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1. Name of the medicinal product

Podosal Paint

2. Qualitative and quantitative composition

Each 10ml contains Podophyllum resin 20% w/w,

3. Pharmaceutical form

Topical solution

4. Clinical particulars

4.1 Therapeutic indications

Podosal is indicated for treatment of warts

4.2 Posology and method of administration

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

Podosal Paint should be applied twice daily, morning and evening (every 12 hours) for 3 consecutive days. The treatment should then be withheld for the next 4 consecutive days.

Application to the surrounding normal tissue should be avoided.

If residual warts persist, this 3-day treatment may be repeated weekly until there is no visible wart tissue or for a total of 4 weeks of treatment.

Podosal Paint solution should be applied to the warts with the applicator supplied with the solution.

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

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

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 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 cm^2, it is recommended that treatment takes place under the direct supervision of a healthcare professional.

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

Avoid applying the solution to surrounding healthy tissue.

Avoid contact with eyes. Should the solution accidentally come into contact with 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 solution.

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 solution should be washed immediately from the treatment area with mild soap and water, treatment discontinued and the patient advised to seek medical advice.

Podosal Paint Solution 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 solution 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

Pregnancy

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. Podosal Paint Solution 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, and 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

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: D06B B Antivirals

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

Tincture Benzoin Compound 0.895

Rectified Spirit)

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Should be stored below 30°C.

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

6.5 Nature and contents of container

10ml amber coloured glass bottle, 22 mm Aluminium caps, Podosal 10 ml unit box, Podosal literature, Podosal suspension 10 ml sticker labels 40x200 ml shippers Brown BOPP tapes

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorization holder

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8. Marketing authorization number(s)

H2006/270

9. Date of first authorization/renewal of the authorization

02/08/2006

10. Date of revision of the text

13 July 2022