Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Warticon 0.15% w/w Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Podophyllotoxin 1.5 mg/g (0.15% w/w).

Excipients with known effect:
Methyl parahydroxybenzoate (E218) 0.100 %w/w
Propyl parahydroxybenzoate (E216) 0.030 %w/w
Sorbic acid 0.120 %w/w
Stearyl alcohol 2.000 %w/w
Cetyl alcohol 2.000 %w/w
Butyl hydroxyanisole (BHA) (E320) 0.015 %w/w

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Topical cream
A homogenous white cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Route of administration: Topical

For the topical treatment of condylomata acuminata affecting the penis or the external female genitalia.

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 cm^2, 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.

Warticon 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.

This cream contains:

- methyl and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).
- sorbic acid, stearyl alcohol and cetyl alcohol which may cause local skin reactions, (e.g. contact dermatitis).
- butylhydroxyanisole which may cause local skin reactions (e.g.contact dermatitis), or irritation to the eyes and mucous membranes.

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. Warticon 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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

Purified Water
Methyl parahydroxybenzoate E218
Propyl parahydroxybenzoate E216
Sorbic acid
Phosphoric acid
Stearyl alcohol

Cetyl alcohol
Isopropyl myristate
Paraffin, liquid
Triglycerides, medium chain
Butyl hydroxyanisole (BHA) E320
Macrogol –7 stearyl ether
Macrogol – 10 stearyl ether

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

A collapsible aluminium tube with imperforate nozzle membrane and internally coated with a protective lacquer.
Tube cap of polyethylene with a spike on the upper end aimed to perforate the membrane when opening the tube for the first time.
Size 5g and 10g.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/131/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 September 1996

Date of last renewal: 17 January 2010

10 DATE OF REVISION OF THE TEXT

April 2016