PODOPHYLLUM b (Topical)

Introduction

VA CLASSIFICATION (Primary)¾DE500

Commonly used brand name(s):Podocon-25; Podofin.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

b Not commercially available in Canada.

Category

Cytotoxic (topical).

Indications

General considerations

Podophyllum contains a number of unidentified ingredients, and its activity may vary widely depending on the source of the material.

Accepted

Condyloma acuminatum (treatment)¾Podophyllum is indicated for the treatment of condyloma acuminatum (venereal warts). 1, 2, 3, 4, 5, 6

Epitheliomatosis, multiple superficial (treatment) or

Keratoses, pre-epitheliomatosis (treatment) or

Papilloma, of the larynx, juvenile (treatment)¾ Podophyllum is used in the treatment of multiple superficial epitheliomatosis, such as multiple superficial or infiltrating basal cell epithelioma, squamous cell epithelioma (prickle cell epithelioma), and basal-squamous cell epithelioma (mixed or transitional cell epithelioma); 1 seborrheic, actinic, and roentgen ray keratoses; 1 and juvenile papilloma of the larynx. 1, 9

Unaccepted

Podophyllum has been used in the treatment of general types of verrucae, such as vulgaris (common warts), filiformis (filiform warts), plana (flat warts), and plantaris (plantar warts); 1 however, it is much less effective in these types of warts than in venereal warts. Also, podophyllum therapy is less effective than other types of treatment for these warts. 1

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Source¾Dried resin from the roots and rhizomes of Podophyllum peltatum (mandrake or May apple plant), the North American variety; active constituents are lignans including podophyllotoxin (20%), alpha-peltatin (10%), and beta-peltatin (5%) 1, 3, 4.

Mechanism of action/Effect:

Podophyllum resin's major active constituent, podophyllotoxin, is a lipid-soluble compound that easily crosses cell membranes. Podophyllotoxin and its derivatives are potent cytotoxic agents that inhibit cell mitosis and deoxyribonucleic acid (DNA) synthesis in a manner similar to that of colchicine. Cell division is arrested, and other cellular processes are impaired, gradually resulting in the disruption of cells and erosion of the tissue. 3, 4, 5, 6

Absorption:

Topical podophyllum is systemically absorbed; absorption may be increased if podophyllum is applied to friable, bleeding, or recently biopsied warts 1, 4, 5.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to benzoin may be sensitive to this medication also because some preparations may contain tincture of benzoin.

Pregnancy/Reproduction

Pregnancy¾Topical podophyllum is absorbed systemically and can cross the placenta. It should not be used during any phase of pregnancy, because of its teratogenic potential. Following oral administration during pregnancy, podophyllum has been reported to cause fetal abnormalities, such as skin tags on the ears and cheeks, limb malformations, and septal heart defects, as well as polyneuritis. Intrauterine death has occurred following topical application to vulval warts during the 32nd week of pregnancy. In one patient, minor fetal anomalies, including preauricular skin tags and a simian crease on the left hand, occurred following topical application during the 23rd, 24th, 25th, 28th, and 29th weeks of pregnancy.
Warts of the vaginal, perianal, or anal areas requiring treatment during pregnancy should be treated by alternative methods, such as electrodesiccation, diathermy, curettage, surgical excision, or cryosurgery with liquid nitrogen or dry ice. 1, 3, 6

Breast-feeding

Topical podophyllum is systemically absorbed. However, it is not known whether topical podophyllum is distributed into breast milk. Problems in humans have not been documented. 3

Pediatrics

Appropriate studies on the relationship of age to the effects of topical podophyllum have not been performed in the pediatric population. However, no pediatrics-specific problems have been documented to date.

Geriatrics

Appropriate studies on the relationship of age to the effects of topical podophyllum have not been performed in the geriatric population. However, no geriatrics-specific problems have been documented to date.

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alkaline phosphatase and

Aspartate aminotransferase (AST [SGOT]) and

Lactate dehydrogenase (LDH)

(serum values may be increased in association with renal failure and hepatotoxicity)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

>> Friable, bleeding, or recently biopsied warts

(risk of systemic toxicity may be increased 3)

Sensitivity to podophyllum

Side/Adverse Effects

Note: Podophyllum resin topical solution is highly irritating to the eye and to mucous membranes in general.
Podophyllum can cause severe systemic toxicity, which may result from either topical application or ingestion. The toxic effects are usually reversible but have been fatal. Death can occur with ingestion of podophyllum in amounts as small as 300 mg.
Serious systemic toxicity has occurred following topical application of podophyllum to large areas or in excessive amounts, or when the medication was allowed to remain in contact with the skin or mucous membranes for a prolonged period of time.

The risk of systemic toxicity may be increased when podophyllum is applied to friable, bleeding, or recently biopsied warts, or when the medication is inadvertently applied to normal skin or mucous membranes surrounding the affected area(s).
Renal failure and hepatotoxicity have occurred following topical application of podophyllum.
Adverse effects on the nervous system may occur following topical application of podophyllum; these are usually delayed in onset and prolonged in duration.
Cerebral toxicity (manifested by altered sensorium ranging from mild confusion to coma) may occur following topical application of podophyllum and continue for 7 to 10 days during which the electroencephalogram (EEG) may show generalized slowing.
The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Burning, redness, or other irritation of affected area; skin rash or itching¾allergic reaction to benzoin, which may be present in some preparations

Overdose

For specific information on the agents used in the management of podophyllum overdose, see:
· Charcoal, Activated (Oral-Local) monograph.
For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Initial symptoms of systemic toxicity

Abdominal or stomach pain; clumsiness or unsteadiness; confusion; decreased or loss of reflexes; diarrhea¾sometimes severe and prolonged; excitement, irritability, or nervousness; hallucinations; leukopenia sore throat and fever); muscle weakness; nausea or vomiting; thrombocytopenia unusual bleeding or bruising)
Delayed symptoms of systemic toxicity

Autonomic neuropathy (difficult or painful urination; dizziness or lightheadedness, especially when getting up from a lying or sitting position; fast heartbeat); difficulty in breathing; drowsiness; paralytic ileus (constipation; nausea and vomiting; pain in upper abdomen or stomach, mild, dull, and continuing); peripheral neuropathy (numbness, tingling, pain, or weakness in hands or feet); seizures

Note: If peripheral neuropathy occurs, it usually appears about 2 weeks after podophyllum application, may worsen progressively for up to 3 months, and may persist for up to 9 months or longer. 1, 2, 3, 4, 5, 7, 8

Treatment of overdose

Treatment of systemic toxicity or accidental ingestion is essentially supportive and may include the following:
To decrease absorption¾If podophyllum is accidentally ingested and the patient is conscious, emesis should be immediately induced. If the patient is unconscious, gastric lavage should be performed. Activated charcoal may also be administered.
To enhance elimination¾Charcoal hemoperfusion may be beneficial in life-threatening or deteriorating conditions.
Monitoring¾Electrolytes, serum calcium, and hemoglobin concentrations should be closely monitored.
Supportive care¾Intravenous therapy and respiratory support should be administered if necessary. Patients in whom intentional overdose is known or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Podophyllum (Topical) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to podophyllum or benzoin
Pregnancy¾Podophyllum should not be used during pregnancy, because it is absorbed through the mother's skin
Breast-feeding¾Podophyllum is absorbed through the mother's skin
Other medical problems, especially friable, bleeding, or recently biopsied warts, because of increased risk of systemic toxicity
Proper use of this medication

>> Importance of keeping away from mouth; medication is poisonous

>> Avoiding contact with the eyes and mucous membranes; if contact occurs, immediately flushing eyes with water for 15 minutes, and thoroughly washing skin with soap and water or (if preparation contains tincture of benzoin) swabbing it with rubbing alcohol

>> Not using near heat, open flame, or while smoking

>> Importance of not using more medication than the amount prescribed

>> Not using on moles or birthmarks

>> Not using on friable, bleeding, or recently biopsied warts

Proper administration

Preventing dissemination of podophyllum to uninvolved skin¾Applying petrolatum around affected areas before applying podophyllum and/or applying talcum powder to treated area immediately after applying podophyllum

Using a toothpick or a cotton-tipped or glass applicator to apply medication

Applying one drop at a time, allowing time between drops for drying, until affected area is covered

Following application of podophyllum, allowing medication to remain on affected area for 1 to 6 hours as directed by physician; removing medication by thoroughly washing affected area with soap and water or, if preparation contains tincture of benzoin, swabbing it with rubbing alcohol

Washing hands immediately after using medication

>> Proper dosing
Missed dose: Applying as soon as possible
>> Proper storage
Side/adverse effects

Signs of potential side effects, especially burning, redness, or other irritation of affected area; skin rash or itching; or initial or delayed symptoms of systemic toxicity

General Dosing Information

Some clinicians recommend that podophyllum be used only under medical supervision because of its potentially serious adverse effects.
Old, discolored, dried, or gritty preparations of podophyllum should not be used.
Podophyllum should not be applied to friable, bleeding, or recently biopsied warts, because systemic absorption of the medication may be increased.
Podophyllum should not be used on moles or birthmarks, since acute inflammation or ulceration may occur.
Podophyllum is most frequently used in a concentration of 25%; however, concentrations of 5 to 10% have been recommended for very large lesions (> 10 to 20 cm 2) in order to minimize the risk of toxicity.
Also, to minimize the risk of toxicity, application of podophyllum should be limited to small areas of intact skin.
If podophyllum is to be self-administered, patients should be instructed to use the medication with great caution. It should be applied only to the affected areas, avoiding contact with normal tissue. This medication can cause severe erosive damage to normal skin.
If podophyllum accidentally comes in contact with normal tissue, it should be removed, preferably by thoroughly washing with soap and water, or, if the podophyllum preparation contains tincture of benzoin, swabbing with rubbing alcohol.
Great care should be taken to avoid contact with the eyes because podophyllum can cause corneal damage. If contact does occur, the eyes should be immediately and thoroughly flushed with water for 15 minutes.
To prevent dissemination of the medication to uninvolved skin, petrolatum may be applied to normal skin surrounding the affected areas prior to application of podophyllum and/or talcum powder may be applied to the treated area immediately following application of podophyllum.

A toothpick or a cotton-tipped or glass applicator should be used to apply the topical solution one drop at a time, until the affected area is covered. Sufficient time should be allowed between drops for drying.
For condyloma acuminatum

Following application of podophyllum, the medication should be allowed to remain on the affected area for a period of 1 to 6 hours as prescribed by the physician.
At the end of the treatment period, the medication should be removed, preferably by thoroughly washing with soap and water. Some clinicians recommend removing podophyllum preparations that contain tincture of benzoin by swabbing with rubbing alcohol; however, this may be more irritating than washing with soap and water.
A minimum of 7 days should elapse between treatments because of the risk of systemic toxicity. Treatment may be repeated at weekly intervals for up to 6 weeks; however, if a beneficial effect does not occur within 6 weeks, alternative therapy should be considered.
For multiple superficial epitheliomatosis or pre-epitheliomatosis keratoses

Before each subsequent application of the medication, the necrotic tissue should be removed by curettage or wiped away with gauze. 1

In response to treatment, the lesion usually sloughs off leaving a superficial ulcer and a moderate degree of dermatitis of the immediate surrounding tissue. When treatment is discontinued, the lesion may be dressed with a mild antiseptic ointment; healing usually occurs in a few days, except in very large lesions, 1 which may take longer to heal.

Topical Dosage Forms

PODOPHYLLUM RESIN TOPICAL SOLUTION USP

Usual adult and adolescent dose

Condyloma acuminatum¾
Topical, to the skin, as a 10 to 25% solution for a period of one to six hours; treatment may be repeated at one-week intervals for up to six weeks. 1, 2, 3

Multiple superficial epitheliomatosis or
Pre-epitheliomatosis keratoses¾
Topical, to the skin, as a 25% solution once a day; treatment should be continued for several days following the initial slough. 9

Juvenile papilloma of the larynx¾
Topical, to the lesion, as a 12.5% solution once a day. The intervals of treatment can be gradually increased as the lesions become smaller; however, applications at short intervals give the best results. 1

Usual pediatric dose

See Usual adult and adolescent dose .

Strength(s) usually available

U.S.¾25% (Rx)[Podocon-25 3] [Podofin 2]

Note: Other strengths are currently not commercially available; compounding required for prescriptions.
Canada¾Podophyllum resin of the North American variety is not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container. Protect from freezing.

Preparation of dosage form:

For treatment of juvenile papilloma of the larynx, the 25% solution should be diluted with an equal volume of 95% alcohol to yield the 12.5% solution. 1

A 25% Podophyllum Resin Topical Solution USP may be prepared extemporaneously by mixing 25 grams of the alcohol-soluble extractive of podophyllum resin in alcohol and 10 grams of the alcohol-soluble extractive of benzoin in alcohol, and diluting with alcohol to make 100 mL.
The solution should be prepared with native North American podophyllum resin, rather than a mixture of North American and Indian resins, because the Indian resin is stronger and more irritating than the North American variety. Also, the resin should be free of guaiacium gum, which may be a sensitizer.
Other vehicles that may be used for preparation of podophyllum resin topical solution include mineral oil or collodion.

Stability:

Exposure to light, air, and warmth may cause precipitation and darkening of the solution because of evaporation and decomposition; such solutions should be discarded.

Auxiliary labeling:

- Poison.
- For external use only.
- Shake well.
- Keep container tightly closed.