PRODUCT MONOGRAPH

[Pr]RETISOL-A®

tretinoin, octinoxate and avobenzone cream
(0.01%, 0.025%, 0.05%, 0.1%) / 7.5% / 2% w/w

TOPICAL ACNE THERAPY WITH SUNSCREENS

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THERAPEUTIC CLASSIFICATION

TOPICAL ACNE THERAPY WITH SUNSCREENS

ACTION AND CLINICAL PHARMACOLOGY

RETISOL-A® cream contains 0.01%, 0.025%, 0.05%, or 0.1% w/w tretinoin with 7.5% w/w octinoxate and 2% w/w avobenzone.

The precise mechanism of action of tretinoin on the skin is not fully understood. It is known that tretinoin is both pharmacologically and structurally related to vitamin A which regulates epithelial cell growth and differentiation. Tretinoin itself is known to have an irritant and keratolytic effect on the skin. These two actions which occur simultaneously have been shown histologically in both animal and man to be associated with an increased growth rate and with a decrease in the cohesiveness of the epidermal cells. The result is a slightly thickened epidermis with an accelerated turnover rate and shedding of keratinized cells as very fine barely perceptible scales.

In acne vulgaris the induced fine scaling of the skin surface is accompanied by an increased production of less cohesive epidermal sebaceous cells which consequently flow out of the follicle at a more rapid rate. The thickened mass of sebaceous cellular debris, the comedones, appears to be initially extruded and then prevented from recurring by these actions. Histopathologically, acne is the impaction plus distention of the sebaceous follicles by tightly packed horny cells and disruption of the follicular epithelium. It has been postulated that tretinoin

inhibits the synthesis or quality of the substance which binds the horny cells within the sebaceous follicle.

The sunscreens octinoxate, 7.5% and avobenzone, 2% may provide limited sun protection when RETISOL-A® is used as directed.

INDICATIONS AND CLINICAL USE

RETISOL-A® (tretinoin 0.01%, 0.025%, 0.05%, or 0.1% w/w, octinoxate 7.5% w/w and avobenzone 2% w/w) Cream is indicated in the treatment of acne vulgaris, primarily where comedones, papules and pustules predominate. RETISOL-A® is not effective in most cases of severe pustular and deep cystic nodular varieties (acne conglobata).

Geriatrics (> 65 years of age): Safety and effectiveness of RETISOL-A® in patients aged 65 years and above have not been established.

Pediatrics (< 12 years of age): Safety and effectiveness of RETISOL-A® in patients below the age of 12 years have not been established.

CONTRAINDICATIONS

RETISOL-A® is contraindicated in patients with known hypersensitivity to retinoids, or to octinoxate, avobenzone, or to any ingredients contained in the preparation or component of the container. For a complete listing, see Composition and Availability of Dosage Forms.

WARNINGS

RETISOL-A® is intended for external use only and should be kept away from abraded skin, lips, eyes, nose, mouth, and other mucous membranes because of its irritant effect. In case of accidental contact with the eye and if sensitivity or chemical irritation occurs, the medication should be

discontinued. Rinse profusely with water and refer the patient to the ophthalmologist.

Do not apply to eyelids or to the skin at the corners of the eyes and mouth. Avoid the angles of the nose, skin fold areas and nasolabial fold (if treatment in these areas is necessary, apply very sparingly with care not to let the medicine accumulate).

Topical use may induce severe local erythema and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use the medication less frequently, discontinue use temporarily or discontinue use altogether.

RETISOL-A® should be used with caution in patients using medications that are known photosensitizers (see DRUG INTERACTIONS).

Tretinoin has been reported to cause severe irritation of eczematous skin and RETISOL-A® should only be used with utmost caution in patients with this condition.

Fertility

There are no data on the effect of topical tretinoin on fertility in humans.

Special Populations

Pregnant Women

Topical tretinoin should not be used by pregnant women. Topical tretinoin is not recommended for women of childbearing years without the proper use of an effective method of contraception.

Observational studies of varying sample size involving a total of 1535 women presumed exposed to topical tretinoin during the first trimester of pregnancy did not detect an increased incidence of congenital abnormalities, including retinoic acid embryopathy or major structural defects.

Cases of temporally associated congenital abnormalities have been reported during clinical use of topical tretinoin during pregnancy, including the rare birth defect category, holoprosencephaly.

Orally administered retinoids are known teratogens, causing a high incidence of severe birth defects, and are contraindicated during pregnancy.

Nonclinical reproductive toxicity studies of topical retinoids have found evidence of developmental toxicity at doses ≥ 80-fold the anticipated clinical dose.

The magnitude of risk to the embryo/fetus from topical use of tretinoin is uncertain. When used in accordance with the prescribing information, there is an approximate 1% to 6% systemic absorption from topically administered tretinoin. However, even though systemic absorption is low from topically administered tretinoin, risk cannot be excluded since there may be other factors that contribute to an increased systemic exposure such as dose used, skin barrier integrity, concurrent use with other products, hypervitaminosis A and dietary intake of vitamin A and/or provitamin A (beta-carotene) or ingestion of these as supplements.

Nursing Women

It is not known whether tretinoin is excreted in human milk. A risk to the newborns/infants cannot be excluded. Therefore, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the benefit of breastfeeding to the child and the benefit of the drug to the mother.

Pediatrics (< 12 years of age)

Safety and effectiveness in patients below the age of 12 years have not been established, therefore RETISOL-A® cream is not recommended for use in this population.

PRECAUTIONS

General

Tretinoin has irritant properties, heightens susceptibility to ultraviolet light radiation, is sensitive to oxidation and is photolabile.

RETISOL-A® should be used with caution in patients with:

- a history of local tolerability reactions, photoallergy, or local hypersensitivity.
- a personal or family history of skin cancer.
- inflammatory skin conditions that coexist with acne.
- sensitive skin and/or fair complexion.

During early weeks of therapy, an apparent exacerbation of the acne lesions may occur due to an expected drug effect on previously unseen deep lesions. This is an anticipated therapeutic effect and therapy should be continued. Dosing frequency may be reduced or a lower strength of RETISOL-A® may be used, if applicable, to help prevent exacerbation of acne lesions.

Skin

Due to the irritant nature of tretinoin, caution should be used when applying to sensitive areas of skin, such as the neck, or in patients with inflammatory skin conditions that coexist with acne.

The skin of certain sensitive individuals, particularly those with fair complexions, may become excessively red, edematous, blistered or crusted when exposed to RETISOL-A®.

If skin irritation (redness, peeling or discomfort) or effects of other acne or other treatments with irritating potential are present, this should be resolved before initiating treatment with RETISOL-A®.

Patients should be advised that excessive application will not improve efficacy, but may increase the risk of severe skin irritation. If severe irritation occurs, interrupt dosing to allow the skin to recover, and re-evaluate the dosing regimen with the patient.

Environmental Factors

As tretinoin may cause increased sensitivity to ultraviolet radiation, exposure to sunlight and sun lamps should be avoided or minimized during the use of RETISOL-A®. Application of RETISOL-A® to affected areas may provide limited sun protection on treated areas for a limited time only. When exposure to strong sunlight cannot be avoided (e.g., patients whose occupations require considerable exposure to the sun), patients should be instructed to use a broad spectrum sunscreen with an SPF of at least 15, to re-apply sunscreen regularly and to wear protective clothing over treated areas.

Due to the potential for photosensitivity, resulting in greater risk for sunburn, RETISOL-A® should be used with caution in patients with a personal or family history of skin cancer.

If a patient has sunburn, this should be resolved before initiating treatment with RETISOL-A®. If sunburn occurs while using RETISOL-A®, it is advisable to interrupt therapy until the severe erythema and peeling subside.

Weather extremes, such as wind or cold, may be more irritating to patients using tretinoin-containing products.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with RETISOL-A® have not been conducted. Studies in hairless mice suggest that concurrent dermal exposure to isotretinoin, an isomer of tretinoin, may enhance the tumorigenic potential of ultraviolet irradiation.

DRUG INTERACTIONS

Concomitant application of oxidising agents, such as benzoyl peroxide, should be avoided since they may reduce the efficacy of topical tretinoin. If combination therapy is required, the products should be applied at different times of the day (e.g., one in the morning and the other in the evening).

Augmented Photosensitivity

Medications known to be photosensitizers (e.g., thiazides, tetracyclines, fluroquinolones, phenothiazines, sulphonamides) should be used with caution with RETISOL-A® because augmented photosensitivity may occur.

Cumulative Irritation

Concomitant topical acne therapy and other topical medications should be used with caution because cumulative irritation may occur. Particular caution should be exercised during concomitant use of preparations containing a peeling agent (such as sulfur, resorcinol, or salicylic acid) with RETISOL-A®. If irritation or dermatitis occur (redness, peeling or discomfort), reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

In patients whose skin has been subjected to procedures such as depilation, chemical hair treatments, chemical peels, dermabrasion or laser resurfacing, allow the skin to recover before initiating treatment with RETISOL-A®.

Cosmetics that have a strong drying effect, including products with high concentrations of alcohol and/or astringents, or that have a potential irritating effect (abrasive agents, products containing spices or limes, etc.) should be used with caution as cumulative irritation may occur.

Patients may use noncomedogenic, hypoallergenic and oil-free cosmetic products.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

The following very common adverse drug reactions (≥ 10%) have been reported in clinical trials involving topical tretinoin-containing products:

Skin and subcutaneous disorders: Pain, burning sensation, tenderness, irritation or pruritus, application site erythema, skin exfoliation, application site stinging and dry skin.

The following adverse drug reactions (< 10%) have also been reported in clinical trials involving topical tretinoin-containing products:

Skin and subcutaneous disorders: edematous (1.1%), blistered (1.6%) or crusted skin (0.5%), contact dermatitis (2.2%).

Post-Market Adverse Drug Reactions

Immune system disorders: allergic reaction

Skin and subcutaneous disorders: skin hyperpigmentation, skin hypopigmentation, photosensitivity reaction, application site rash, application site edema/swelling, skin atrophy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

If topical medication is applied excessively, marked redness, peeling or discomfort may occur. If severe irritation occurs, suspend treatment and appropriate symptomatic measures should be taken.

The highest strength formulation of RETISOL-A® contains 0.1% tretinoin. Therefore, a 45 g tube would contain 45 mg tretinoin.

In case of suspected overdosage, a symptomatic and supportive treatment should be instituted. Inadvertent oral ingestion of RETISOL-A® cream may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A including teratogenesis in women of childbearing years. Therefore in such cases, pregnancy testing should be carried out in women of childbearing years.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- RETISOL-A® cream is for topical use only.
- RETISOL-A® contains sunscreens and may provide limited sun protection for a limited time (see PRECAUTIONS). Patients should be instructed to use a broad spectrum sunscreen with an SPF of at least 15, to re-apply sunscreen regularly and to wear protective clothing.

Recommended Dose and Dose Adjustment

RETISOL-A® should be applied sparingly to the affected area once a day for up to 12 weeks.

Therapeutic results may be noticed after two to three weeks of therapy; however, results may not be optimal until after eight to ten weeks of treatment. Once the acne lesions have responded satisfactorily, it may be possible to maintain the improved state with less frequent applications; however a maintenance dose has not been studied or established.

Excessive application will not improve efficacy, but may increase the risk of severe skin irritation.

The efficacy and safety of RETISOL-A® has not been studied beyond 12 weeks in acne vulgaris clinical trials.

During the first three weeks of treatment, RETISOL-A® may be applied every second day to allow the patient's skin to adjust to the medication, especially for patients with sensitive skin and/or a fair complexion.

Formulation strength should be selected and adjusted according to the patient's tolerance.

In case of an apparent exacerbation of the acne lesions during early weeks of therapy, dosing frequency may be reduced or a lower strength of RETISOL-A® may be used (see PRECAUTIONS).

Concomitant medicated and non-medicated therapies should be used with caution (see DRUG INTERACTIONS).

In cases of undue skin irritation (redness, peeling, or discomfort), the frequency of application should be reduced (e.g., application every other day), use a lower strength of the product, if applicable, or temporarily interrupt treatment. The normal frequency of application should be resumed once the skin irritation subsides. Treatment should be discontinued if skin irritation persists.

Renal impairment: No dosage adjustment is necessary.

Hepatic impairment: No dosage adjustment is necessary.

Administration

The area under treatment (not just clinical lesions) should be thoroughly cleansed with a mild soap or cleanser and dried, followed by application of RETISOL-A® with a gentle application. Hands should be washed before and after application. Application may be accompanied by a transitory feeling of warmth or a stinging sensation. Patients may also use a moisturiser as needed.

Do not apply RETISOL-A® to eyelids or to the skin at the corners of the eyes and mouth. Avoid the angles of the nose, skin fold areas and nasolabial fold. If treatment in these areas is necessary, apply very sparingly. Caution should be used when applying to sensitive areas of skin, such as the neck, or in patients with inflammatory skin conditions that coexist with acne (see WARNINGS).

Patients being treated with RETISOL-A® may continue to use water-based, noncomedogenic, hypoallergenic and oil-free cosmetics. Following application of RETISOL-A®, the patient should be instructed to allow the skin to dry before applying cosmetics (see DRUG INTERACTIONS).

If combination therapy is required, consideration should be given to applying the products at different times of the day (e.g. one in the morning and the other in the evening (see DRUG INTERACTIONS).

Missed Dose

If patients forget to take a dose of RETISOL-A®, they should be instructed to apply the next dose at the usual time. Patients should be instructed to not apply a double dose to make up for forgotten doses.

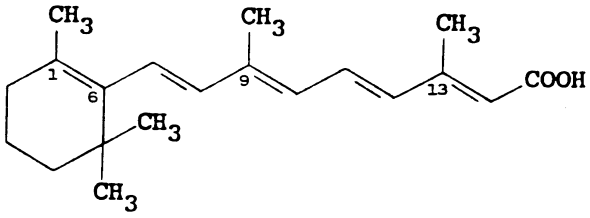
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Names: Tretinoin, retinoic acid, vitamin A acid.

Chemical Name: 3,7-dimethyl-9-(2,6,6,-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid.

Structural Formula:

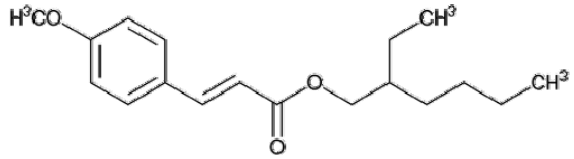
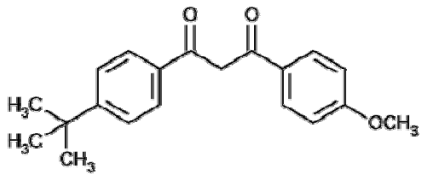


Molecular Formula: $C_{20}H_{28}0_2$

Molecular Weight: 300.44

Description: Tretinoin is a yellow to light orange crystalline powder.
Insoluble in water.
Slightly soluble in alcohol and chloroform.

Melting point: 180°-182°C.

Sunscreen Drug Substances	
Proper name: octinoxate	Proper name: avobenzone
Chemical name: 2-ethyl hexyl-P-methoxycinnamate	Chemical name: 1-(p-tert-butylphenyl)-3-(p-methoxyphenyl)-1,3-propanedione
Molecular formula: $C_{18}H_{26}O_3$	Molecular formula: $C_{20}H_{22}O_3$
Molecular Mass: 290.4 g/mol	Molecular Mass: 310.39 g/mol
Structural formula: 	Structural formula: 
Physicochemical properties: A pale yellow slightly oily practically odourless liquid.	Physicochemical properties: Off-white to yellow powder.

DRUG PRODUCT

Composition: RETISOL-A® cream contains 0.01%, 0.025%, 0.05%, or 0.1% (Forte) tretinoin (w/w) in a moisturizing cream base with 7.5% (w/w) octinoxate and 2% (w/w) avobenzone; also contains Elefac I-205, glycerin, diisopropyl adipate, stearyl alcohol, sorbitan monostearate, D.C. Fluid Nos. 556 and 344, light mineral oil, polysorbate 60, carbopol 934, germaben II, butylated hydroxytoluene, sodium hydroxide as pH adjustor and purified water.

Stability and Storage Recommendations: Store between 15°and 25°C. Do not freeze. Keep the tube tightly closed when not in use. Keep out of the sight and reach of children.

AVAILABILITY OF DOSAGE FORMS

Available in 45 g aluminum tubes with polypropylene caps. Each tube contains tretinoin, in strengths of 0.01%, 0.025%, 0.05%, or 0.1% (Forte), in a moisturizing cream base with sunscreens octinoxate 7.5% w/w and avobenzone 2% w/w.

PHARMACOLOGY

Tretinoin is a known metabolite of vitamin A. It appears to form oxidation products which are excreted in the urine and glucuronides excreted in the feces.

In human cutaneous absorption of retinoic acid was studied by application of 3 grams of ^{14}C labelled 0.1% retinoic acid cream on 200 cm^2 of skin. After administration, radio-activity was detected in samples of blood, urine, stool and on skin occlusive dressings.

In subjects pretreated with unlabelled material, slight increases in their blood radio-activity were observed 8 hours after application of the labelled material. In patients not pretreated, no significant increases in radio-activity were observed.

Urine recovery studies in the subjects not pretreated showed a 1.24 to 2.60% (mean: 1.82%) urinary excretion of the applied dose. The mean urinary excretion of the pretreated subjects was 4.45%. Between 0.3 and 2.89% (mean: 1.58%) of the material was recovered in the stool of the pretreated subjects. Extraction of radio-activity from skin occlusive dressings accounted for 73 to 96% (mean: 85.9%) of the applied dose.

In a further study, 2 and 4 hours after application of radio-actively labelled tretinoin to normal human skin, tretinoin was minimally detectable in the horny layer and sebaceous glands, but appreciably higher levels were found in the hair follicles and apocrine glands. After 24 hours, no penetration of radio-activity was detected beyond the Malpighian layer.

No systemic exposure of clinical significance is expected to arise if renal and hepatic impairment is present during topical use of tretinoin. This is because there is negligible percutaneous absorption of tretinoin when applied topically.

Clinical evaluation of the photosensitivity potential of topical tretinoin cream (0.3%, 0.1% and 0.05%) in one short-term study of topical tretinoin cream has shown the preparation to be free of phototoxic properties.

Relatively large systemic doses of tretinoin produced minor changes in the circulatory system of the cat. With 100 mg/kg, reduced perfusion in the hind extremities was noted, but there was no influence on blood pressure or respiration. Using 250 mg/kg, a mild reduction in blood pressure and a slight increase in pulse rate and circulation in the hind extremities were apparent. At a higher dose (1000 mg/kg) a pronounced increase in blood pressure and irregular respiration were observed; cardiac arrest followed fifteen minutes later.

Tretinoin, when administered orally or intraperitoneally, was shown to have a therapeutic effect on chemically induced skin papillomas and skin carcinomas in mice. The extent of the regression of the papillomas appeared to be dependent on the dose and duration of treatment. Tretinoin was also shown to have not only a prophylactic effect on the induction of papillomas but on the development of carcinomas in mice. It has been observed in mice, that tretinoin applied to experimentally produced dermatologic wounds, stimulated wound healing.

The effect of tretinoin on the survival of skin grafts in mice has been investigated. Tretinoin is thought to increase the susceptibility of skin homographs to the process of immunological rejection.

In several studies, tretinoin was administered orally to rats. It appears that little, if any, free tretinoin could be detected in the bile. Retinoyl ß-glucuronide is apparently the only naturally occurring metabolite in rat bile. The glucuronide undergoes ester interchange or dehydration reactions which result in the formation of all trans- or cis-methyl retinoates and retinoyl ß-glucurono-γ-lactone, respectively. Retinoyl ß-glucuronide was also identified in the liver and intestine.

TOXICOLOGY

Acute Toxicity

LD_{50} (mg/kg*)				
Species	**Tretinoin Pure Substance**		**0.1% and 0.3% Cream Formulation**	**0.05% Solution**
	p.o.	**i.p.**	**p.o.**	**p.o.**
Mice	2580	791	>40 (0.1%) >60 (0.3%)	9.5±0
Neonatal Rats	225±14	-	-	-
Rats	1995	786	>60 (0.3%)	13±1
Rabbits	-	-	>60 (0.3%)	>5

*As active ingredient

In the animals receiving the 0.05% solution decreased motor activity, hypnosis, salivation and vasodilation occurred. Tretinoin pure substance suspended in 5% gum acacia produced sedation, respiratory depression, diarrhea and alopecia in mice and rats. In neonatal rats receiving the pure substance, cyanosis and stunted growth were noted.

In a dog tolerance study, tretinoin pure substance was tolerated at an oral dose of 320 mg/kg. A single oral dose of 10 mL/kg of the cream formulation (0.3%) produced emesis and an elevation of AST (SGOT) and ALT (SGPT) levels.

In another dog tolerance study, 2 mL/kg of the solution formulation produced emesis and the polymorphonuclear leucocyte/lymphocyte ratio increased in one dog.

Subacute Toxicity

Tretinoin was administered orally to rats at levels of 0.78, 1.56, 3.12, 6.25 or 12.5 mg/kg/day per day for 11 days. All the high dose animals died within five days and one animal from each of the next three lower dose groups died during the study, while all animals survived at the lowest dose level. Intestinal irritation and diarrhea were noted. Skeletal fractures were observed in several animal.
In a four week oral study in rats, (2.5, 5, 10 or 20 mg/kg tretinoin per day), body weight gain was poor in the 20 mg/kg/day dose group. No bone fractures were observed in this study.

In a subsequent nine week study in rats, tretinoin was administered orally at 1.56 and 3.12 mg/kg/day levels and no mortality occurred. Females had a slight increase in body weight gain and the males showed a slight decrease.

Four groups of rats received topical applications of a 0.3% cream at levels corresponding to 0, 1.5, 3 or 6 mg/kg/day of tretinoin 5 days per week for thirteen weeks. Food consumption and body weight gain were slightly reduced in the high dose group. Skin lesions with irritation and inflammation were noted and appeared to be dose dependent. Elevated total and polymorphonuclear leucocyte counts were observed in all dose groups. With the exception of a 3 mm mammary tumor in a control animal, there were no gross changes observed at autopsy. Microscopic examination of the skin revealed focal ulcerations and inflammatory changes of significant degree in the high and mid dose groups.

In another thirteen week rat study, 6 mg/kg of tretinoin per day administered 7 days per week in the diet was well tolerated, although body weight gain, red blood cell count, packed cell volume, hemoglobin concentration and serum protein values all decreased.

On the other hand, plasma alkaline phosphatase values were markedly elevated. Histological examination revealed hyperplasia of blood-forming elements, increase in number and size of Kupffer liver cells, hydropic changes in the protoplasm of hepatocytes, increased number of foam cells and lymphatic elements of the lung, thinning of the epidermis and proliferation around the hair follicles.

In a thirteen week dog study, tretinoin was administered orally to four groups of dogs at dose levels of 0, 3, 10 or 30 mg/kg/day for 7 days per week. No mortality occurred in any of the groups. In the high dose group, one dog lost about 25% of his initial body weight. Eczema, acanthotic proliferation of the epidermis and diarrhea were also noted in the 10 and 30 mg/kg groups. Low erythrocyte count, hemoglobin concentration on and packed cell volume were noted in the 30 mg/kg

group. Changes in the albumin and gamma globulin fractions were seen and blood sedimentation rates increased in the two highest dose groups. Lack of spermatogenesis and atrophy of the tubular epithelia occurred; there was hyperplasia of the blood-forming elements in bone marrow in the high dose group.

Topical Applications

Eye and skin irritation studies were performed on rabbits with the tretinoin cream formulation at concentrations ranging from 0.01% to 0.5%. In the eye irritation test slight reddening of the conjunctiva occurred. Very slight edema and well-defined to moderate erythema were produced when applied to abraded and unabraded rabbit skin.

In subsequent irritation studies in rabbits, tretinoin, a 0.3% cream and a placebo cream were compared. The same degree of irritation was noted in the three groups. Tretinoin substance produced slight erythema, while the cream and placebo produced well defined erythema and slight edema to rabbit skin.

In another study, the 0.05% tretinoin solution and a placebo were tested in rabbits. There appeared to be a very slight reddening of the conjunctiva and very slight discharge with both placebo and test solution groups. The placebo and test solution were considered non-irritating to the skin.

Teratology

Female mice received tretinoin in oral doses of 1, 3, 9, 17, 43, 86 or 130 mg/kg from the 9th to 10th day of gestation. A slight increase in the incidence of skeletal malformations was observed in the low dose group (1 mg/kg). A pronounced teratogenic effect was produced with 3 mg/kg and higher doses. Multiple malformations of the head (cleft palate, exencephaly) were observed most frequently.

A slight increase in rate of resorption occurred at 3 mg/kg. With 9 mg/kg, 50% of all implanted embryos were resorbed. At still higher doses complete resorption occurred.

In a study in which 10 mg/kg/day was administered by gavage to 11 pregnant monkeys from days 20 to 45 of gestation several teratogenic defects were observed. Specific defects such as cleft palate, auricular malformation, open eye with unilateral ablepharia, kyphosis, scoliosis, missing digits and severe curvature of the radius were observed6. Vaginal hemorrhage was observed frequently in the mothers. Abortion or fetal death with intrauterine retention (in 6 of the 11 mothers) was also observed. Three normal fetuses resulted, two of which aborted before term.

In one study no teratogenic effects were seen in the fetuses when vitamin A acid was topically applied daily to the skin of pregnant rats during the second third of gestation.

Results from topical teratology studies in rats and rabbits have been inconclusive.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with RETISOL-A® have not been conducted. Studies in hairless mice suggest that concurrent dermal exposure to isotretinoin, an isomer of tretinoin, may enhance the tumorigenic potential of ultraviolet irradiation.

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CONSUMER INFORMATION

PrRETISOL-A®
tretinoin, octinoxate and avobenzone cream
(0.01%, 0.025%, 0.05%, 0.1%) / 7.5% / 2% w/w

This leaflet is designed specifically for consumers. This leaflet is a summary and will not tell you everything about RETISOL-A® topical cream. Contact your doctor or pharmacist if you have any questions about the drug.

What the medication is used for:
RETISOL-A® topical cream is used in the treatment of acne. RETISOL-A® is not effective in most cases of severe acne.

RETISOL-A® topical cream is not for use in children under 12 years of age or in adults over 65 years of age.

What it does:
RETISOL-A® topical cream is believed to accelerate skin growth and turn-over of cells and increase the flow of cellular debris such as dead skin cells and oils to the surface for elimination, thereby helping to reduce the acne condition.

RETISOL-A® topical cream also contains sunscreens (octinoxate and avobenzone) which may provide limited sun protection for a limited time.

When it should not be used:
Do not use RETISOL-A® topical cream if you are allergic to tretinoin, retinoids, octinoxate, avobenzone or to any of the other ingredients of RETISOL-A® cream (see **What the nonmedical ingredients are**).

What the medicinal ingredients are:
RETISOL-A® topical cream contains tretinoin, in strengths of 0.01%, 0.025%, 0.05%, or 0.1% (Forte), with sunscreens octinoxate 7.5% w/w and avobenzone 2% w/w.

What the nonmedicinal ingredients are:
RETISOL-A® topical cream contains Elefac I-205, glycerin, diisopropyl adipate, stearyl alcohol, sorbitan monostearate, D.C. Fluid Nos. 556 and 344, light mineral oil, polysorbate 60, carbopol 934, germaben II, butylated hydroxytoluene, sodium hydroxide as pH adjustor and purified water.

What dosage forms it comes in:
RETISOL-A® topical creams, in strengths of 0.01%, 0.025%, 0.05%, or 0.1% (Forte), are available in 45 g tubes.

WARNINGS AND PRECAUTIONS

BEFORE you use RETISOL-A® topical cream talk to your doctor or pharmacist if:

- You are currently or about to start using any other acne or skin medications.
- You have had a previous reaction to any other acne or skin medication.
- You have a family history of skin cancer.
- You have any other skin condition, such as eczema, any inflammatory skin condition, photoallergy, sensitive skin, or a fair complexion.
- You have any ongoing skin irritation. This irritation should be resolved before starting treatment with RETISOL-A®.
- You are pregnant or planning to become pregnant. Topical tretinoin should not be used by pregnant women as rare birth defects have been reported with the use of topical tretinoin. It is not known if the birth defects were caused by topical tretinoin.
- You are breastfeeding or planning to breastfeed.
- You cannot avoid extensive exposure to sunlight, e.g., due to work requirements.

If you are a female of childbearing age, you should only use RETISOL-A® topical cream after consulting your doctor and seeking his/her advice for contraceptive counselling. If you are pregnant or nursing a child, you should discontinue the use of RETISOL-A® topical cream and consult your doctor. There is no information on how RETISOL-A® might affect fertility.

RETISOL-A® topical cream is for external use only. If you accidentally get RETISOL-A® on irritated skin, in the eyes, mouth or lips, rinse the affected area immediately with plenty of water.

Avoid or minimize exposure to sunlight and sun lamps because RETISOL-A® topical cream heightens the susceptibility of your skin to the adverse effects of the sun. RETISOL-A® contains sunscreens and may provide limited sun protection for a limited time.Use of a broad spectrum sunscreen with a sun protection factor (SPF) of at least 15 and protective clothing over treated areas is recommended when exposure cannot be avoided. If you have a sunburn, allow the sunburn to settle before starting treatment with RETISOL-A®. If sunburn occurs while using RETISOL-A®, stop using RETISOL-A®and call your doctor for advice.

Extreme weather (e.g. cold or wind) may irritate your skin, avoid or minimize exposure.

Stop treatment and see your doctor if skin irritation is severe (severe redness, dryness, itching, stinging or burning) or your acne does not improve.

INTERACTIONS WITH THIS MEDICATION

Some medicines, skin procedures, or cosmetic products may affect how RETISOL-A® topical cream works and may make it more likely that you will have side effects. Some of these may include:

- Other acne or skin preparations including peeling agents (e.g. sulfur, resorcinol, salicylic acid). If irritation or dermatitis (redness, peeling, or discomfort) occurs, reduce the number of times you apply RETISOL-A® or temporarily stop using RETISOL-A®. Start using RETISOL-A® again when the irritation goes away.
- Drugs that make you more sensitive to light (e.g. thiazides, tetracycline, fluoroquinolones, phenothiazines, sulphonamides).
- Drugs that contain benzoyl peroxide.
- Skin procedures such as depilation, chemical hair treatments, chemical peels, dermabrasion or laser resurfacing. Following these procedures, allow skin to recover before starting treatment with RETISOL-A®.
- Cosmetics or skin products that have a strong drying effect (e.g., products with a high alcohol content, astringents, skin drying agents, after shave lotions) as they may irritate your skin. It is best to use only water-based cosmetics.
- Cosmetic products that have a potential irritating effect (e.g., abrasive agents, products containing spices or limes).

Tell your doctor or pharmacist about all your other medications, including those you can buy without a prescription as well as herbal and alternative medications.

PROPER USE OF THIS MEDICATION

RETISOL-A® topical cream should only be applied to your skin.

If your doctor recommends (prescribes) another topical acne product, this should be applied at a different time of day as RETISOL-A® topical cream.

Do not apply RETISOL-A® to areas of skin where you have problems such as eczema, severely inflamed skin or other open lesions.

Do not use on sensitive, areas such as irritatied skin,eyes, mouth, lips, angles of nose, and corners of eyes and mouth, and mucous producing areas.

How to Apply RETISOL-A® Topical Cream:

1. Wash your hands thoroughly before applying RETISOL-A®.
2. Completely remove any make-up.
3. Wash affected area gently with warm water and a mild, non-irritating soap or cleanser, and pat dry.
4. Apply RETISOL-A® sparingly and evenly once daily, as prescribed by your physician. Use your finger-tip to apply enough to cover the required area, and smooth in. Allow your skin to dry fully before applying cosmetics.
5. Wash your hands thoroughly after applying RETISOL-A®

At the beginning, you may experience redness, a burning sensation, peeling, or possibly a worsening of your acne, while your skin adjusts to the medication.

Your doctor may recommend a daytime moisturizer if your skin is particularly dry.

To minimize these reactions, your doctor may start you on the mildest strength of RETISOL-A® and go up gradually until you reach the strength that your doctor feels is most suitable for your skin type. Your doctor may advise you to apply the RETISOL-A® less frequently than every day.

It takes several weeks of regular use of RETISOL-A® before you can expect noticeable improvement and 8-10 weeks for optimal results, so be patient. Treat your acne with RETISOL-A® for as long as your doctor tells you.

Applying too much or applying it more frequently will not help your skin clear up more quickly, and may cause skin irritation.

It is important to understand that your doctor has given you a prescription specially suited to your particular needs and skin type. **Do not allow others to use it.** Always use RETISOL-A® exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Overdose:

In case of drug overdose, contact your healthcare professional, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

If you accidentally swallow RETISOL-A®, seek medical advice.

Missed Dose:

If you forget to apply RETISOL-A® topical cream at your

regular time, apply RETISOL-A® at the next usual time. Do not apply more than once a day to make up for forgotten applications.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

During the first weeks of using RETISOL-A® topical cream, you may notice some skin irritation such as redness and skin flaking. These symptoms will normally subside if you use RETISOL-A® less often or stop using it for a few days and then start again.

Other side effects that have been reported are: skin pain, itching/itchy skin, skin irritation, tenderness, warm skin, especially when first applied, stinging or burning sensation, dry skin, swelling at the site of application, rash at the site of application, redness at the site of application, skin blistering, skin crusting, allergic reaction, darkening of skin, lightening of skin, sensitivity to sunlight and skin thinning. Talk to your doctor if any of the side effects become severe or troublesome.

Severe skin reactions (severe burning, peeling or itching of your skin) have also been reported. Stop taking RETISOL-A® and contact your doctor immediately if you get any of these symptoms.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	**Allergic reaction:** difficulty breathing or swallowing caused by sudden swelling of the throat, face, lips or mouth or notice sudden swelling of hands, feet and ankles, or an itchy rash (hives)			✓

This is not a complete list of side effects. For any unexpected effects while taking RETISOL-A® topical cream contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C and 25°C. Do not freeze. Keep the tube tightly closed when not in use. Keep out of the sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

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1. **Report online at www.healthcanada.gc.ca/medeffect**
2. **Call toll-free at 1-866-234-2345**
3. **Complete a Canada Vigilance Reporting Form and:**
   - **Fax toll-free to 1-866-678-6789, or**
   - **Mail to: Canada Vigilance Program**
     Health Canada
     Postal Locator 0701E
     Ottawa, Ontario
     K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.stiefel.ca or by contacting the sponsor,

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