PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrRETIN-A®

Tretinoin Cream and Gel, Mfr. Std.
Gel 0.025% w/w and 0.01% w/w
Cream 0.1% w/w, 0.05% w/w, 0.025% w/w and 0.01% w/w

Comedolytic Agent

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West
Laval (Quebec) H7L 4A8
Canada

Date of Revision:
January 24, 2022

Submission Control Number: 255590

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RETIN-A tretinoin is indicated for:

- topical application in the treatment of acne vulgaris.

1.1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of RETIN-A in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric patients (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

1.1.2 Geriatrics

Geriatrics (**≥ 65 years of age)**: A limited number of subjects aged ≥ 65 years have been treated with RETIN-A in clinical trials; therefore, the safety and efficacy of RETIN-A have not been established in this patient population (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

2 CONTRAINDICATIONS

RETIN-A is contraindicated in patients who have demonstrated a hypersensitivity to the drug or to any ingredient in the formulation, or any component of the container.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Apply daily a pea-sized amount of RETIN-A to the affected areas after cleansing with a mild, non-medicated soap and water.

Maintenance dose should be the least number of applications that will prevent recurrence of the condition. Maintenance therapy should be administered daily for best results.

Application of RETIN-A may cause a transitory feeling of warmth or slight stinging. When administered according to recommended guidelines, RETIN-A may produce a slight erythema similar to that of mild sunburn. In cases where it is necessary to temporarily discontinue therapy or reduce the frequency of application, therapy should be resumed, or the frequency of application increased when the patient becomes able to tolerate the treatment.

Therapeutic effects may be noticed after two to three weeks of use, but more than six weeks of therapy may be required before definite beneficial effects are seen. During the early weeks of treatment, an apparent exacerbation of inflammatory lesions may occur. This is due to the action of the medication on deep, previously unseen lesions and should not be considered a reason to discontinue therapy. Once a satisfactory response has been obtained, it may be possible to maintain this improvement with less frequent applications.

Discontinue treatment if a severe local inflammatory response is experienced. Reinstitute therapy

when the reaction has subsided and apply preparation every other day or less frequently. Should discomfort still be experienced, stop treatment completely.
Excess application of RETIN-A does not provide more rapid or better results. In fact, marked redness, peeling or discomfort can occur. If excess application occurs accidentally or through over-enthusiastic use, RETIN-A should be discontinued for several days before resuming therapy.

4.4 Administration

A pea-sized amount of RETIN-A should be squeezed onto a clean fingertip and a thin layer should be spread to the affected areas. The treated area should be washed no more than twice per day. After washing, the skin should be dried gently and completely without rubbing it. Allow at least 20 to 30 minutes to dry before applying medication. Only a sufficient quantity of medication should be applied to cover the affected areas lightly, using a gauze swab, cotton wool or the tips of clean fingers. Over-saturation should be avoided since excess medication could run into the eyes, angles of the nose or other areas where treatment is not intended. Avoid eyes, mouth, paranasal creases, and mucous membranes. Not for ophthalmic, oral or intravaginal use.

5 OVERDOSAGE

If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. RETIN-A is intended for topical use only. In the event of accidental ingestion, if the ingestion is recent, the stomach should be emptied immediately by gastric lavage or by induction of emesis. All other treatment should be appropriately supportive. Oral ingestion of the drug may lead to the same side 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. Reduce amount or frequency of application if undesirable reactions occur.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Gel 0.025% w/w and 0.01% w/w.	Butylated Hydroxytoluene, Ethanol Pharma Undenatured, Hydroxypropyl Cellulose
	Cream 0.1%, 0.05% w/w, 0.025% w/w and 0.01% w/w.	Butylhydroxytoluene, Isopropyl Myristate, Polyoxyl 40 Stearate, Stearic Acid, Stearyl Alcohol, Sorbic Acid, Xanthan Gum and Purified Water

7 WARNINGS AND PRECAUTIONS

General

RETIN-A is for external use only. Not for ophthalmic use.

Avoid contact with the eyes, eyelids, angles of the nose, lips, mucous membranes, severely inflamed skin or to open lesions or to other areas where treatment is not intended.

RETIN-A should be applied only to the affected areas. Excessive use should be avoided.

Tretinoin may cause irritation of circumoral and other sensitive skin areas. Tretinoin should not be applied to severely inflamed skin or to open lesions.

Exposure to sunlight, including ultraviolet sunlamps, may provoke additional irritation. Therefore, exposure should be avoided or minimized during the use of tretinoin. A patient experiencing considerable sun exposure due to occupational duties, and/or any patient inherently sensitive to the sun, should exercise particular caution. When exposure to sunlight cannot be avoided, use of sunscreen products and protective clothing over treated areas is recommended.

Hyper- or hypopigmentation has occasionally been reported when the product is used to the point of producing severe irritation. This is reversible when the medication is stopped.

Cosmetics may be used, but the areas to be treated should be cleansed thoroughly before the medication is applied. Astringent toiletries should be avoided. Simultaneous use of harsh abrasives and other skin treatments, including sun lamp, should be avoided if possible.

Patients will be able to remove hair as usual (e.g. plucking, electrolysis, depilatories) but should avoid these procedures at night before applying RETIN-A as they might result in skin irritation. Permanent wave solutions, waxing preparations, medicated soaps and shampoos can sometimes irritate even normal skin. Caution should be used so that these products do not come into contact with skin treated with RETIN-A.

In some patients temporary skin irritation may occur, especially in early weeks of treatment. Should these reactions occur to an excessive degree, and the skin becomes extremely red, swollen and crusted, use of tretinoin should be discontinued immediately.

An apparent exacerbation may develop due to the drug effect on previously seen deep lesions. This is an anticipated part of the therapeutic effect. Therapy should be continued.

GELS ARE FLAMMABLE. Note: Keep away from heat and flame. Keep tube tightly closed.

Skin

Local Irritation
Weather extremes, such as wind, cold and low humidity may be irritating to skin treated with RETIN-A and may increase its dryness.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition. If a patient experiences severe or persistent irritation, the patient should be advised to discontinue application of RETIN-A completely, and if

necessary, consult a physician.

It is not recommended to initiate treatment with RETIN-A or continue its use in the presence of skin irritation (e.g., erythema, peeling, pruritus, sunburn, etc.) until these symptoms subside.

In certain sensitive individuals, RETIN-A may induce severe local erythema, swelling, pruritus, warmth, burning or stinging, blistering, crusting and/or peeling at the site of application. If the degree of local irritation warrants, the patient should be instructed to either apply the medication less frequently or discontinue its use temporarily.

7.1 Special Populations

7.1.1 Pregnant Women

Topical tretinoin should be used by women of childbearing years only after contraceptive counselling. Topical tretinoin should not be used by pregnant women and by women planning a pregnancy.

There have been a few reports of birth defects among babies born to women exposed to topical tretinoin during pregnancy. To date, there have been no adequate and well-controlled prospective studies performed in pregnant women and the teratogenic blood level of tretinoin is not clear. However, a well-conducted retrospective cohort study of babies born to women exposed to topical tretinoin during the first trimester of pregnancy found no excess birth defects among these babies when compared with babies born to women in the same cohort who were not similarly exposed.
Oral tretinoin has been shown to be teratogenic and fetotoxic in rats when given in doses 1000 and 500 times the topical human dose, respectively.

In nine (9) out of ten (10) topical teratology studies of tretinoin conducted in rats and rabbits using several formulations, there has been no evidence of teratogenicity. In one (1) out of ten (10) studies there was an increase in fetal malformations; however, a clear causal relationship of topical tretinoin in these findings could not be established. In a repeat of this study, there were no fetal malformations. Topical tretinoin can produce treatment-related fetal effects (delayed ossification of bones and an increase in supernumerary ribs). The fetal no-effect dose is 1.0 mg/kg/day (200 times the recommended clinical dose).

7.1.2 Breast-feeding

It is not known whether RETIN-A are excreted in human milk. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Since many drugs are excreted in human milk, caution should be exercised when RETIN-A Cream and Gel are administered to a nursing mother.

7.1.3 Pediatrics

Pediatrics (< 18 years): The safety and efficacy of RETIN-A in pediatric patients have not been established; therefore, Health Canada has not authorized an indication in children <18 years of age.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): A limited number of subjects aged ≥ 65 years have been treated with RETIN-A in clinical trials; therefore, the safety and efficacy of RETIN-A have not been established in this patient population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

True contact allergy to topical tretinoin is rarely encountered.

Changes in the skin may be anticipated, indicating an active effect of the medication. Expected changes include mild erythema and flaking or peeling of the stratum corneum. In certain very sensitive patients, the skin may become very erythematous, edematous, blistered or crusted. In such cases, application of tretinoin should be discontinued until the skin has fully recovered. Further applications should be at a level that the individual can tolerate. All adverse reactions observed are reversible when treatment is discontinued.

Some degree of local irritation is expected. The most commonly reported undesirable effects are dry skin, burning, stinging, warmth, erythema, pruritus, rash, peeling and temporary hypo- and hyperpigmentation. Rarely reported undesirable effects are blistering and crusting of the skin, eye irritation and edema. These reactions were usually mild to moderate in severity, generally well-tolerated and self-limiting, occurred early during the course of therapy and generally decreased over time with the exception of dry skin, which tended to persist.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution because of possible interaction with tretinoin. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid with tretinoin. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of tretinoin is begun.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tretinoin is a synthetic retinoic acid (all-trans retinoic acid) and vitamin A is retinol. Retinoic acid is naturally synthesized from Vitamin A.

Tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RARα, RARβ, and RARγ) which act to modify gene expression, subsequent protein synthesis, and epithelial cell

growth and differentiation. It has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both.

Repeated skin applications of Vitamin A acid over a period of days have produced detectable changes in the skin. Initially, the change is mild erythema, followed by flaking or peeling of the stratum corneum, which in itself is associated with a marked thinning of the stratum corneum and increased cellular turnover in the skin.

Local application of Vitamin A has been reported to have reduced abnormal cornification in follicular orifices, and Vitamin A acid was reported to be more potent than Vitamin A alcohol or its esters when applied locally in ointments to human skin.

Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular cells with decreased microcomedo formation and melanin content. Additionally, tretinoin is associated to increased epidermal thickness and alterations of the stratum corneum. Tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells, causing extrusion of the comedomes.

10.2 Pharmacodynamics

The pharmacodynamics of RETIN-A in the treatment of acne vulgaris are unknown.

10.3 Pharmacokinetics

Radioactive Vitamin A and retinoic acid were introduced into the duodenum of rats. C14-tagged Vitamin A was found largely in the lymph, while C14-tagged retinoic acid was found mostly in the bile.

After hydrolysis of the ester, retinol is partially transported to other tissues, partially conjugated to the ß-glucosidaronate, and partially oxidized to retinoic acid. The retinoic acid may be partly decarboxylated and further degraded, or may form a ß-glucuronide, which is secreted in the bile. A portion of the glucuronides is returned to the liver by enterohepatic circulation, but the major portion is excreted in the feces, some also being excreted in the urine.

Johnson conducted a study to measure the extent of percutaneous absorption of topically applied radioactive retinoic acid by normal individuals, and by patients with psoriasis or acne. The extent of absorption was judged by measuring the amount of radioactivity in (a) urine, (b) feces, (c) plasma, (d)respiratory carbon dioxide, and (e) remaining at the site of application. The urine data were felt to be the most reliable indicator of absorption because of the low levels of radioactivity obtained in the other samples examined. Two formulations were evaluated. One formulation consisted of 0.11% retinoic acid in a petrolatum base. The second formulation consisted of 0.11% retinoic acid in solution in a polyethylene glycol-ethanol vehicle. Both formulations were the same as those prepared for non-radioactive clinical evaluations.

The urinary excretion of radioactivity following application of retinoic acid ointment or solution was compared to that seen with the ointment in normal subjects. In addition, the total absorption was calculated using the data of Maibach following i.v. administration of retinoic acid. The results suggest that after a single administration of the ointment, absorption is greater (4x) in psoriatics than in normal. On repeated application for 10 days absorption may increase as much as 12 x (relative to normal) to an average maximum of 8% of the administered dose.

11 STORAGE, STABILITY AND DISPOSAL

Storage:
Keep container closed when not in use. Store between 15-25°C.

Packaging:
- Gel 0.025% w/w and 0.01% w/w are supplied in tubes containing 30 g.
- Cream 0.1% w/w, 0.05% w/w, 0.025% w/w and 0.01% w/w are supplied in 30 g tubes in a bland, hydrophilic base.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

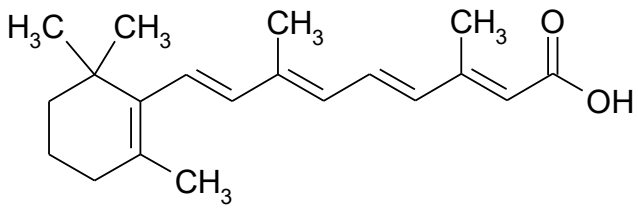
Proper Name: Tretinoin

Chemical Name: (2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl) nona-2,4,6,8,-tetraenoic acid

Molecular Formula: $C_{20}H_{28}O_2$

Molecular Mass: 300.44 g/mol

Structural Formula:



Physicochemical Properties

Description: Tretinoin is a yellow to light-orange, crystalline powder which is extremely light- and oxygen- sensitive.

Solubility: It is insoluble in water, slightly soluble in alcohol and in chloroform.

Chemically, tretinoin is related to Vitamin A, differing only in having a carboxyl as the end group on the side chain.

14 CLINICAL TRIALS

The clinical trial data based on which the original indication was initially authorized are not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

NOTE: The term "active Vitamin A acid acne preparation" will be substituted by the term retinoic acid solution.

Acute Toxicity Studies

Acute oral toxicity studies were carried out in dogs, rats and mice to determine the effects of 0.1% (w/w) retinoic acid solution when compared with the Vitamin A acid acne preparation vehicle.

Rat
In rats, for example, the 0.1% retinoic acid solution had an acute oral LD_{50} of 20.3 mL/kg while the vehicle had an LD_{50} of 20.3 mL/kg.

The LD_{50} values of the product and its vehicle, following 0.10% i.v. administration, were 5.2 ml/kg and 5.0 mL/kg in mice, respectively, and 8.7 mL/kg and 8.8 mg/kg in rats. Apparently retinoic acid does not contribute to the lethal potential of the product.

Dog
When 0.1% doses of 5 and 10 mL/kg of either formulation were administered to dogs, pronounced emetic effects were produced. Emesis was inconsistent at doses of 1 mL/kg, and the dogs that retained this dose subsequently exhibited no untoward effects.

Rabbit
Both the active preparation and the vehicle caused slight to moderate conjunctival irritation when instilled into the eyes of rabbits. No corneal or iritic effects were noted.

A primary skin irritation was carried out in rabbits, employing a standard patch test technique as described in "Principles and Procedures for Evaluating the Toxicity of Household Substances". Retinoic acid solution (0.1%) had a primary irritation rating of 1.40 and thus would be classified as a mild primary irritant.

An acute dermal toxicity study was carried out in which single doses of up to 9.4 mL/kg of the retinoic acid solution (0.1%) were applied for 24-hour exposures to the intact and abraded skin of rabbits. No evidence of systemic toxicity was found during or after the test.

A six-week subacute dermal toxicity study was performed in rabbits. Within this period, dosage levels of 0.1, 0.5 and 1.0 mL/kg/day of retinoic acid solution (0.1%) were applied to the abraded

and intact skin of the animals. These daily doses were estimated to be 3-30 times the calculated maximum clinical dose. Locally there was marked erythema, hyperkeratosis, mummification, loss of elasticity and cracking of the skin. These responses were dose-related and reached their maximum in about three weeks. The washed high-dose group had less local reaction than the unwashed high-dose group. In those animals studied four weeks after application of retinoic acid was discontinued, the local reactions subsided. Little evidence of irritation remained at the end of the observation period.
Other findings were considered to be indirectly attributable to the irritation produced by the test materials. These dose-related effects include impaired growth, depression of the erythrocyte-hemoglobin-hematocrit system, and accelerated sedimentation rates. An increased frequency of gross lesions in all treated groups was observed at necropsy. Ophthalmologic and radiologic examinations, and the chemistry assays gave no indication of toxicity. Tissue histopathology only revealed changes in the skin. There was no evidence found of systemic toxicity directly attributable to topical application of the retinoic acid solution. Those changes that did occur were considered related to the known local irritant properties of retinoic acid.

In separate tests, the investigators found no evidence of retinoic acid phototoxicity in either mouse skin in vivo or in yeast cells in vitro.

Human
Dermal toxicity studies in humans have shown that the retinoic acid solution (0.1%) did not cause contact sensitization, phototoxicity or photosensitization in any of the subjects investigated. Further studies have shown the expected local effects of erythema, tenderness and pooling. However, there was no evidence of systemic toxicity.

Kligman et al. studied the histology of normal skin treated with 0.1% vitamin A acid in an alcoholic vehicle, and reported "As initial clinical inflammation developed, the epidermis thickened (acanthosis) and the cornified cells retained their nuclei (parakeratosis). A quite characteristic change was the intercellular accumulation of fluid causing the cell membranes to be pushed apart. This prominent intercellular edema was not usually accompanied by evidence of cell damage. Surprisingly, little inflammatory cell infiltrate was seen in the dermis; these changes related to mild inflammation.

With high concentrations, there may be severe epidermal damage with vesiculation. In the chronic phase, after weeks or months of application, the characteristic findings were moderate acanthosis, a decidedly thickened and conspicuous granular cell layer, and a thin, loose stratum corneum which was frequently lost in sectioning. Again, dermal inflammatory changes were scarcely discernible."

Studies of retinoic acid in topical application to human skin have produced no evidence of toxic effects other than local irritation. One investigator who applied 0.1% retinoic acid in fatty cream topically to 53 patients for as long as a year of continuous therapy reported occasional skin irritation "which disappears quickly".

Studies have been conducted to determine the amount of tretinoin that can penetrate human skin when it is applied topically. These studies involved application of C14-tagged tretinoin topically to volunteers with normal skin, and others with psoriasis or acne whose skin was irritated by repeated applications of tretinoin before the studies with radioactive material were conducted. In normal, absorption of the solution was greater (1.8 x) than with the ointment. Absorption after single administration was increased 6 x in subjects with acne, and increased 37 x in these subjects, on repeated (10 day) application, to an average maximum absorption of 26% of the

administered dose.
Based on the recovery of radioactivity from the site of application, the average maximum absorption with the ointment was 4% in normal subjects, 6% in subjects with psoriasis following single administration, and 14% in the same subjects following repeated (10 day) administration. The average maximum absorption with the solution was 14% in normal subjects, 20% in subjects with acne following single administration, and 1% following repeated 10-day administration. These figures are reasonable estimates for maximum possible absorption; however, they may tend to overestimate the actual extent of absorption because of the technical problems associated with quantitative removal of the applied dose 6 hours after application.

This study has shown that, under the time limits stated, the average maximum extent of absorption of retinoic acid from a petrolatum base ointment in subjects with psoriasis is approximately 8% of the dose and does not exceed 14% of the administered dose. The average maximum extent of absorption of retinoic acid from a solution in subjects with acne is approximately 26% of the administered dose and does not exceed 31% (on the average) of the administered dose. Knowing the greatest amount absorbed in one individual (58%), the "high average" absorption (31%), and the maximum amount applied topically (rounded off to 1.6 g), it is possible to calculate a "safety index" as follows:

Table 8: Study Parameters and Results

Dose Applied	1.6 g	1.6 g
Patients Weight	50 kg	50 kg
Concentration of Drug	0.05%	0.05%
Extent of Absorption	31%	58%
Amounts absorbed	0.005 mg/kg	0.009 mg/kg
No effect dose (in rats) *	1.0 mg/kg	1.0 mg/kg
Safety Index	200:1	111:1

* Species most sensitive to teratogenic effects.

Although the foregoing figures are based on the most extensive application that might occur (entire face, back and chest) and the highest absorptions determined experimentally, it is worth noting that even if 100% were absorbed, the safety factor would still be in excess of 62-fold, based on the 1 mg/kg systemic dose determined to be safe in pregnant rats. If the concentration of tretinoin were doubled to 0.1%, the safety factor would still be more than 31-fold with 100% absorption. At 0.1% concentration the safety factor would be 55:1 when calculated in relation to the tested maximum absorption through damaged skin.

Carcinogenicity Studies

Mouse
Studies in hairless albino mice suggest that tretinoin may accelerate the tumorigenic potential of ultraviolet radiation. The significance to humans is not clear.

Four groups of 60 hairless mice each were used in the 18-month study. Groups II, III and IV were treated daily with simulated solar ultraviolet radiation (UVR). The mice were exposed for 2 hours on each of 196 consecutive days to 180 J/M2/day erythema effective energy (approximately one-half human skin erythema dose of UVR). After each UVR exposure, the groups were painted topically with 100 mL of either vehicle alone (methanol) or 0.001% retinoic acid (RA) or 0.01% RA, in methanol. Group I received vehicle alone without UVR. Beginning at 20 weeks, the two groups III and IV receiving UVR plus RA developed a substantial number of tumors; there were no tumors in Group I. The mean latent period for tumor appearance in the vehicle plus UVR

Group II was longer than the mean latent periods of the RA-treated groups. The mechanism of the RA-enhanced photocarcinogenesis is not yet known.

A 2-year dermal mouse carcinogenicity study was conducted with topical administration of 0.005%, 0.025% and 0.05% of a tretinoin gel formulation. Although no drug-related tumors were observed in surviving animals, the irritating nature of the drug product precluded daily dosing, confounding data interpretation and reducing the biological significance of these results.

Genotoxicity

The genotoxic potential of tretinoin was evaluated in an in vitro bacterial reversion test, an in vitro chromosomal aberration assay in human lymphocytes and an in vivo rat micronucleus assay. All tests were negative.

Reproduction and Teratology Studies

Rat

In a dermal rat teratogenicity study, animals received 0.1 or 1.0 mL/kg/day of 0.05% tretinoin gel which corresponds to 0.05 or 0.5 mg/kg/day pure drug applied topically throughout organogenesis. There was no evidence of maternal, embryo or fetal toxicity or teratogenicity. In the high dose, there was an increase in the anatomical variations of incomplete ossification of parietal, interparietal and supraoccipital bones of the skull. These effects are not considered to be teratogenic responses.

Topical administration of all-trans retinoic acid to pregnant rats at dose levels of 1, 2.5, or 5 mg/kg/day during the period of organogenesis (days 6 - 16 of gestation) was not teratogenic even at maternally toxic doses (> 2.5 mg/kg). There was evidence of fetal toxicity at 5 mg/kg; an increase in the incidence of supernumerary ribs was noted as was a decrease in body weight.
A dermal rabbit study was conducted to evaluate the teratogenic and/or embryotoxic potential of three 0.1% tretinoin formulations, ointment, cream and alcoholic solution. Drug was applied to a shaven area of the backs of animals in the following amounts: 150 and 600 mg/kg for the ointment, 50 and 200 mg/kg for the cream, 0.4 and 1.6 mL/kg for the solution. Well defined erythema was recorded in all the animals receiving the high dose levels of both the ointment and cream from the second to the last day of treatment. A milder degree of erythema was seen in the animals treated with 1.6 mL/kg of the solution. Slight edema was noted only in the high dose ointment animals on examination at the end of the treatment period. In all cases the adverse reaction quickly regressed and was no longer visible by the end of gestation. Dose levels of up to 600 mg/kg tretinoic acid ointment, 200 mg/kg retinoic acid cream and 1.6 mL/kg retinoic acid solution had no teratogenic activity or adverse effects on weaning when injuncted onto the backs of New Zealand White rabbits daily from Day 6 to Day 18 of gestation. The cream and solution at the high dose levels did produce a slight increase in embryotoxicity, but it was thought unlikely that this would be reproduced in clinical practice.

In a separate dermal rabbit teratogenicity study, animals received 0.1 or 1.0 mL/kg/day of 0.05% tretinoin gel which corresponds to 0.05 or 0.5 mg/kg/day pure drug applied topically throughout organogenesis. Dose related moderate to severe dermal irritation was observed in the dams. There was a slight increase in resorption in the high dose group and a treatment-related increase in incomplete ossification of parietal bones as was previously reported in rats. No evidence of teratogenicity was found.

A rabbit study utilizing topically applied dosages of 0.05 and 0.5 mg/kg/day of tretinoin

(1 mL/kg/day of 0.005% and 0.05% RENOVA® formulation, respectively) was conducted to assess embryo-fetal toxicity and teratogenic potential. The RENOVA® formulation (indicated for the treatment of photodamaged skin) was not teratogenic at maternally toxic dosages of up to 0.5 mg/kg (100 times the clinical dose). Marked maternal toxicity (severe dermal irritation, decreased body weight) was observed at 0.05 and 0.5 mg/kg/day. At the high dose (0.5 mg/kg/day of tretinoin) increased incidence of spontaneous abortions and fetal toxicity (decreased body weight and increased resorptions probably secondary to maternal toxicity) were observed.

A rat study using an investigational topical formulation of tretinoin at dosages of 0.2, 0.5, and 1.0 mg/kg/day was conducted to assess embryo-fetal toxicity and teratogenic potential. Maternal toxicity was observed in all treated groups. No adverse effects on embryo-fetal viability, fetal body weights, or fetal morphology were observed at the doses tested.

A rabbit study utilizing topically applied dosages of the same investigational formulation of tretinoin in dosages of 0.2, 0.5, and 1.0 mg/kg/day was conducted to assess embryo-fetal toxicity and teratogenic potential. Rabbits wore Elizabethan collars during the treatment period. Maternal toxicity was observed in all treated groups. Evaluation of the incidence of specific fetal findings revealed an association with the 0.5 and 1.0 mg/kg/day dosages. These included slight-to-moderate dilations of the lateral and/or third ventricles of the brain, and hydrocephaly, and, in these fetuses, cleft palate, hemorrhagic brain, or deformations of limb and/or rib. A causal relationship of topical treatment and these findings could not be established because the fetal observations were not consistently dose-dependent, oral and/or inhalation exposure could not be ruled out and, hydrocephaly is known to occur spontaneously in rabbits. Therefore, a follow-up study was designed to clarify the etiology of the fetal alterations.

In the follow-up rabbit study, animals were exposed to topically applied dosages of 0.5 and 1.0 mg/kg/day of the investigational formulation of tretinoin for 6 hours/day, or 1.0 mg/kg/day for 24 hours/day. Animals exposed for 6 hours/day were restrained during the exposure period. Animals exposed for 24 hours/day were not restrained. Maternal toxicity was observed in all treated groups. No fetal abnormalities were observed in either group exposed. Therefore, the fetal alterations in the previous study may have been spontaneous events or the result of possible oral ingestion during the study.

Oral administration of tretinoin to pregnant rats at doses of either 1.0 or 2.5 mg/kg/day throughout organogenesis produced no maternal toxicity. The higher dose produced only a modest increase in intrauterine death. There was a treatment-related, but not dose-related increase in the anatomical variations of increased thoracic rib or sternebrae. Tretinoin at either dose did not interfere with implantation or fetal weight, nor did it produce a teratogenic response.

In another study, pregnant rats received a suspension of all-trans retinoic acid orally at doses of 1, 2.5, 5, or 10 mg/kg/day on days 6 through 15 of gestation. At 10 mg/kg an increase in the production of cleft palate was observed.

Orally administered tretinoin during pregnancy produces dose-dependent and stage-dependent fetal anomalies in several species. In Segment II oral and dermal teratology studies in Wistar rats, frank fetal malformations were observed only after oral administration of 10 mg/kg tretinoin where one fetus in each of 3 litters showed cleft palate. No fetal malformations resulted after oral or dermal application of tretinoin at 1, 2.5, or 5 mg/kg doses. Oral and dermal doses of >2.5 mg/kg tretinoin produced an increased incidence of fetuses with skeletal variations (greater in oral), e.g., vestigial ribs. Skeletal variations, while treatment-related, are not categorized as

teratogenic outcomes, but as segmental variations of embryonic pattern formation, and as such are not incompatible with normal development. While oral tretinoin produced a higher incidence of fetal effects than dermal tretinoin, the overall fetal no-observable-effect-level by either dosage route is 1 mg/kg (200 times the estimated clinical dose). The findings in the two above-mentioned studies are consistent with results reported from numerous earlier studies.

Tretinoin, administered topically in a different formulation, produced teratogenic effects (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) at doses up to 500 mcg tretinoin/kg/day, approximately 4 times the clinical dose, assuming 100% absorption and based on body surface area comparison. Oral tretinoin was teratogenic in rats at doses greater than 1 mg/kg/day (approximately 8 times the clinical dose, based on body surface area comparison). The clinical relevance of the animal findings is not clear.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrRETIN-A®
Tretinoin Cream and Gel, Mfr. Std.

Read this carefully before you start taking **RETIN-A** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RETIN-A**.

What is RETIN-A used for?
RETIN-A is applied to the skin to treat acne. Acne is a condition in which the skin has blackheads, whiteheads, papules, pustules, or cysts.

How does RETIN-A work?
RETIN-A belongs to a group of medicines called retinoids. It works by causing the outer skin layer to grow faster and becomes thinner. It is also associated with the thickening of the epidermis (the outermost of the three layers that make up the skin). This helps prevent build-up of debris in the oil glands of the skin which can cause acne.

What are the ingredients in RETIN-A?
Medicinal ingredients: Tretinoin

Non-medicinal ingredients:
Gel: Butylated Hydroxytoluene, Ethanol Pharma Undenatured, Hydroxypropyl Cellulose.
Cream: Butylhydroxytoluene, Isopropyl Myristate, Polyoxyl 40 Stearate, Stearic Acid, Stearyl Alcohol, Sorbic Acid, Xanthan Gum and Purified Water.

RETIN-A comes in the following dosage forms:
Gel 0.025% w/w and 0.01% w/w
Cream 0.1% w/w, 0.05% w/w, 0.025% w/w and 0.01% w/w

Do not use RETIN-A if:
If you are allergic to the medicinal ingredients in RETIN-A or of any of its ingredients (see "What are the ingredients in RETIN-A")

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RETIN-A. Talk about any health conditions or problems you may have, including if you:
- Have sensitive skin
- Are exposed to the sun a lot due to work duties

Other warnings you should know about:

<u>Skin</u>

- Skin reactions such as site dryness, peeling, burning, itching, stinging, redness and eye irritation may occur during the first one or two weeks of use. These reactions can be minimized by following the instructions carefully. Should the effects become severe,

discontinue use and consult your doctor.
- RETIN-A can make your skin more sensitive and increase the possibility of sunburn. Minimize exposure of areas treated with RETIN-A to sunlight or sunlamps during treatment. Wear protective clothing whenever you have to go out in the sun, even on hazy days. Use a sunscreen on areas treated with RETIN-A.
- Avoid excessive exposure to wind or cold as skin treated with RETIN-A may be more sensitive to these extremes.
- Hyper – or hypopigmentation (darkening or lightening of the skin) has occasionally been reported when the product is used to the point of severe irritation. This side effect is reversible when the medication is stopped or discontinued.

General Use

- Use RETIN-A as your doctor instructed. Excessive medication will not produce better results and marked redness, peeling and discomfort may occur. Apply a moisturizer or a moisturizer with sunscreen that will not aggravate your acne (this is know as non-comedogenic) every morning after you wash.
- Do not apply on eyes eyelids, angles of the nose, mouth, mucous membranes or other areas where treatment is not intended.
- Do not apply on skin that is severely inflamed, sunburnt, or has open lesions or eczema.
- Do not use if reactions are severe and the skin becomes extremely red, swollen and crusted.
- Avoid using medicated or abrasive topical products with a high concentration of alcohol, spices, or lime. They cause needless stinging and burning on treated skin.
- Cosmetic can be used. Clean the skin thoroughly of any cosmetics before RETIN-A use.
- Avoid hair removal procedures before RETIN-A use.
- Gels are flammable. Keep gel away from heat and flame. Keep tube tightly closed.

Pregnancy and breast-feeding

- Consult your doctor for contraceptive counselling. RETIN-A should be used by women of childbearing years only after contraceptive counselling.
- Do not use if you are pregnant, plan to become pregnant, or think you are pregnant. It may harm your unborn baby.
- Talk to your healthcare professional if you are breast-feeding. It is not known if RETIN-A passes in breast milk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
- There are no known interactions with RETIN-A

How to take RETIN-A:
RETIN-A should only be applied to your skin.

1. Wash with a mild soap and dry skin gently. Do not wash more than twice per day.

2. Wait twenty to thirty minutes before applying medication so that your skin is completely dry.

3. Apply RETIN-A once daily as directed by your doctor.

4. Squeeze a small amount (about the size of a pea) on your fingertip. Spread on the skin where acne lesions appear, using enough to cover the entire affected area, using a gauze swab, cotton wool or the tips of clean fingers. Only use enough medication to cover the affected areas lightly.

5. Keep the medication away from the corners of the nose, mouth, eyes and mucous membranes or other areas where treatment is not intended. Spread away from these areas when applying.

6. Keep container closed when not in use.

7. The medication should become invisible almost immediately. If it is still visible or if dry flaking occurs within a minute or so, you are using too much.

8. If your doctor has prescribed another topical acne treatment (i.e., benzoyl peroxide or topical antibiotic), do not apply RETIN-A at the same time of day as the other products.

After 3 to 6 weeks of therapy some patients notice new blemishes. At this stage it is very important to continue using RETIN-A. Do not expect an overnight cure. With the use of RETIN-A, you will notice a gradual improvement over eight to twelve weeks.

Usual dose
Apply daily to the affected areas after cleansing with a mild, non-medicated soap and water. Safety and effectiveness have not been established in children.

Overdose
In case of accidental oral ingestion, in addition to the boxed warning above, if you are in your childbearing years discuss with your doctor if a pregnancy test should be done.

If you think you have taken too much RETIN-A, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, it is not necessary to make up the missed dose. Just wait until the next evening and use RETIN-A as usual. Apply the same amount you usually would. Do not apply an extra amount.

What are possible side effects from using RETIN-A?

Similar to all retinoids, there is some skin irritation that is expected. These are not all the possible side effects you may feel when taking RETIN-A. If you experience any side effects not listed here, contact your healthcare professional.
Side effects which may occur when using RETIN-A are primarily local effects on the skin such as:

- Skin redness, swelling, irritation or exfoliation of the skin
- Warmth, burning, stinging or blistering of the skin
- Crusting, flaking, or peeling of the skin

- Temporary hyper- or hypopigmentation (darkening or lightening) of the skin
- Eye irritation
- Feeling unwell (malaise)
- Fever

RETIN-A may affect your blood and urine test results. Tell your healthcare professional you are taking RETIN-A before doing these tests.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Skin Irritation at the application site: dryness, pain, erythema, photosensitivity (sun allergy) reaction	√		
UNCOMMON			
Allergic Reactions: itching, hives, rash, site ulcer	√		
Infections and infestations: Upper respiratory tract infection (symptoms include headache, cough, sore throat, runny nose, nasal congestion, fever),			√
Gastrointestinal (stomach) disorders: Vomiting, nausea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage

Keep container closed when not in use. Store between 15°C – 25°C.

Keep out of reach and sight of children.

If you want more information about RETIN-A:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website www.bauschhealth.ca, or by calling 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

Last Revised: January 24, 2022