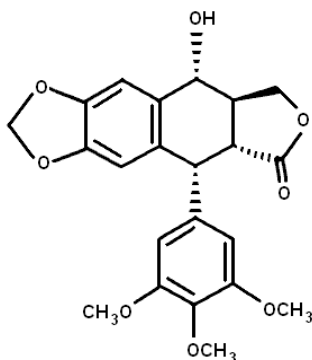


PRODUCT INFORMATION

WARTEC[®] CREAM

NAME OF THE MEDICINE

WARTEC Cream contains podophyllotoxin as the active ingredient.



CAS number:518-28-5

DESCRIPTION

WARTEC Cream is a white cream for topical use.

WARTEC Cream contains 0.15% w/w podophyllotoxin.

WARTEC Cream also contains purified water, stearyl alcohol, cetyl alcohol, isopropyl myristate, liquid paraffin, medium chain triglycerides, butylated hydroxyanisole (BHA), steareth-7, steareth-10, phosphoric acid, methyl hydroxybenzoate, propyl hydroxybenzoate and sorbic acid.

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 μ L 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 4.7 ng/mL following all doses and T_{max} ranged from 0.5 to 36 hrs; in some subjects

concentrations were below the limit of detection. The 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 μ L. Outpatients who received less than 100 μ L 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 μ L on extraordinary large en-plaque lesions, peak level variations from 1 to 17 μ L were observed within 1-2 hours.

INDICATIONS

For the topical treatment of external condylomata acuminata (anogenital warts).

CONTRAINDICATIONS

Do not use:

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

PRECAUTIONS

Use in lesions area greater than 4 cm^2 and individual lesions more than 1 cm^2 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. Care should be taken to ensure the patient fully understands the treatment regime (twice daily applications for three days followed by four treatment free days, for a maximum of four weeks).

Wartec Cream 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).

Avoid contact with the eyes. Should the cream accidentally come into the eyes, the eye should be thoroughly rinsed with water and seek medical advice.

Avoid applying Wartec Cream to surrounding healthy tissue since the cream 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.

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 percutaneous 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 reproduction study in rats.

Use in Pregnancy

Category D:

Wartec Cream 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 ≥ 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 cream 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 study 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 presently 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 affected area should be thoroughly washed with soap and water, and dried prior to application.

Using a finger stall or gloves, the cream is applied twice daily (every 12 hours) for three consecutive days using only enough cream to just cover each wart, and then withheld for the next four consecutive days. The minimum quantity should be used to minimise any possible adverse effect.

Hands should be washed thoroughly after application.

Application to the surrounding tissue should be avoided.

Residual warts should be treated with further courses of twice daily applications for three days after a four day treatment free period, if necessary for a total of 4 weeks of treatment.

Where lesions are greater than 4 cm², 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 Cream 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 Cream contains 0.15% w/w podophyllotoxin in a cream formulation for topical application. The product is presented in lacquered aluminium membrane sealed tubes fitted with a polyethylene cap. A small mirror is supplied with the pack.

Pack size: 5 g and 10 g.

Not all pack sizes may be distributed in Australia.

Store below 30°C.

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):

6 June 2001

DATE OF MOST RECENT AMENDMENT:

09 September 2013

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Version 5.0

