Condylox® Gel - Package Insert

Condylox® (podofilox gel) Gel, 0.5%
(con’ de lox)

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).

Condylox® Gel 0.5% is formulated for topical administration. Each gram of gel contains
5mg of podofilox in a buffered alcoholic gel containing alcohol, glycerin, lactic acid,
hydroxypropyl cellulose, sodium lactate, and butylated hydroxytoluene.

Podofilox has a molecular weight of 414.4 daltons, and is soluble in alcohol and sparingly
soluble in water. Its chemical name is [2R-(3α,5α,Rα,Rα)]-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 anogenital 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 0.05mL of an ethanolic solution containing 0.5% podofilox to external genitalia did not result in detectable serum levels. Applications of 0.1 to 1.5mL 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.1

CLINICAL STUDIES
In the first multicenter clinical study in 326 patients with anogenital warts, Condyloma® Gel 0.5% and its vehicle were applied in a double-blind fashion to comparable patient groups. Of the 260 patients with efficacy data, 176 were treated with Condyloma® Gel 0.5%. Patients applied Condyloma® Gel 0.5% twice daily for three consecutive days followed by a 4 day "rest" period.

At the end of 4 weeks, 38.4% of the patients had complete clearing of the wart tissue when treated with Condyloma® Gel 0.5%.

In the second multicenter clinical trial in 108 evaluable patients with anogenital warts, Condyloma® (podofilox solution) Solution 0.5% was compared with Condyloma® Gel 0.5% for efficacy. As in the first clinical trial, patients applied Condyloma® Gel 0.5% twice daily for three consecutive days followed by a four day "rest" period.

Similar clearance rates were observed. At the end of 4 weeks, 25.6% of the patients had complete clearing of the wart tissue when treated with Condyloma® Gel 0.5%.

INDICATIONS AND USAGE

Condyloma® Gel 0.5% is indicated for the topical treatment of anogenital warts (external...
genital warts and perianal warts). This product is not indicated in the treatment of mucous
membrane warts (see PRECAUTIONS).

Diagnosis

Although anogenital warts have a characteristic appearance, histopathologic confirmation
should be obtained if there is any doubt of the diagnosis. Differentiating warts from
squamous cell carcinoma and "Bowenoid papulosis" is of particular concern. Squamous
cell carcinoma may also be associated with human papillomavirus which should not be
treated with Condylomax* Gel 0.5%.

CONTRAINDICATIONS

Condylomax* Gel 0.5% is contraindicated for patients who develop hypersensitivity or
intolerance to any components of the formulation.

WARNINGS

Correct diagnosis of the lesions to be treated is essential. See the Diagnosis subsection of
the INDICATIONS AND USAGE section. Condylomax* Gel 0.5% is intended for
cutaneous use only. Avoid contact with the eyes. If contact with the eyes occurs,
patients should immediately flush the eyes with copious quantities of water and seek medical advice.

Drug Product is Flammable. Keep Away From Open Flame.

PRECAUTIONS

General

Data are not available on the safe and effective use of this product for treatment of warts occurring 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

Patients using Condylomax® Gel 0.5% should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not intended to disclose all possible adverse or intended effects.

1) This medication should be used only as directed by the health care provider.
Patients should be instructed to wash their hands thoroughly before and after each application. It is for external use only. Avoid contact with the eyes.

2) Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.

3) Patients should report any signs of adverse reactions to the health care provider.

4) If no improvement is observed after 4 weeks of treatment, discontinue the medication and consult the health care provider.

Carcinogenesis, Mutagenesis and Impairment of Fertility

An 80-week carcinogenicity study in the mouse was performed using a 0.5% podofilox solution applied dermally at 0.04, 0.2 and 1.0 mg/kg/day. There were no differences between the podofilox treated mice at any dose level and vehicle control in the incidence of neoplasia. Published animal studies, in general, have not shown the drug substance, podofilox, to be carcinogenic. There are published reports that, in 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 one reported experiment, epidermal carcinoma of the vagina
and cervix was found in 1 out of 18 mice after 120 applications of podophyllin\(^9\) (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 5mg/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 0.008µg/mL, without metabolic activation and 12µg/mL podofilox with metabolic activation. Results from the mouse micronucleus in vivo assay using podofilox 0.5% solution at doses up to 25 mg/kg (75 mg/m\(^2\)), indicate that podofilox should be considered a potential clastogen (a chemical that induces disruption and breakage of chromosomes).

Daily topical application of 0.5% podofilox solution at doses up to the equivalent of 0.2mg/kg (1.18 mg/m\(^2\), approximately equivalent to the human daily dose) to rats throughout gametogenesis, mating, gestation, parturition and lactation for two generations demonstrated no impairment of fertility.

Pregnancy
Pregnancy Category C: 0.5% podofilox solution was not teratogenic in the rabbit following topical application of up to 0.21 mg/kg (2.85 mg/m², approximately 2 times the maximum human dose) once daily for 13 days. The scientific literature contains references that podofilox is embryotoxic in rats when administered intraperitoneally at a dose of 5mg/kg (29.5 mg/m², approximately 19 times the recommended maximum human dose). Teratogenicity and embryotoxicity have not been studied with intravaginal application. Many antimiotic drug products are known to be embryotoxic. There are no adequate and well-controlled studies in pregnant women. Condylox® Gel 0.5% 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 with Condylomax® Gel 0.5%, the following local adverse reactions were reported during the treatment of anogenital warts. The severity of local adverse reactions were predominantly mild or moderate and did not increase during the treatment period.

Severe reactions were most frequent within the first 2 weeks of treatment.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>32.2%</td>
<td>30.4%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Burning</td>
<td>37.1%</td>
<td>25.9%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Erosion</td>
<td>27.0%</td>
<td>20.8%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Pain</td>
<td>23.7%</td>
<td>20.4%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Itching</td>
<td>32.2%</td>
<td>16.0%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>19.2%</td>
<td>3.0%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Other local adverse reactions reported included stinging (7%), and erythema (5%); less commonly reported local adverse events included desquamation, scabbing, discoloration, tenderness, dryness, crusting, fissures, soreness, ulceration, swelling/edema, tingling,
rash, and blisters.

The most common systemic adverse event reported during the clinical studies was headache (7%).

**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 podophyllin 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 overdose should include washing the skin free of any remaining drug and symptomatic and supportive therapy.
DOSAGE AND ADMINISTRATION

The prescriber should ensure that the patient is fully aware of the correct method of therapy and identify which specific warts should be treated.

Apply twice daily for 3 consecutive days, then discontinue for 4 consecutive days. This one week cycle of treatment may be repeated until there is no visible wart tissue or for a maximum of four cycles. If there is incomplete response after four treatment cycles, discontinue treatment and consider alternative treatment. Safety and effectiveness of more than four treatment cycles has not been established.

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.

Condylox® Gel 0.5% should be applied to the warts with the applicator tip or finger. Application on the surrounding normal tissue should be minimized. Treatment should be limited to 10 cm² or less of wart tissue and to no more than 0.5g of the gel per day.
Care should be taken to allow the gel to dry before allowing the return of opposing skin surfaces to their normal positions. Patients should be instructed to wash their hands thoroughly before and after each application.

HOW SUPPLIED

Condylar® Gel 0.5% is supplied as 3.5g of clear gel in aluminum tubes with an applicator tip. NDC 55515-102-01. Store at controlled room temperature between 15°C-30°C (59°F-86°F). Avoid excessive heat. Do not freeze.

Caution: Federal law prohibits dispensing without prescription.

REFERENCES

1. von Krogh G. Podophyllotoxin in serum: Absorption subsequent to three day repeated applications of a 0.5% ethanolic preparation on condylomata acuminata. Sex Trans Dis 1982: 9: 26-33.


3. Kaminetzky HA, Swerdlov M. Podophyllin and the mouse cervix: assessment of


10. Savel H.: Clinical experience with intravenous podophyllotoxin. Proc Amer
Condylox® Gel 0.5%
(podofilox gel)

Condylox® Gel (podofilox gel) and Anogenital Warts

Patient Information

1. APPLY CONDYLOX® GEL ONLY ON THE WARTS POINTED OUT BY YOUR DOCTOR.
2. YOU MAY FEEL SOME MILD TO MODERATE DISCOMFORT DURING TREATMENT.
3. STOP TREATMENT AND CALL YOUR DOCTOR IF YOU HAVE BLEEDING, SWELLING, OR EXCESSIVE PAIN, BURNING, OR ITCHING.
4. DO NOT USE MORE THAN TWO TIMES A DAY.
5. DO NOT USE FOR MORE THAN THREE DAYS IN A ROW.
6. DO NOT HAVE SEXUAL INTERCOURSE ON THE DAYS YOU ARE APPLYING CONDYLOX® GEL.
7. WASH HANDS AFTER EVERY USE.

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

HOW TO USE CONDYLOX® GEL
Follow these and your doctor's instructions carefully. Apply Condylox® Gel only on the warts pointed out by your doctor. Do not use it on any other warts or on inside your body, or for any other skin growth.

1. Unscrew the entire applicator cap. Invert the cap and puncture the tube seal. Replace the applicator cap. To apply Condylox® Gel, remove the protective cap on the applicator tip and apply to the warts using the applicator tip or fingerprint. Make sure to replace the applicator cap tightly after use.

APPLY CONDYLOX® GEL ONLY WHERE YOUR DOCTOR HAS INSTRUCTED YOU.

2. Apply a small amount of Condylox® Gel to the wart(s). 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 Condylox® Gel dry before letting the skin folds return to their normal position. Wash your hands well with soap and water after you use Condylox® Gel.
3. Apply Condylox® Gel once in the morning and once in the evening for three days in a row. Then stop applying Condylox® Gel and wait four days. Using Condylox® Gel like this is called a treatment
week. You should not wash Condylox® Gel off the wart area unless you experience excessive pain, burning, or itching.

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

4. If the warts do not go away, repeat the Condylox® Gel treatment for another week. You can use Condylox® Gel 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 Condylox® Gel and contact your doctor.

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

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

SPECIAL CAUTIONS:
- Anogenital warts are contagious. You can give them to or get them from your sexual partner. Make sure your sexual partner has been checked for anogenital warts.
- Condoms may help prevent giving anogenital warts to your sexual partner. Do not have sexual intercourse for the three days you are applying Condylox® Gel.
- Women should make sure to use birth control so they will not get pregnant while on Condylox® Gel. The effects on the unborn baby are not known. Women can use Condylox® Gel during their menstrual period.
- Condylox® Gel is prescribed only for your external anogenital warts. Do not let anyone else use it.

REMEMBER:
- Always wash your hands after using Condylox® Gel.
- Do not get it in your eyes. If you do, immediately flush your eyes with water and contact your doctor.
- Keep the tube cap tightly closed.
- Be sure to keep this and all medications out of the reach of children.

CONTACT YOUR DOCTOR IF YOU HAVE QUESTIONS ABOUT CONDYLOX® GEL.

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Revised October 31, 1996.
WARNING: FOR TOPICAL USE ONLY. NOT FOR USE IN THE EYES. KEEP OUT OF REACH OF CHILDREN.

See and of course for expiration date and lot number.

Drug product is Flammable. Keep away from open flame.

Condylol Gel 0.5%
(podofoil gel)

Each g contains 5 mg podofilox. A 10% sulfonated alcohol gel containing sodium, glycine, lactic acid, sodium pyrophosphate, sodium fluoride, and preserved with phenoxyethanol.

Instructions for Use: See accompanying patient information for precautions and complete instructions for use.

Insert cap to prevent seal to tack. After each use recap the seal tightly. Always wash hands after use. Store at controlled room temperature (15°C to 30°C, 59°F to 86°F) and protected from light. Do not freeze.

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Dr. Niles
Condylox Gel 0.5% (podofilox gel)

Odessen

FOR TOPICAL USE ONLY

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Each g contains 5 mg podofilox gel in a hydrophilic gel containing alcohol, glycerin, lactic acid, hydroxypropyl cellulose, sodium lactate, and hydroxyethylcellulose.

Instructions For Use: See accompanying patient information for precautions and complete instructions for use.

Insert cap to puncture seal in tube. After each use, recap the tube tightly. Always wash hands after use.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Avoid excessive heat. Do not freeze.

Alcohol 75%

R. Ques

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