**PRODUCT MONOGRAPH**

# NERISALIC®

(0.1% diflucortolone valerate and 3% salicylic acid)

OILY CREAM

## THERAPEUTIC CLASSIFICATION

TOPICAL CORTICOSTEROID-KERATOLYTIC

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## ACTIONS AND CLINICAL PHARMACOLOGY

NERISALIC® (0.1% diflucortolone valerate and 3% salicylic acid) Oily Cream combines the anti-inflammatory, anti-pruritic and vasoconstrictive activity of diflucortolone valerate and the keratolytic effects of salicylic acid.

Both diflucortolone valerate and its split ester are topically active.

## INDICATIONS AND CLINICAL USE

NERISALIC® (0.1% diflucortolone valerate and 3% salicylic acid) Oily Cream is indicated in the topical treatment of chronic eczema, psoriasis vulgaris, neuro-dermatitis and scaly crusty dermatoses which respond to corticosteroid therapy.

NERISALIC® Oily Cream is not suitable for the treatment of perioral dermatitis and rosacea.

## CONTRAINDICATIONS

NERISALIC® (0.1% diflucortolone valerate and 3% salicylic acid) Oily Cream is contraindicated in patients who have shown hypersensitivity, allergy or intolerance to diflucortolone valerate or other corticosteroids or salicylic acid or to any excipients in the preparation. NERISALIC® Oily Cream should not be applied to skin areas with fissures, erosions, scratches or excoriations.

Topical steroids are contraindicated in untreated bacterial and/or fungal skin infections. Topical steroids should not be applied in cases of tuberculosis of the skin, or syphilitic skin infections, chicken pox, eruptions following vaccinations and viral diseases of the skin in general.

## WARNINGS

NERISALIC® (0.1% diflucortolone valerate and 3% salicylic acid) Oily Cream is not for ophthalmic use and, consequently, should not be used in or near the eyes.

NERISALIC® Oily Cream should not to be applied in rhagades and ulcerations (e.g. lower leg ulcers). Inclusion of salicylic acid in this preparation increases steroid penetration into the viable epidermis thereby increasing the potential for skin atrophy.

Use in Pregnancy:

The safety of NERISALIC® Oily Cream during pregnancy has not been established. Teratogenic and embryotoxic effects of diflucortolone valerate have been reported following dermal application in animal studies. NERISALIC® Oily Cream should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Use in Nursing Mothers:

Systemically administered corticosteroids can appear in human milk and can suppress growth, interfere with endogenous corticosteroid production or cause adverse effects. Caution should be exercised when NERISALIC® Oily Cream is administered to a nursing woman since it is not known whether the ingredients of NERISALIC® Oily Cream are excreted in human milk.

## PRECAUTIONS

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria in some patients.

Significant systemic absorption may occur when steroids are applied over large areas of the body or if used under an occlusive dressing. To minimize this possibility when long term therapy is anticipated, interrupt treatment periodically or treat one area of the body at a time. It is recommended that patients receiving a large dose of a potent topical steroid applied over a large surface area be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests.

If HPA axis inhibition is observed, an attempt should be made to withdraw the drug, to reduce the frequency of application or substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

If irritation or hypersensitivity reactions develop, NERISALIC® Oily Cream (diflucortolone valerate 0.1% and 3% salicylic acid) should be discontinued and appropriate therapy initiated.

Prolonged use of topical corticosteroid products may produce atrophy of the skin and of subcutaneous tissues, particularly on flexor surfaces and on the face, telangiectasias, hirsutism and steroid induced acne. If this is noted, discontinue use of the product. Long-term therapy with NERISALIC® Oily Cream should be avoided.

In cases of bacterial or fungal skin infections, appropriate antibacterial agents should be used as primary therapy. If it is considered necessary, NERISALIC® Oily Cream may be used as an adjunct to control inflammation, erythema and itching.

NERISALIC® Oily Cream should be used with caution in patients with stasis dermatitis and other skin diseases associated with impaired circulation, on extremities of diabetics with impaired circulation or on patients with inherent compromised cardiovascular circulatory problems.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Systemic absorption of the corticosteroid and salicylic acid may be increased with elevated body temperature or occlusive dressings. Patients with elevated temperatures should be monitored for HPA axis effects and occlusive dressings should not be used.

Occlusive dressings should not be applied if there is an elevation of body temperature.

Because of the risk of salicylate intoxication, long term or large area and occlusive use of NERISALIC® Oily Cream should be avoided in patients with impaired renal function.

Since salicylic acid is absorbed almost completely, the simultaneous topical or internal use of other preparations containing salicylic acid or salicylate is inadvisable. The concentration of salicylic acid contained in the preparation is not high enough for the treatment of secondary skin diseases caused by bacteria or fungi. Additional antibacterial or anti-mycotic therapy is recommended in these cases.

Use in children:

Due to their larger skin surface area to body weight ratio, children may demonstrate a greater susceptibility to the topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients.

Suppression of the HPA axis, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papilledema.

Administration of topical corticosteroid to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of the children.

The following tests may be helpful in evaluating HPA axis suppression due to corticosteroid component: urinary free cortisol test and ACTH stimulation test.

Because of the risk of salicylate intoxication, long term or large area and occlusive use of NERISALIC® Oily Cream should be avoided in babies, infants and in children.

## ADVERSE REACTIONS

The following local adverse reactions are reported when topical corticosteroids are used as recommended. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, telangiectasia, striae and miliaria. Hypothalamic-pituitary-adrenal axis suppression have also been reported following topical corticosteroid therapy.

Posterior sub-capsular cataracts have been reported following systemic use of corticosteroids.

In addition, the salicylic acid contained in the preparation may produce some desquamation, local reddening of the skin, pruritus, burning, pain and stinging. Hypersensitivity to salicylic acid may occur. If this occurs, discontinue use.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific antidote is available. Treatment should be symptomatic.

Symptoms:

Percutaneous absorption of corticosteroids can occur when large amounts of corticosteroids are applied. Toxic effects may include ecchymosis of skin, peptic ulceration, hypertension, aggravation of infection, hirsutism, acne, edema and muscle weakness due to protein depletion.

High levels of salicylates may cause temporary hearing or visual disturbance, drowsiness and nausea.

Treatment:

Appropriate symptomatic treatment of corticosteroid and/or salicylic acid overdosage is indicated. Acute hypercorticoid symptoms are usually reversible. Treat electrolyte imbalance, if necessary. In cases of chronic toxicity, slow withdrawal of corticosteroid is advised.

## DOSAGE AND ADMINISTRATION

NERISALIC® (0.1% diflucortolone valerate and 3% salicylic acid) Oily Cream should be applied as a thin film to diseased areas two to three times daily in the first week of treatment. During subsequent weeks, one or two applications per day are sufficient. The duration of the treatment should not exceed a total of four weeks.

The total dose of NERISALIC® Oily Cream applied weekly should not exceed 100 grams. If improvement is not noted within a few days to a week, the local application of NERISALIC® Oily Cream should be discontinued and the patient re-evaluated.

## PHARMACEUTICAL INFORMATION

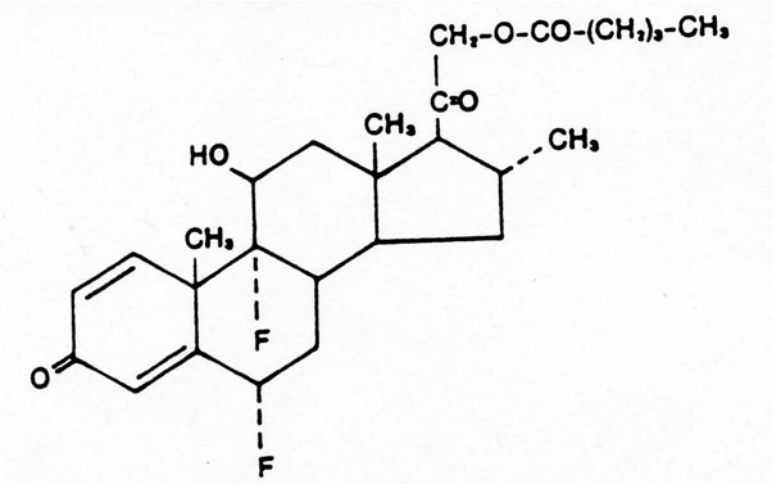
DRUG SUBSTANCE:

A. Diflucortolone valerate

Proper Name: Diflucortolone-21-valerate

Chemical Name: 6α, 9-difluoro-11ß, 21-dihydroxy-16α-methyl-pregna-1, 4-diene-3, 20-dione 21-valerate.

Structural Formula:




Molecular Formula: $C_{27}H_{36}F_2O_5$ Molecular Weight: 478.58

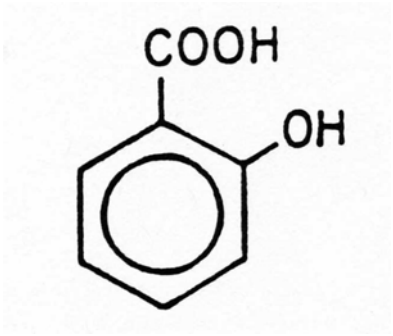
Description: Diflucortolone valerate is a white to slightly cream-white crystalline, odorless powder, easily soluble in chloroform, slightly soluble in methanol and sparingly soluble in ether. It melts between 200°C and 205°C and has a specific rotation within +98° to +103° in dioxane.

B. Salicylic Acid

Proper Name: Salicylic acid, micro

Chemical Name: 2-hydroxybenzoic acid

Structural Formula:




Molecular Formula: $C_7H_6O_3$ Molecular Weight: 138.12

Description: White crystals, usually in fine needles, or fluffy white crystalline powder. Freely soluble in alcohol and ether, sparingly soluble in chloroform and glycerol, slightly soluble in benzene and water 25°C. It melts between 158.5 - 161.0°C

Composition: Each g of NERISALIC® Oily Cream contains:

0.1% diflucortolone-21-valerate, micro 20
3.0% salicylic acid, micro

in a water-in-oil emulsion. The external, lipo-philic phase contains hydrocarbons (white petrolatum, paraffin), white wax and dehymuls E. There is no preservative.

Storage: NERISALIC® Oily Cream should be stored at 15° to 30°C. Avoid freezing.

## AVAILABILITY OF DOSAGE FORMS

NERISALIC® Oily Cream: 30g tubes containing 0.1% diflucortolone-valerate and 3% salicylic acid in a water-in-oil emulsion.

## PHARMACOLOGY

### A. HUMAN STUDIES

Diflucortolone valerate

On dermal application of diflucortolone valerate, both the un-split ester and the free diflucortolone arising from cleavage of the ester exert anti-inflammatory, anti-proliferative and pharmaco-logical effects.

In the vasoconstriction test on human skin, in which hyperemia has been experimentally induced, a water/oil emulsion with 0.001% diflucortolone valerate is as effective as a similar preparation containing 0.1% fluocortolone.

Salicylic Acid

Salicylic acid or hydrobenzoic acid is mainly a keratolytic and keratoplastic agent. Salicylic acid enhances the shedding of human corneocytes by acting on the cement binding the stratum corneum cells together without affecting the mitotic activity and the function of the normal living epidermis.

NERISALIC® (0.1% diflucortolone valerate and 3% salicylic acid) Oily Cream

The solubilizing effect on the stratum corneum was demonstrated in humans where the mean stratum corneum thickness (MSCT) was measured following application under an occlusive dressing of NERISALIC® Oily Cream, 3% salicylic acid ointment and an ointment without active ingredient (base). The MSCT, following application of the base ointment, was 29.2 ± 8.6 µm, application of NERISALIC® Oily Cream and 3% salicylic ointment decreases MSCT to 7.9 ± 2.2 µm and 17.3 ± 6.0 µm respectively. These results are supported by another pharmacodynamic study where the rate of shedding of the stratum corneum was evaluated using fluorescence technique following application of the three same compounds stated above. The results which were given as a total score, shedding rate obtained with NERISALIC® Oily Cream and 3% salicylic ointment is significantly superior to the one obtained following application of the base ointment.

A pharmacokinetic study on healthy subjects shows that following a large application of NERISALIC® Oily Cream, the plasma salicylate levels averaged over time 3.6 µg/mL (range 0.3 - 10.7µg/mL) which is well under the toxic salicylate level of 300 µg/mL.

## B. ANIMAL STUDIES

Diflucortolone valerate

Experiments in rats and guinea pigs demonstrate that shortly after absorption in the skin, diflucortolone valerate is broken down into diflucortolone and valeric acid.

In experimentally produced inflammation of the rat ear, the anti-inflammatory effect of diflucortolone valerate is about 3 times greater than that of fluocortolone. In the same trial-design, the local anti-inflammatory effect of diflucortolone valerate is equal to that of fluocinolone acetonide and betamethasone-17-valerate but greater than that for beclomethasone dipropionate.

On subcutaneous administration in the rat adjuvant-paw-edema test, the anti-inflammatory effect of diflucortolone valerate is about 30 times greater than that of fluocortolone and about 3 times more than dexamethasone. In contrast in this type of study, fluocinolone acetonide, which is almost equipotent topically with diflucortolone valerate, is systemically 20 times more active in its anti-inflammatory effect.

Diflucortolone valerate is about 10 times as active as fluocortolone in the ring-granuloma test.

On oral administration to adrenalectomized rats, the effect of diflucortolone is equal to that of dexamethasone as measured by decrease in body weight, elevation of blood sugar and the increased elimination of potassium, phosphorus and nitrogen via urine and feces.

Endocrinological action on systemic administration is characterized by the absence of estrogenic, anabolic androgenic and anti-androgenic properties. Exceptions are a progestational effect in the Clauberg test in the rabbit and an anti-estrogenic effect in the mouse uterus test.

Salicylic Acid

A study on guinea pigs shows that salicylic acid acts on the cementing substances binding the stratum corneum cells together and not on the cell itself.

# TOXICOLOGY

## ACUTE TOXICOLOGY

## A. DIFLUCORTOLONE VALERATE

A summary of acute toxicology studies of diflucortolone valerate in various species is shown in Table I.

### TABLE I - RESULTS OF ACUTE TOXICOLOGY STUDIES IN VARIOUS SPECIES

| DRUG | SPECIES | ROUTE | $LD_{50}$ (g/kg) | SYMPTOMS |
|---|---|---|---|---|
| DIFLUCORTOLONE VALERATE (DFV) | Mouse | Oral | >4.0 | Transient apathy |
| | Rat | Oral | 3.1 | Cachexia pronounced apathy ventricumbence |
| | Dog | Oral | >1.0 | None |
| DFV OILY CREAM 0.1% | Rat | Oral | >38.1 | None |

## B. Salicylic Acid

The $LD_{50}$ for different animal species are presented in the following table:

| Species | Administration Route | Clinical Symptoms | $LD_{50}$ mg/kg |
|---|---|---|---|
| Mouse | IP | - Somnolence<br>- Respiratory depression | 300 |
| Mouse | IV | - Convulsion<br>- Effect on seizure threshold | 184 |
| Cat | Oral | - Toxic effects not yet reviewed | 400 |
| Mouse | Oral | - Toxic effects not yet reviewed | 480 |
| Rat | Oral | - Toxic effects not yet reviewed | 891 |
| Rabbit | Oral | - No toxic effect noted | 1300 |

Data collected from: Registry of toxic effects of chemical substances 1985-86 Edition Volume 5 Edited by Doris V. Sweet, U.S. Dept. of Health and Human Services.

## SUBACUTE TOXICITY

### A. Diflucortolone valerate

Following daily subcutaneous administration over 6 weeks, the tolerance limit for rats was 0.4 µg/kg/day and for dogs 40 µg/kg/day. All side effects observed at these or higher doses, such as thymolysis and atrophy of the adrenal cortex, correspond to those produced by subcutaneous administration of any systemically potent corticoid.

In topical tolerance studies over 28 days on the intact and scarified skin of the beagle dog and rabbit, no macroscopic or histological differences were seen when a daily application of 0.25g of oily cream were compared with the corresponding base.

Following daily application of the 0.1% oily cream formulation to the shaved and scarified skin of dogs over a period of 13-14 weeks, systemic corticoid effects occurred only after application of amounts in excess of 100 mg/kg.

## TERATOLOGY

A. Diflucortolone valerate

Following dermal application of 0.1% diflucortolone valerate ointment preparation to scarified skin during the phase of organogenesis in pregnancy, embryotoxic and typical steroidal teratogenic effects occurred at doses in excess of 500 mg/kg/day in rats and 50 mg/kg/day in rabbits. This included delayed ossification, umbilical hernia, caudal aplasia, reduced fetal weights, increased perinatal mortality, cleft palate and shortened limbs.

## BIBLIOGRAPHY


1. Grejs J. Vergleichende PrÜgunh bon Figluvotyolon-21-valerat Creme und Hydrocortison-17-butyrat Creme bei Hautkranken. Therapie der Gegenwart 1978;117,12:1930-1937.

2. Hoppe G. Treating skin diseases in Asia with diflucortolone valerate. Modern Medicine of Asia 1977;13,7:17-22.

3. Hoppe G. A multicentric clinical trial with diflucortolone valerate in S-E Asia (with comparison to the results obtained worldwide). Filipino Family Physician 1977;15,2:32-38.

4. Langen M, Sastre Y, Hernandez M. Results of a multicentre, multinational clinical trial of diflucortolone valerate (Nerisona) (trans.) Zeitschrift fÜr Hautkrankheiten 1976;51(Suppl 1):1-16.

5. Langen ML. Topical treatment of various skin diseases with diflucortolone valerate in 360 patients. Clinical Therapeutics 1979;2,2:124-133.

6. Lofferer O. Study of a new, topically effective corticosteroid (diflucortolone valerate) using the psoriasis - plaque test (trans.). Dermatologia venezolana 1975;14,1-2:37-47.

7. Mackey JP. Diflucortolone valerate and fluocinolone acetonide in eczema: a double-blind trial. Pharmatherapeutica 1977;1,7:462-465.

8. Reckers R, Wendt H. Multicentre clinical trial of the new corticosteroid diflucortolone valerate as a cream, ointment and fatty ointment.

   PART 1: Comparative studies of diflucortolone valerate and fluocortolone, fluocortolone caproate and pivalate applied topically in a double-blind contralateral design.

PART II: Comparative studies with various commercial preparations. (trans.) Arzneimittel-Forschung (Drug Research) 1976;26,7b:1499-1509.

9. Straehl B. Behandlung verschiedener Dermatosen mit Diflucortolon-valerat 0.1% (Nerisona). Schweizerische Rundschau fÜr Medizin (Praxis) 1978;67,35:1277-1284.

10. Van Zuiden E. Diflucortolonvalerianat und Fluocinolonacetonid bei Ekzem und Dermatitis. Therapie der Gegenwart 1978;117,8:1248-1264.

11. Davies MG, Marks R. Studies on the effect of salicylic acid on normal skin. Brit J Dermatol 1976;95:187-192.

12. Roberts DL, Marshall R, Marks R. Detection of the action of salicylic scid on the normal stratum corneum. Brit J Dermatol 1980;103:191-196.

13. Huber C, Christophers E. "Keratolytic" effect of salicylic acid. Arch Dermatol Res. 1977;257:293.

14. Griffiths WAD, Ive FA, Wilkinson JD. Topical Therapy. In "Textbook of Dermatology". Editors: Rook A, Wilkinson DS, Ebling FJG, Champion RM, Burton JL. Blackwell Scientific Publications 1986;Chapter 67:2551-2552.