Serious side effects

If you experience any of the following serious side effects, stop using WARTEC® and seek emergency medical attention:

- Severe burning, stinging, pain, bleeding or swelling of the treated skin. If these symptoms occur, wash WARTEC® from your skin with soap and water immediately, discontinue WARTEC® and **contact your doctor immediately.**

Tell your doctor or pharmacist if any of the side effects listed becomes severe or troublesome, or if you notice any side effects not listed in this leaflet.

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(Ireland) Ltd., Ireland

Distributed by:
Paladin Labs Inc.
Montréal, Canada
H4P 2T4

PHARMACOLOGY

CYTOLOGY

The action of Podofilox on dividing cells is almost indistinguishable from that of colchicine. Thus, Podofilox inhibits the mitotic process during the metaphase of cell division. This effect is exerted through binding to tubulins which are required for the spindle formation being essential for cell division. When binding is complete the conformation of the protein is altered so that it is no longer suitable as a building stone for the microtubuli participating in this process. At high concentration, Podofilox also inhibits the intracellular nucleoside transport.

The chemotherapeutic action of Podofilox is assumed to be due to inhibition of growth and the ability to invade the tissue of the virus-infected cells. Podofilox prevents cell division in the virus infected cells of the condylomata acuminata.

At concentration of l.0 µg/mL in *in-vitro* studies no toxicity has been shown to human lymphocytes or human thymocytes over 24 hours.

CLINICAL PHARMACOLOGY

The use of Wartec solution is designed for self-treatment of condylomata acuminata. In the majority of cases topical administration of venereal warts only requires volumes in the range of 100 µL to 200 µL. Because of small volumes applied dermally and the weak solution, no systemic effect is expected after treatment with Wartec 0.5% solution.

A pharmacokinetic study has been performed to measure the degree of absorption. 69 patients with condylomata acuminata, were treated with 0.5% Podofilox twice a day for 3 days. The drug was not detectable in the serum of ten men treated with ≤ 50 µL. In serum of seven patients receiving 100-1,500 µL on extraordinarily large en-plaque lesions, peak levels of 1-17 ng/mL were measured within 1-2 hours. The drug did not accumulate in serum. The halflife ranged from 1.0 to 4.5 hours.

TOXICOLOGY

ACUTE TOXICITY STUDIES:

The acute toxicity of Podofilox was examined in mouse, rat and rabbit by the oral, dermal and intravenous routes. In all cases a margin of safety was shown.

The table below presents the approximate LD_{50} values obtained.

Species	**Route of administration**	**LD_{50}, mg/kg**
Mouse	i.v.	20-40
Mouse	p.o.	<100
Rabbit	dermal	>200
Rat	p.o.	>100
Rat	i.v.	10
Rat	dermal	>500

LONG TERM TOXICITY STUDIES

Sub-acute and chronic toxicity of Podofilox. Podofilox was examined in two species, the rat and the dog.

No changes that could reasonably be attributed to the treatment were seen in the 26-week oral studies in rats or in dogs. The highest dose level was 0.30 mg/kg in these studies. In the 90 day dermal study in rats epidermal hyperplasia and marked inflammatory response on the site of application were seen at dose levels 2-20 mg/kg. For the dermal application Podofilox was dissolved in a 70% aqueous acidified ethanol.

Table 1 summarizes the results obtained in these studies.

Table 1 Sub-acute and chronic toxicity of Podofilox

Species and strain	Duration Route of adminis-tration	Dose levels mg/kg	Behavioural changes	Biochemistry/ haematology	Gross pathology	Histology
Rat CD-1 (1CR) BR	90 days dermal	0.25-0.5	No significant effect	No significant effect	Slight eschar formation after 1 week which improved by the end of the study	No significant effect
		2.0-4.0	Reduced bodyweight gain and food consumption in the males	Blood and protein in urine. Raised AP, ALT and AST levels in females	Moderate to severe eschar formation Ulceration of the mouth. Swollen penises. Changes in organ weights	Epidermal hyperplasia and marked inflammatory response at the site of application
		10.0-20.0	Hypoactivity Reduced bodyweight gain and food consumption	Raised total WBC, High levels BUN, AP, ALT, and AST. Blood and protein in urine	Severe reaction at site of application. Changes in organ weight seen	Epidermal hyperplasia and marked inflammatory response at the site of application
Rat CD-1 (1CP1)BR	26 weeks p.o. (dietary)	0.03 0.15 0.30	No changes were seen that could reasonable be attributed to treatment			
Dog Beagle	26 weeks p.o.	0.03 0.15 0.30	No changes were seen that could reasonable be attributed to treatment			

Reproductive Studies

Reproduction toxicity of Podofilox. Podofilox was examined for its effect on fertility and fetuses of the rat and rabbit.

The compound was administered orally, by gavage to the rat, and dermally to the rabbit.

Fertility, reproductive capacity studies and peri- and post natal studies were performed in rats at dose levels 0.4-2.5 mg/kg.

Table 2 summarizes the results obtained.

Table 2 Reproduction toxicity of Podofilox

Study	Species/strain	Route of administration	Dose level mg/kg	Observations
Fertility and Reproductive Capacity	CD-1 (1CR)BR	p.o.	0.4 1.0 2.5	Reaction to treatment seen only at 2.5 mg/kg F0 generation mothers, increase in lengths of partus. F generation offspring reduction in survival and development of offspring. F1 generation reduced bodyweight gain during suckling in males only.
Peri and post Natal	Rats CD-1(1CR)BR	p.o.	0.4 1.0 2.5	No significant changes related to treatment were observed
Teratogenicity	Rats CD-1(1CR)BR	p.o.	0.4 1.5 5.0	Weight loss and reduction of food intake at 5.0 mg/kg. No teratogenic effect seen at any dose level.
Teratogenicity	Rabbit New Zealand White	dermal	0.02% 0.1% 0.5% (alcoholic solution)	Dose related skin irritation seen. Fetal weight reduced at 0.5%. No other changes seen. No teratogenic effect seen at any dose level.

Teratology

No teratogenic effect has been seen at any dose levels 0.4 - 5.0 mg/kg p.o. administration.

Podofilox.was neither teratogenic in the rat following oral administration of up to 5.0 mg/kg nor in the rat following topical application of up to 20 mg/kg.

Mutagenicity

Podofilox was not mutagenic in the Ames plate incorporation assay when tested at concentrations up to 5 mg/plate, with and without metabolic activation.

An *in-vitro* Metaphase analysis in human lymphocytes showed that Podofilo·x is not a clastogen. 90 µg/mL was used at the highest concentration in the chromosomal aberration assay.

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