**Verrumal®**

## 1. NAME OF THE MEDICINAL PRODUCT

Verrumal Solution
Solution, topical

Fluorouracil, Salicylic acid

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 g of solution contains:
Fluorouracil 0.5 g; salicylic acid 10.0 g

Other excipient with known effect: dimethyl sulfoxide 8.0 g and 160 mg alcohol (ethanol) per g.

For a full list of excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM

Solution, topical.
Verrumal Solution is a clear, colourless to slightly yellow-orange solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Common warts (special form: plantar warts, on areas of the sole of the foot that are subjected to pressure), plane juvenile warts of the extremities.

### 4.2 Posology and method of administration

Posology

Generally Verrumal Solution is applied to every wart two to three times daily.

The average duration of treatments is six weeks. It must be applied consistently every single day.

After successful treatment further treatment should follow for approx. one week.

Children

Verrumal Solution must not be used on babies.

Method of administration

For application to the skin.

Verrumal Solution must only be used on the wart and not on the healthy skin around the wart; if necessary, cover the surrounding skin with a paste or cream. It is recommended that wipe the brush on the neck of the bottle before dabbing it on. With very small warts you should use a toothpick or something instead of a brush for more precise application.

Before reapplying Verumal Solution the coating should be removed every time by simply pulling it off.

In case of periungual and in particular subungual warts, make sure that the nail matrix is not damaged and that Verrumal Solution does not get into the nail bed.

The area to be treated should not be larger than 25 cm².

Experience has shown that in many cases, e.g. with very prominent common warts and planar warts on the soles of the feet, it is better if the dead tissue is removed by a doctor after treatment with Verrumal Solution.

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in Section 6.1.

Verrumal Solution must not be used while breastfeeding, during a pregnancy and also not by women who cannot rule out a pregnancy (see Section 4.6).

Verrumal Solution must not be used on babies and on patients with renal failure.

Verrumal Solution must not be used at the same time as Brivudine, Sorivudine and analogues. Brivudine, Sorivudine and analogues are potent inhibitors of the fluorouracil-degrading enzyme dihydropyrimidine dehydrogenase (DPD) (also see Sections 4.4).

Verrumal Solution is not intended for use on large skin areas (an area of skin no larger than 25 $cm^2$) and it must not come into contact with the eyes or mucous membranes.

**4.4 Special warnings and precautions for use**

Verrumal Solution contains the cytostatic 5-fluorouracil.

The dihydropyrimidine dehydrogenase (DPD) enzyme plays an important part in the fluorouracil degradation. An inhibition, deficiency or reduced activity of this enzyme can result in fluorouracil accumulation. However, as percutaneous absorption of fluorouracil is negligible when Verrumal is administered as per the approved prescribing information, no differences in the safety profile of Verrumal are expected in this subpopulation and no dose adjustments are considered necessary.

Patients who are taking phenytoin at the same time as fluorouracil should regularly be examined for elevated phenytoin plasma levels.

If areas of skin with thin epidermis are affected by warts, Verrumal Solution shall be applied less frequently and checked more often during treatment, as scars may form due to the salicylic acid contained in Verrumal Solution severely softening the corneous layer.

With warts that are very prone to cornification, it is sometimes appropriate to pretreat them with a salicylic acid plaster.

Verrumal Solution should not be used on bleeding lesions.

Strict medical supervision is required with patients with somatosensory disorders (e.g. with Diabetes mellitus).

Close the bottle tightly after every use as the preparation may otherwise dry out quickly and no longer be able to be applied properly. Once dried, Verrumal Solution cannot be used anymore. Apart from this, the solution must no longer be used if crystals have formed.

Make sure that the Verrumal Solution does not come into contact with textiles or acrylic (e.g. acrylic baths) when applying, as the solution may cause stains that cannot be removed (before the coating is formed).

Dimethyl sulfoxide may cause skin irritation.

This medicine contains 160 mg of alcohol (ethanol) in each gram. It may cause burning sensation on damaged skin

Fire warning: Do not light a cigarette or stay near open flames until the film is completely dry.

**4.5 Interaction with other medicinal products and other forms of interaction**

The dihydropyrimidine dehydrogenase (DPD) enzyme plays an important part in the fluorouracil degradation. Antiviral nucleoside analogues such as Brivudine and Sorivudine may lead to a drastic increase in plasma concentrations of fluorouracil or other fluoropyrimidines and therefore to an associated rise in toxicity.
For this reason, a time interval of at least 4 weeks should be adhered to between the use of fluorouracil and Brivudine, Sorivudine and analogues.
In the event of nucleoside analogues, such as Brivudine and Sorivudine, accidentally being administered to patients who are being treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Admission to hospital is also advised, as necessary. All measures should be taken to prevent systemic infection and dehydration.

With the simultaneous administration of phenytoin and systemic fluorouracil, an increase in the plasma concentration of phenytoin was reported that led to phenytoin intoxication symptoms (see Section 4.4).

Resorbed salicylic acid may interact with methotrexate and sulphonylureas.

**4.6 Fertility, pregnancy and lactation**

Verrumal Solution is contraindicated during pregnancy and lactation (see Section 4.3).

**4.7 Effects on ability to drive and use machines**

Verrumal Solution has no or only negligible effect on the ability to drive and use machines.

**4.8 Undesirable effects**

Undesirable effects are listed hereunder in accordance with the MedDRA System Organ Class and in decreasing frequency. Assessment of frequency of the undesirable effects is based on the following categories: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); unknown (frequency unable to be assessed from available data).

| System organ class | Frequency | Side effect |
|---|---|---|
| General diseases and complaints at the site of application | Very common | Appearing at the administration site: erythema, inflammations, irritations (including burning), pain, pruritus |
| | Common | Appearing at the administration site: bleeding, skin erosion, crusting |
| | Uncommon | Appearing at the administration site: dermatitis, edema, ulceration |
| Diseases of the skin and subcutaneous tissue | Common | Skin exfoliation |
| Diseases of the nervous system | Common | Headaches |
| Eye diseases | Uncommon | Dry eyes, eye itching, increased tear secretion |

In rare cases, severe burning may lead to treatment being stopped.

Due to the effect of the severe softening of the corneal layer there may be whitish discolorations or exfoliation of the skin, particularly in the area around the wart.

As a result of the salicylic acid content slight irritation such as dermatitis or contact-allergic reactions which may also manifest themselves by itching, reddening and blisters beyond the area of contact (so-called spreading reactions) may occur with accordingly susceptible patients when using this medicinal product.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

**4.9 Overdose**

When applying Verrumal Solution to a 25 cm² area of skin, an amount of 0.2 g Verrumal Solution and therefore 1 mg of fluorouracil (FU) is applied. 1 mg of FU corresponds to a dose of 0.017 mg/kg of body weight with a person weighing 60 kg. Systemic intoxications occur with intravenous administration of 15 mg per kg body weight and are therefore ruled out as a result of this thousandfold safety profile. The safety profile also increases even more considerably as FU is not percutaneously resorbed to any significant degree from Verrumal Solution (see also Section 5.2).

As a serum level of barely over 5 mg/dl is reached after the percutaneous resorption of salicylic acid (also see Section 5.2), salicylate intoxications are practically ruled out if Verrumal Solution is used as prescribed (also see Section 5.2).

Early symptoms of salicylate intoxication can only occur with serum levels over 30 mg/dl. They include ringing in the ears, tinnitus with hearing difficulty, nosebleeds, nausea, vomiting, irritability a feeling of dryness with mucous membranes.

Therefore, systemic intoxications are unlikely for both active ingredients if applied to the skin as prescribed (see above). However, clearly exceeding the recommended frequency of application increases the frequency and the severity of local reactions at the site of application.

Children

Small children have a different ratio of body surface to body mass to adults. Therefore significantly exceeding the maximum recommended treatment area or treatment frequency increases the risk of salicylate intoxication, especially in small children.

## 5. PHARMACOLOGICAL PROPERTIES

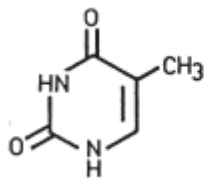
### 5.1 Pharmacodynamic properties

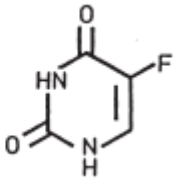
Pharmacotherapeutic group: other dermatics, wart product and keratolytic treatment
ATC code: D11AF

Mechanism of action of fluorouracil

The active ingredient fluorouracil (FU) belongs to the cytostatics that act as anti-metabolites.

As a result of its structural similarity with to Thymine (5-Methyluracil), which is present in nucleinic acids, FU prevents formation and use of this and in this way inhibits both DNA and RNA synthesis.
Consequently the growth of the wart virus is inhibited resulting in the inhibited growth of the kinds of cells in particular which are in the accelerated growth stage, as with warts, and therefore absorb FU in increased amounts.




Thymine Fluorouracil

Mechanism of action of salicylic acid

Salicylic acid was added because of its keratolytic properties, to facilitate penetration of the active ingredient, which is especially difficult in warts. The same is achieved by the solubilizing agent for the active ingredient FU, dimethyl sulfoxide. The keratolytic action of salicylic acid is based on direct effect on the intercellular glue substances or desmosomes promoting the keratinization process.

**5.2 Pharmacokinetic properties**

In a resorption study on pigs it could be proved that there was no fluorouracil in the serum after the cutaneous application, even in large amounts of Verrumal Solution i.e. the active ingredient was not resorbed in an amount that could be detected using standard analytical methods (HPLC).

According to more recent analysis, the fluorouracil resorption rate in people after use of Verrumal Solution is significantly less than 0.1 %.

After application on the skin, Verrumal Solution forms a strong white looking film on the skin once the solution has evaporated. Thus, an occlusive effect is achieved to benefit the difficult penetration of the active ingredient particularly with warts.

Animal experiments and human pharmacokinetic studies show that salicylic acid penetrates quickly depending on the basis and penetration influencing factors, such as skin condition.

Salicylic acid is metabolized by the conjugation with glycine into salicyluric acid, with gluconic acid from the phenolic OH group into ether glucuronide and on the COOH group into ester glucuronide, while via hydroxylation it is metabolized into gentisic or dihydroxybenzoic acid. The half-life of systemically resorbed salicylic acid is between 2 and 3 hours in the normal dose range and can increase to 15 to 30 hours with high posology as a consequence of the liver's limited capacity to conjugate salicylic acid.

With a topical application of salicylic acid, no toxic undesirable effects are generally expected (if all contraindications are observed!) as a serum level over 5 mg/ml can barely be reached. Early symptoms of salicylate intoxication can only occur with serum levels over 30 mg/dl.

**5.3 Preclinical safety data**

There are no known mutagenic, carcinogenic and teratogenic effects from salicylic acid to date.

**6. PHARMACEUTICAL DATA**

**6.1 List of the excipients**

Ethyl acetate
Ethanol, anhydrous
Dimethyl sulfoxide
Methacrylic acid methyl ester/methacrylic acid butyl ester copolymer
Pyroxyline

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

The expiry date of the product is indicated on the packaging materials.
Once opened : 6 months

**6.4 Special precautions for storage**

Do not store above 25° C.
Do not store at temperature below 10° C.
Flammable!

**6.5 Nature and contents of container**

13 ml glass bottle
14 ml glass bottle

**6.6 Special precautions for disposal**

No special requirements.

**7. MANUFACTURER**

Almirall Hermal GmbH
Scholtzstrasse 3
D-21465 Reinbek
Hamburg, Germany

**8. REGISTRATION HOLDER**

Neopharm Ltd.
Hashiloah 8, POB 7063
Petach Tiqva 49170
Israel

**9. REGISTRATION NUMBER:**

010-34-24061

Revised in November 2020.