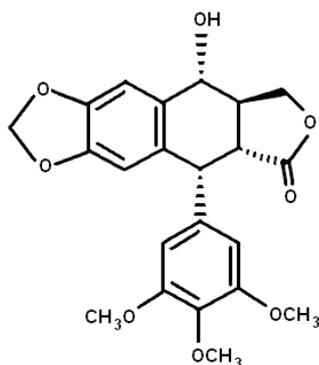


## **PRODUCT INFORMATION**

### **WARTEC® SOLUTION**

#### **NAME OF THE MEDICINE**

WARTEC Solution contains podophyllotoxin as the active ingredient.



CAS number: 518-28-5

#### **DESCRIPTION**

WARTEC Solution is a blue solution for topical use.

WARTEC Solution contains 0.5% w/v podophyllotoxin.

WARTEC Solution also contains ethanol, phosphoric acid, Patent Blue V and purified water.

#### **PHARMACOLOGY**

Podophyllotoxin is a metaphase inhibitor in dividing cells, binding to at least one binding site on tubulin. Binding prevents tubulin polymerisation required for microtubule assembly. At higher concentrations podophyllotoxin also inhibits nucleoside transport through the cell membrane.

The chemotherapeutic action of podophyllotoxin is assumed to be due to inhibition of growth and the ability to invade the tissue of the viral infected cells.

#### **Pharmacokinetic properties**

##### **Absorption / Distribution / Metabolism / Excretion**

Systemic absorption of podophyllotoxin after topical application of 100 mg of 0.3% cream or 100 µL of 0.5% solution has been studied (extravaginally in 10 healthy females [mean age 24 years], and within the preputial cavity in 10 healthy males [mean age 24 years], each on 2 occasions separated by 8 hours).  $C_{max}$  was at or below 4.7ng/mL following all doses and  $T_{max}$  ranged from 0.5-36 hours.; in some subjects concentrations were below the limit of detection.  $C_{max}$  and  $T_{max}$  were comparable for the 0.3% cream and 0.5%

solution in both males and females. It can be concluded that systemic absorption of recommended doses of podophyllotoxin cream or solution is expected to be low.

In a study, a total of 69 patients received 0.5% podophyllotoxin (WARTEC) solution. The toxin was not detected in the serum of patients treated with less than 50 µL. Out-patients who received less than 100 µL gave rise to peak levels of podophyllotoxin of ≤5.0 ng/mL. In the serum of 7 patients treated at the hospital with 100-1,500 µL on extraordinary large en-plaque lesions, peak level variations from 1 to 17 µL were observed within 1-2 hours.

## **INDICATIONS**

For the treatment of external condyloma acuminata (anogenital warts).

## **CONTRAINDICATIONS**

Do not use:

- on open or bleeding wounds (e.g. following surgical procedures)
- in children.
- concomitantly with other podophyllotoxin containing preparations.
- if there is hypersensitivity to podophyllotoxin
- in pregnancy or lactation.

## **PRECAUTIONS**

Use in lesions area greater than 4 cm<sup>2</sup> and individual lesions more than 1 cm<sup>2</sup> is not recommended unless under the direct supervision of a healthcare professional due to the possibility of systemic toxicity.

Total number of topical applications of podophyllotoxin should not exceed 24 applications.

WARTEC Solution should be used with caution in patients with known hypersensitivity to any of the excipients.

Avoid applying podophyllotoxin to warts occurring on mucous membranes of the genital area (including the urethra, rectum and vagina).

Be careful to apply WARTEC Solution to the warts only; if any spreads onto healthy skin it should be washed off with soap and water.

Avoid contact with the eyes. Following accidental spillage the skin should be washed well with soap and water. In the event of the preparation entering the eye, the eye should be bathed thoroughly with water and seek medical advice.

Avoid applying WARTEC Solution to surrounding healthy tissue since the solution contains an active pharmaceutical substance, which could be harmful on healthy skin.

Occlusive dressings should not be used on areas treated with podophyllotoxin.

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

It is recommended that patients refrain from sexual intercourse while treating warts with podophyllotoxin and until the skin has healed. If a patient does engage in sexual intercourse, a condom must be used.

Due to the flammable nature of WARTEC Solution, patients should avoid smoking or being near an open flame during application and immediately after use.

### **Renal impairment**

As there is very limited percutaneous absorption of podophyllotoxin with the recommended dosage, renal impairment is not expected to result in systemic exposure of clinical significance.

### **Hepatic impairment**

As there is very limited precutaneous absorption of podophyllotoxin with the recommended dosage, hepatic impairment is not expected to result in systemic exposure of clinical significance.

### **Effects on Fertility**

There are no data on the effects of podophyllotoxin on human fertility.

Podophyllotoxin at doses up to 2.5 mg/kg/day, was not judged a hazard to male or female fertility in an oral 2- generation reproductive study in rats.

### **Use in Pregnancy**

#### **Category D**

WARTEC Solution must not be used during pregnancy. (See CONTRAINDICATIONS).

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

Although there is very limited systemic absorption from topically applied podophyllotoxin, antimitotic products such as podophyllotoxin are known to cause embryofetal toxicity. Topical podophyllotoxin is not to be used during pregnancy or in women of childbearing potential not using contraception.

Podophyllotoxin caused embryofetal toxicity (lower number of fetuses and/or lower fetal weight), but not teratogenicity in rats when administered intraperitoneally to pregnant females at a dose of  $\geq 0.5$  mg/kg. In rabbits, dermal administration of 0.5% podophyllotoxin (10 mg/kg/day) caused lower fetal weights but no malformations. In a pre- and post- natal study in rats, podophyllotoxin at 2.5 mg/kg/day orally had an adverse effect on the survival of the offspring until the fourth day post-partum.

## **Use in Lactation**

WARTEC Solution must not be used by nursing mothers. (See CONTRAINDICATIONS).

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

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from podophyllotoxin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## **Paediatric use**

Safety and efficacy of topical podophyllotoxin have not been established in children under the age of 12. (See CONTRAINDICATIONS).

## **Use in the elderly**

There are no specific recommendations for use in the elderly.

## **Genotoxicity**

Podophyllotoxin was not mutagenic in an Ames Test, using *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 up to 5000 µg/plate, the maximum concentration in accordance with current guidelines, and was negative in an *in vitro* human chromosome aberration assay using human lymphocytes and an *in vivo* mouse micronucleus test when tested up to 20 mg/kg orally.

Assessment of mutations at the HPRT locus using Chinese Hamster Ovary (CHO) cells *in vitro* showed evidence of mutagenicity, but the results were inconsistent with regard to the dose response observed across replicate cultures.

In an *in vivo* mouse micronucleus test, intravenous administration of podophyllotoxin ( $\geq 3.1$  mg/kg) was found to be aneugenic. This effect was associated with mitotic arrest in the bone marrow.

## **Carcinogenicity**

No oncogenic effects were observed with podophyllotoxin when assessed in an 80-week mouse dietary carcinogenicity studies and in a 2-year rat dietary carcinogenicity study.

## **Ability to perform tasks that require judgement, motor or cognitive skills**

No effects are anticipated based on the adverse reaction profile.

## **INTERACTIONS WITH OTHER MEDICINES**

None known.

## **ADVERSE EFFECTS**

## **Clinical trial data**

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as:

very common        ( $\geq 1/10$ ),  
common            ( $\geq 1/100$  and  $< 1/10$ ),  
uncommon        ( $\geq 1/1,000$  and  $< 1/100$ ),  
rare                ( $\geq 1/10,000$  and  $< 1/1,000$ ) and  
very rare        ( $< 1/10,000$ ), including isolated reports.

## **Skin and subcutaneous tissue disorders**

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

## **Post Marketing Data**

### **Immune system disorders**

Unknown            Application site hypersensitivity

### **Skin and subcutaneous tissue disorders**

Unknown            Skin ulcer, scab, skin discoloration, blister, dry skin

### **General disorders and administration site conditions**

Unknown            Application site pain, swelling, application site bleeding

### **Injury, poisoning and procedural complications**

Unknown            Caustic injury, excoriation, wound secretion

## **DOSAGE AND ADMINISTRATION**

The following doses and schedules are applicable to adults and the elderly (see PRECAUTIONS).

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

Using the applicator provided, the warts should be painted twice daily (every 12 hours) for three days. The minimum quantity should be used to minimise any possible adverse effect.

The treated area should be allowed to dry before opposing skin surfaces are returned to their normal position.

Residual warts should be treated with further courses of twice daily applications for 3 days after a 4 day treatment –free period. Normally 3-4 treatment courses are sufficient.

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 250µl of WARTEC Solution) may be applied.

Application to the surrounding tissue should be avoided.

Where lesions are greater in area than 4cm<sup>2</sup>, it is recommended that treatment takes place under the direct supervision of medical staff.

There is a possibility of relapse following treatment and in the event that this does occur, alternative treatment may need to be considered.

## **OVERDOSAGE**

In cases of overdosage contact the Poisons Information Centre on 13 11 26.

While serious systemic effects have not been reported with the recommended dosage of topical podophyllotoxin, 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. Excessive use of podophyllotoxin 0.5% solution has been reported as causing two cases of severe local reactions. In cases of excessive use of WARTEC Solution resulting in severe local reaction, the treatment should be stopped, the area washed and symptomatic treatment introduced.

Following oral ingestion, podophyllotoxin may also cause severe gastroenteritis.

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

Treatment of oral podophyllotoxin poisoning is symptomatic and should include supportive care. Further management should be as clinically indicated or as recommended by the Poisons Information Centre.

## **PRESENTATION AND STORAGE CONDITIONS**

WARTEC Solution contains 0.5% w/v podophyllotoxin in a blue solution for topical application. The product is presented in amber glass bottles fitted with screw caps and containing 3 ml of solution. A supply of double-ended applicators is included in the pack. A small mirror is also supplied in the pack.

Store below 25°C.

Keep container tightly closed when not in use. Contents are flammable. Keep away from fire, flame or heat. Do not leave WARTEC Solution in direct sunlight.

## **NAME AND ADDRESS OF THE SPONSOR**

GlaxoSmithKline Australia Pty Ltd  
Level 4  
436 Johnston Street

Abbotsford, Victoria 3067  
AUSTRALIA

**POISON SCHEDULE**

Prescription Only Medicine

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):**

21 February 2001

**DATE OF MOST RECENT AMENDMENT:**

08 October 2013

WARTEC<sup>®</sup> is a registered trade mark of Stiefel Laboratories, Inc.

Version 5.0

