SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

PODOPHYLLINE CREAM 0.15% W/W

2. Qualitative and quantitative composition

Composition:

Podophyllotoxin……..0.15% w/w

Cream base……....q.s.

S No.	Name of Ingredients	Function of ingredients	Quantity required per 1 gm	Overage (%)	Quantity required per 1 gm	Water/LOD content (%)	Total quantity required per 1 gm
Active							
1.	Podophyllum resin	Active Ingredient	3.0 mg	Nil	60.0 mg.	Nil	3.0 mg
Inactive							
2.	Heavy Liquid Paraffin IHS	Emollient	60.0 mg	Nil	1200.0 mg	Nil	60.0 mg
3.	White soft paraffin IHS	Emollient	60.0 mg	Nil	1200.0 mg	Nil	60.0 mg
4.	Cetomacrogol-1000 IHS	Emollient	22.500 mg	Nil	450.0 mg	Nil	22.500 mg
5.	Cetostearyl alcohol IHS	Emollient	72.00 mg	Nil	1440.0 mg	Nil	72.00 mg
6.	Propylene glycol IHS	Stabilizing agent	100.00 mg	Nil	2000.0 mg	Nil	100.00 mg
7.	Benzyl alcohol IHS	Preservative	10.00 mg	Nil	200.0 mg	Nil	10.00 mg
8.	Purified water IHS	Solvent	672.500 mg	Nil	13450.0 mg	Nil	672.500 mg
	Average weight						**20.000 gm**

3. Pharmaceutical form

Cream

Light Brown colored cream.

4. Clinical particulars

4.1 Therapeutic indications

Route of administration: *Topical*

For removal of Corns, warts, including plantar warts and sexually transmitted (Venereal) warts. It is also used topically for treating pre-cancerous white patches on the tongue and mouth (oral hairy leukoplakia).

Intravaginally, podophyllum is used to treat gynecologic infections.

4.2 Posology and method of administration

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

Using a fingertip, the cream should be applied twice daily morning and evening (every 12 hours) for 3 consecutive days using only enough cream to just cover each wart. The cream should then be withheld for the next 4 consecutive days.

Application to the surrounding normal tissue should be avoided.

Residual warts should be treated with further courses of twice daily applications for three days at weekly intervals, if necessary for a total of 4 weeks of treatment.

Hands should be washed thoroughly after application.

Paediatric population

The safety and efficacy of topical podophyllotoxin have not been established in children under the age of 18.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Open or bleeding wounds.

Concomitant use with other podophyllotoxin containing preparations.

4.4 Special warnings and precautions for use

Where the area of treatment is greater than 4 cm2, it is recommended that treatment takes place under the direct supervision of a healthcare professional.

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

Avoid applying the cream to surrounding healthy tissue.

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

Occlusive dressings should not be used on areas treated with the cream.

Local irritation may occur on the second or third day of application associated with the start of wart necrosis. In most cases, the reactions are mild. If severe local skin reactions occur (bleeding, swelling, excessive pain, burning, itching) the cream should be washed immediately from the treatment area with mild soap and water, treatment discontinued and the patient advised to seek medical advice.

Podophylline Cream is not recommended during pregnancy or in women of childbearing potential not using contraception (see section 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

None presently known.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

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 be embryotoxic. Podophylline Cream

is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breastfeeding

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 breastfeeding or to discontinue/abstain from podophyllotoxin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

None presently known.

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Skin and subcutaneous tissue disorders

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

Post-marketing data

The following adverse drug reactions are based on post-marketing reports. Since these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency, however in reality systemic reactions are rarely seen.

Immune system disorders

Not known: Application site hypersensitivity

Skin and subcutaneous tissue disorders

Not known: Skin ulcer, scab, skin discoloration, blister, dry skin

General disorders and administration site conditions

Not known: Application site pain, swelling, application site bleeding

Injury, poisoning and procedural complications

Not known: Caustic injury, excoriation, wound secretion

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

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. Following oral ingestion, podophyllotoxin may also cause severe gastroenteritis.

Treatment

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 National Poisons Centre, where available.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Chemotherapeutics for topical use, Antivirals

ATC code: D06BB

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.

5.2 Pharmacokinetic properties

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 females, and within the preputial cavity in 10 males, 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.

5.3 Preclinical safety data

Carcinogenesis/Mutagenesis

Podophyllotoxin was not carcinogenic following dietary administration up to 0.3 mg/kg/day for 104 weeks in rats and 80 weeks in mice.

Podophyllotoxin was not mutagenic in in vitro Ames Assays, mouse lymphoma assay, and human lymphocyte metaphase assay. Podophyllotoxin showed evidence of mutagenicity in in vitro HPRT mutation assays, however results were inconsistent with regard to the dose response observed across replicate cultures. In mouse micronucleus studies, results were also inconsistent

as one study did not show evidence of mutagenicity and one study did show evidence of an aneugenic effect (increased incidence of micronucleated polychromatic erythrocytes, mitotic arrest). Podophyllotoxin did induce aneuploidy in hamster oocytes.

Reproductive Toxicology

Fertility

In a multi-generational rat fertility and general reproductive performance study, podophyllotoxin administered orally up to

2.5 mg/kg/day had no effect on fertility in female or male rats.

Pregnancy

Podophyllotoxin was not teratogenic in rabbits administered up to 0.5% podophyllotoxin topically or in rats administered up to 5 mg/kg/day intraperitoneally.

6. Pharmaceutical particulars

6.1 List of excipients

Heavy Liquid Paraffin IHS
White soft paraffin IHS
Cetomacrogol-1000 IHS
Cetostearyl alcohol IHS
Propylene glycol IHS
Benzyl alcohol IHS
Purified water IHS

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store between temperature 8° to 25° C. Protect from light.

6.5 Nature and contents of container

20 gm printed lami tube & sealed with white colored plastic cap packed in a printed box with leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

NA

8. Marketing authorisation number(s)

NA

9. Date of first authorisation/renewal of the authorization

NA

10. Date of revision of the text

NA

11. Manufactured by:

KWALITY PHARMACEUTICALS LTD.

Village Nag Kalan, Majitha Road,

Amritsar-143601 (INDIA)