Verrumal®

1. NAME OF THE MEDICINAL PRODUCT

Verrumal®
Cutaneous solution
Fluorouracil, salicylic acid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 g of solution contains:

Fluorouracil 0.5 g; salicylic acid 10.0 g
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cutaneous solution.
Verrumal is a clear, colourless 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

For application to the skin.

In general Verrumal is applied to each wart two to three times daily.

Verrumal must only come into contact with the wart and not with the healthy skin surrounding the wart; if necessary, the surrounding skin should be covered with a paste or ointment. It is advisable to wipe off the brush on the neck of the bottle before application. In the case of very small warts the medicinal product can be more accurately applied by a toothpick or similar item instead of with the brush.

Each time Verrumal is reapplied the existing film coating should be removed beforehand by simply peeling it off.

In the case of periungual warts and - in particular - subungual warts care should be taken that the nail matrix is not damaged and Verrumal is not allowed to enter the nail bed.

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

The average length of application is 6 weeks. Consistent application on a daily basis should be ensured.

Once the therapy has proved to be successful, treatment should be continued for approximately 1 week.

Experience has shown that in many cases, e.g. where there are very prominent common warts and warts on the soles of the feet, it is advantageous if the tissue that has died as a result of the Verrumal treatment is removed by a doctor.

4.3 Contraindications

Hypersensitivity to the active substances or to any other ingredients.

Verrumal may not be used during lactation, an existing pregnancy or by women for whom pregnancy cannot be excluded with certainty.

Verrumal should not be used to treat infants or patients with renal insufficiency.

Verrumal should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the DPD enzyme. DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Verrumal may not be used in conjunction with brivudine, sorivudine and analogues. Brivudine, sorivudine and analogues are potent inhibitors of the fluorouracil-degrading enzyme dihydropyrimidine dehydrogenase (DPD) (see also sections 4.4 and 4.5).

Verrumal is not intended for use to large surfaces of the skin (skin area not greater than 25 cm²).

Verrumal must not be allowed to come into contact with the eyes or mucous membranes.

4.4 Special warnings and precautions for use

Patients should discontinue therapy with Verrumal if symptoms of DPD enzyme deficiency develop (see CONTRAINDICATIONS section).

Rarely, life-threatening toxicities such as stomatitis, diarrhea, neutropenia, and neurotoxicity have been reported with intravenous administration of fluorouracil in patients with DPD enzyme deficiency. One case of lifethreatening systemic toxicity has been reported with the topical use of Verrumal in a patient with DPD enzyme deficiency. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. A similiar case was observed with the use of a topical product containing 5% fluorouracil.

If applicable, the determination of DPD enzyme activity is indicated before starting treatment with fluoropyrimidines.

Nucleoside analogues such as brivudine and sorivudine may lead to a drastic increase in plasma concentrations of fluorouracil or other fluoropyrimidines and thus an associated increase in toxicity. For this reason, an interval of at least 4 weeks between the use of fluorouracil and brivudine, sorivudine and analogues should be observed.

In case of an accidental administration of brivudine to patients who are being treated with fluorouracil, effective measures for reducing fluorouracil toxicity should be taken. Admission to a hospital may be indicated. All necessary measures for protection from systemic infections and dehydration should be introduced.

Patients who take phenytoin concomitantly with fluorouracil should be regularly tested for elevated plasma levels of phenytoin.

Flammable!

The other active ingredient dimethyl sulphoxide may induce skin irritation.

If areas of skin with a thin epidermis are afflicted by warts, Verrumal should be applied less frequently and the course of the therapy monitored more often, as the strong softening effect of the salicylic acid contained in Verrumal on the corneal layer may result in the formation of scars.

With warts that have a very strong tendency to cornification it is sometimes expedient to pre-treat the warts with salicylic acid plasters.

In patients with sensory disturbances (e.g. those with diabetes mellitus) close medical monitoring is required.

The bottle should be properly closed each time the preparation is used as it otherwise dries up quickly and can no longer be used correctly.

Care should be taken that when Verrumal solution is applied it does not come into contact with textiles or acrylics (e.g. acrylic baths) as the solution may cause stains that cannot be removed before the formation of the film.

4.5 Interaction with other medicinal products and other forms of interaction

The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the breakdown of fluorouracil. Nucleoside analogues such as brivudine and sorivudine may lead to a drastic increase in plasma concentrations of fluorouracil or other fluoropyrimidines and thus an associated increase in toxicity.
For this reason, an interval of at least 4 weeks between the use of fluorouracil and brivudine, sorivudine and analogues should be observed.
If applicable, the determination of DPD enzyme activity is indicated before starting treatment with fluoropyrimidines.

Elevated plasma levels of phenytoin leading to symptoms of phenytoin intoxication have been reported with the concomitant administration of phenytoin and fluorouracil (see 4.4).

Absorbed salicylic acid may interact with methotrexate and sulphonylureas.

4.6 Pregnancy and lactation

Verrumal is contraindicated in pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Verrumal has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The following categories of frequencies underlie the evaluation of side effects:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

Common: burning, particularly during application.

Uncommon: erosive skin reactions.

In rare cases an intense burning sensation may lead to the therapy being discontinued.

As the medicinal product has a very strong softening effect on the corneal layer, whitish discolorations and defurfuration of the skin may occur, particularly in the surroundings of the wart.

Due to its salicylic acid content, use of this medicinal product may cause slight signs of irritation, such as dermatitis and contact allergic reactions, in patients of a corresponding disposition. Such irritation may be manifested in the form of itching, reddening and small blisters even outside the area of contact (so-called scatter reactions).

4.9 Overdose

During the application of Verrumal to a 25 cm² area of skin a quantity of 0.2 g of Verrumal and therefore 1 mg of fluorouracil (FU) is applied.

For an individual weighing 60 kg 1 mg of FU corresponds to a dose of 0.017 mg per kilgram of body weight. Systemic intoxications occur in the case of intravenous doses of 15 mg per kilogram of body weight and can therefore be excluded due to the thousand-fold safety margin. Furthermore, the safety margin is also considerably increased by the fact that there is no significant percutaneous absorption of FU from Verrumal (see also section 5.2).

Due to the fact that after the percutaneous absorption of salicylic acid serum levels above 5 mg/dl are hardly ever reached (see also section 5.2), salicylate intoxications are practically excluded when Verrumal is applied in accordance with instructions.

Early symptoms of salicylate intoxication only occur at serum levels of more than 30 mg/dl. These manifest themselves in the form of ringing in the ears, tinnitus with hardness of hearing, epistaxis, nausea, vomiting, irritability as well as a feeling of dryness of the mucous membranes.

5. PHARMACOLOGICAL PROPERTIES

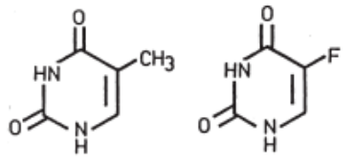
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Wart and anti-corn preparations

ATC code: D11AF

The active substance fluorouracil (FU) is one of the cytostatics that have an antimetabolite effect.

Due to its structural similarity with the thymine (5-methyluracil) occurring in nucleic acids, FU prevents its formation and utilisation and in this way inhibits both DNA and RNA synthesis. As a consequence the growth of the viruses causing the warts is inhibited. The result is growth inhibition of those cells in particular which - as in the case of warts - are at a stage of accelerated growth and therefore absorb FU in increased quantities.



Thymine Fluorouracil

5.2 Pharmacokinetic properties

In an absorption study carried out on pigs no fluorouracil was detected in the serum after the cutaneous application of Verrumal - even in large quantities - i.e. the active substance was not absorbed in quantities which could be detected with standard analytical methods (HPLC).

According to more recent analyses the absorption rate of fluorouracil in humans after the application of Verrumal is markedly below 0.1 %.

After application to the skin Verrumal forms a solid film which appears white after the solvent has evaporated. This produces an occlusive effect which promotes penetration of the active substance into the deeper layers of the warts.

Salicylic acid has been added due to its keratolytic properties in order to improve penetration of the active substance, which is particularly difficult in the case of warts. The same effect is achieved by the dimethyl sulphoxide, which acts as a solubiliser for the active ingredient FU.

The keratolytic effect of salicylic acid is based on its direct action on the intracellular cement substances or desmosomes, which promote the cornification process.
Experiments on animals and human pharmacokinetic trials have shown that salicylic acid penetrates the surface rapidly, depending on the substrate and other factors influencing penetration, such as the condition of the skin.

The metabolisation of salicylic acid occurs by conjugation with glycine to form salicyluric acid, with glucuronic acid on the phenolic OH group to form ether glucuronide and on the COOH group to form ester glucuronide, or by hydroxylation to gentisic acid and dihydroxybenzoic acid. In the normal dose range the half-life of salicylic acid is between 2 and 3 hours, but may increase to 15 to 30 hours in the case of high dosages as a result of the limited capacity of the liver to conjugate salicylic acid.
No toxic side effects are generally to be expected from the topical application of salicylic acid (but see the contraindications!), as serum levels above 5 mg/dl are hardly ever reached. Early symptoms of salicylate intoxication can only occur at serum values of more than 30 mg/dl.

5.3 Preclinical safety data

Salicylic acid is not known to have any mutagenic, carcinogenic or teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Ethyl acetate
Pyroxylin
Poly (butyl methacrylate -
co-methyl methacrylate) (80:20)
Dimethylsulphoxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After opening: 6 months

6.4 Special precautions for storage

Do not store above 25° C.
Verrumal may only be stored below 10°C for a short time.
Flammable!

6.5 Nature and contents of container

13 ml bottle N 1

6.6 Special precautions for disposal and other handling

No special requirements.

If your patient experienced any of the side effects listed above, or any other side effect please contact us: Neopharm Ltd.

7. MARKETING AUTHORISATION HOLDER

Almirall Hermal GmbH
Scholtzstrasse 3
21465 Reinbek
Germany
Tel.: (040) 7 27 04-0
Fax: (040) 722 92 96
info@almirall.de
www.almirall.de

8. REGISTRATION HOLDER

Neopharm Ltd.
Hashiloah 6, POB 7063
Petach Tiqva 49170
Israel

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