PRODUCT MONOGRAPH

PrRETIN-A MICRO®
Tretinoin Gel (microsphere)
0.1% w/w and 0.04% w/w

Comedolytic Agent

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

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Tretinoin Gel (microsphere)
0.1% w/w and 0.04% w/w

CLINICAL PHARMACOLOGY

RETIN-A MICRO tretinoin gel (microsphere) is a novel formulation containing either 0.1% w/w or 0.04% w/w tretinoin by weight for the topical treatment of acne vulgaris.

Tretinoin is a member of the retinoid family of compounds, and an endogenous metabolite of Vitamin A.

Tretinoin is highly effective in the treatment of acne, although the exact mode of action of tretinoin is unknown. Current evidence suggests that this efficacy is due primarily to the ability of tretinoin to modify abnormal follicular keratinization. Comedones form in follicles due to abnormal keratinization and intercellular cohesiveness, with an excess of keratin retained in the follicle. Tretinoin promotes detachment of cornified cells and the enhanced shedding of corneocytes from the follicle. By increasing the mitotic activity of follicular epithelia, tretinoin also increases the turnover rates of thin, loosely adherent corneocytes. Through these actions, the comedo contents are extruded and the formation of the microcomedo, the precursor lesion of acne vulgaris, is reduced.

Additionally, tretinoin acts by modulating the proliferation and differentiation of epidermal cells. These effects are mediated by tretinoin's interaction with a family of nuclear retinoic acid receptors. Activation of these nuclear receptors causes changes in gene expression. The exact mechanisms whereby tretinoin-induced changes in gene expression regulate skin function are not understood.

This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (MICROSPONGE System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel.

Irritation Potential

Although tretinoin is intrinsically irritating to the skin, RETIN-A MICRO (microsphere) 0.1% w/w, was found to be significantly less irritating than RETIN-A Cream, 0.1% w/w, in a cumulative 21-day irritation test in subjects with normal skin. In addition, a half-face comparative irritation trial conducted for up to 14 days in women with sensitive skin, without acne, RETIN-A MICRO (microsphere) 0.1% w/w, was statistically less irritating than tretinoin cream, 0.1% w/w (Table 1). [See PHARMACOLOGY –Irritation Potential subsection.] There were no comparative studies conducted between RETIN-A MICRO (microsphere) 0.1% w/w and 0.04% w/w to assess comparative irritation potential.

Table 1: RETIN-A MICRO 0.04% w/w
Overview of Cutaneous Treatment Effects. Percentage of patients experiencing symptoms

	Treatment	
Cutaneous Treatment Effect Response	**RETIN-A MICRO 0.04% w/w**	**vehicle**
Erythema	64.0	53.5
Peeling	67.6	27.0
Dryness	59.6	31.9
Burning/Stinging	31.1	11.5
Itching	32.4	18.6

Pharmacokinetics

Tretinoin is an endogenous metabolite of Vitamin A metabolism in man. Percutaneous absorption of RETIN-A MICRO (microsphere), as determined by the cumulative excretion of radio-labelled drug into urine and feces, was assessed in 44 healthy men and women. Estimates of *in vivo* bioavailability, mean (SD) %, following both single and multiple daily applications, for a period of 28 days, were 0.82 (0.11) % and 1.41 (0.54) %, respectively. The plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid, all-*trans*-4-oxo-retinoic acid, and 13-*cis*-4-oxo-retinoic acid, generally ranged from 1 to 3 ng/mL and were essentially unaltered after either single or multiple daily applications relative to baseline levels.

Clinical Trials RETIN-A MICRO (microsphere) 0.04% w/w

In two large vehicle-controlled clinical studies, RETIN-A MICRO (microsphere) 0.04% w/w, applied once daily was significantly more effective than vehicle in reducing the severity of acne lesion counts. A total of 451 subjects with acne vulgaris were enrolled in the 2 controlled clinical studies. Of these 225 subjects applied RETIN-A MICRO (microsphere) 0.04% w/w. The severity of acne experienced by patients enrolled in these studies is shown in Table 2.

Table 2: Baseline severity of acne

Total facial lesion count	20 - 150
Comedones (open and closed)	10 - 100
Inflammatory lesions	10 - 50
No more than 2 nodules (deep inflammatory lesions of ≥1 cm)	

The mean reductions in lesion counts from baseline after treatment for 12 weeks are shown in Table 3.

Table 3: Mean (LS Mean) Percent Reduction in Lesion Counts from BL to Week 12 RETIN-A MICRO 0.04% w/w ITT/LOCF

Lesion Count	RETIN-A MICRO 0.04% w/w		vehicle	
	Study 1 N=108	Study 2 N=111	Study 1 N=110	Study 2 N=103
Non-inflammatory	-37.7	-28.5	1.8	-14.4
Inflammatory	-43.5	-40.7	-13.4	-28.3
Total	-39.7	-34.2	-8.0	-19.5

It takes 6-8 weeks to see significant clinical benefit from applying RETIN-A MICRO (microsphere) 0.04% w/w to acne lesions. There are no comparative studies between RETIN-A MICRO (microsphere) 0.04% w/w and 0.1% w/w.

RETIN-A MICRO (microsphere) 0.04% w/w was also significantly superior to the vehicle in the investigator's global evaluation of the clinical response. In study #1 14% of subjects using RETIN-A MICRO (microsphere) 0.04% w/w achieved an excellent result compared to 5% ($p < 0.0001$) of patients on vehicle control. In study #2, 19% of subjects using RETIN-A MICRO (microsphere) 0.04% w/w achieved an excellent result compared to 9% ($p=0.0052$) of subjects on vehicle control.

Clinical Trials RETIN-A MICRO (microsphere) 0.1% w/w

In two vehicle-controlled clinical studies, RETIN-A MICRO (microsphere) 0.1% w/w applied once daily was significantly more effective than vehicle in reducing the severity of acne lesion counts. The mean reductions in lesion counts from baseline after treatment for 12 weeks are shown in Table 4.

Table 4: Mean percent reduction from BL to Week 12 RETIN-A MICRO 0.1% w/w studies

	RETIN-A MICRO 0.1% w/w		Vehicle gel	
Lesion Count	Study #1	Study #2	Study #1	Study #2
Non-inflammatory	-49	-32	-22%	-3%
Inflammatory	-37	-29	-18%	-24%
Total	-45	-32	-23%	-16%

Therapeutic results may be noticed after two weeks, but more than four weeks are required before consistent beneficial results are observed. In each study, at each return visit, there was a greater mean percent reduction in total lesion count with RETIN-A MICRO (microsphere) 0.1% w/w than with vehicle (Table 5).

Table 5: Mean percent reduction from baseline in total lesion counts over time, subjects valid for efficacy RETIN-A MICRO 0.1% w/w studies

Return Visit Week	RETIN-A MICRO 0.1% w/w		Vehicle		p-value
	N	Mean	N	Mean	
Study #1					
2	77	18.3	80	6.3	0.006
4	77	22.3	78	14.4	0.127
7	75	38.9	77	18.2	<0.001
10	74	45.6	74	19.6	<0.001
12	72	44.5	72	22.8	<0.001
Study #2					
2	71	5.6	75	2.9	.205
4	74	9.2	77	2.7	0.026
7	70	16.1	71	4.9	0.016
10	68	31.0	66	9.7	<0.001
12	71	32.3	67	16.2	0.002

RETIN-A MICRO (microsphere) 0.1% w/w was also significantly superior to the vehicle in the investigator's global evaluation of the clinical response. In study #1, 35% of patients using RETIN-A MICRO (microsphere) 0.1% w/w achieved an excellent result compared to 11% of patients on vehicle control. In study #2, 28% of patients using RETIN-A MICRO (microsphere) 0.1% w/w achieved an excellent result compared to 9% of patients on vehicle control.

INDICATIONS AND CLINICAL USE

RETIN-A MICRO tretinoin gel (microsphere) is indicated for topical application in the treatment of acne vulgaris.

CONTRAINDICATIONS

RETIN-A MICRO tretinoin gel (microsphere) is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS

General

The skin of certain sensitive individuals may become excessively dry, red, swollen, or blistered. If these effects occur, the medication should be either discontinued until the integrity of the skin is restored or the medication should be adjusted temporarily to a level the patient can tolerate. Excessive skin dryness may also be experienced; if so, use of an appropriate emollient during the day may be helpful.

RETIN-A MICRO tretinoin gel (microsphere) should be kept away from the eyes, the mouth, angles of the nose, and mucous membranes.

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 reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. [See PRECAUTIONS – General Precautions subsection.]

Use in Pregnancy: **Topical tretinoin should be used by women of childbearing years only after contraceptive counselling. It is recommended that topical tretinoin should not be used by pregnant women.**

There have been isolated 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 known. 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) teratology studies of topical 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). [See TOXICOLOGY - Reproduction and Teratology subsection.]

Nursing Mothers

It is not known whether RETIN-A MICRO (microsphere) is 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 tretinoin is administered to a nursing mother.

PRECAUTIONS

General Precautions

RETIN-A MICRO tretinoin gel (microsphere) is for external use only.

Although recent studies have shown that RETIN-A MICRO (microsphere) does not cause phototoxicity or photoallergy, unprotected exposure to sunlight, including sunlamps, should be minimized during the use of RETIN-A MICRO (microsphere).

Patients with sunburn should be advised not to use the product until fully recovered because of the possibility of a heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to their occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products (at least SPF 15) and protective clothing over treated areas are recommended when exposure cannot be avoided. [See DOSAGE AND ADMINISTRATION Section.]

Local Irritation

Excessive skin dryness may be experienced; if so, use of an appropriate emollient during the day may be helpful.

The skin of certain sensitive individuals may become excessively dry, red, swollen, or blistered. If these effects occur, the medication should be either discontinued until the integrity of the skin is restored or the medication should be adjusted temporarily to a level the patient can tolerate.

RETIN-A MICRO (microsphere) should be kept away from the eyes, the mouth, angles of the nose and mucous membranes. Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

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. Avoid contact with the peel of limes.

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 MICRO (microsphere) as they might result in skin irritation.

Weather extremes, such as wind or cold, also may be irritating to patients being treated with tretinoin.

Drug Interactions

Caution should be exercised with the simultaneous use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with RETIN-A MICRO (microsphere). It also is advisable to allow the effects of such preparations to subside before use of RETIN-A MICRO (microsphere) is begun.

Concomitant topical medication medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, or spices should be used with caution because of possible interaction with tretinoin.

Avoid contact with the peel of limes.

Pediatric Use

Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS

The skin of certain sensitive individuals treated with RETIN-A MICRO tretinoin gel (microsphere) may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should be either discontinued until the integrity of the skin is restored, or the medication should be adjusted temporarily to a level the patient can tolerate. True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin. To date, all adverse effects of tretinoin have been reversible upon discontinuance of therapy. [See DOSAGE AND ADMINISTRATION Section.].

SYMPTOMS AND TREATMENT OF OVERDOSAGE

RETIN-A MICRO tretinoin gel (microsphere) 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 females of childbearing age.

DOSAGE AND ADMINISTRATION

RETIN-A MICRO tretinoin gel (microsphere) should be applied once a day, to acne-prone skin areas, after washing with mild, non-medicated soap and dry skin gently. The gel may be applied at any time during the day or at bedtime. Use only a sufficient quantity of medication to cover the entire affected area lightly. Application of excessive amounts of gel may result in "caking" of the gel and will not provide incremental efficacy.

A transitory feeling of warmth or slight stinging may be noted on application. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed, or the frequency of application increased as the patient becomes able to tolerate the treatment. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. RETIN-A MICRO (microsphere) applied once daily is effective in reducing the severity of acne and reducing the number of lesions. Efficacy has not been established for less than once daily dosing frequencies.

During the early weeks of therapy, an apparent exacerbation of inflammatory lesions may occur. This may be due to the action of the medication on deep, previously unseen lesions and should not be considered a reason to discontinue therapy.

Therapeutic results may be noticed after two weeks, but more than four weeks of therapy are required before consistent beneficial effects are observed. Patients in clinical trials were treated for 12 weeks.

Patients treated with RETIN-A MICRO (microsphere) may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied.

Patients treated with RETIN-A MICRO (microsphere) should use effective sunscreens with a minimum SPF of 15 as well as protective clothing when exposure to sun cannot be avoided.

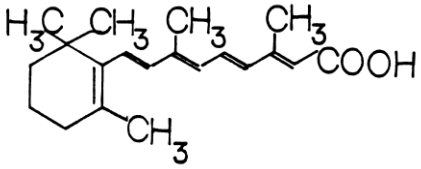
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Tretinoin

Chemical Name: 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclo-hexen-1-yl) -2,4,6,8, -no natetraenoic acid.

Structural Formula:



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

Molecular Weight: 300.44 g/mol

Physicochemical Properties

Description: Tretinoin is a yellow to orange crystalline powder having a characteristic odor.

Solubility: It is practically insoluble in water and propylene glycol, insoluble in glycerin, and slightly soluble in chloroform and ethanol.

Melting Point: It has a melting point of 182.8°C.

DRUG PRODUCT

Composition

RETIN-A MICRO tretinoin gel (microsphere) is a low irritancy formulation. This formulation uses patented acrylates copolymer porous microspheres (MICROSPONGE System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel, without the use of oils or organic solvents like ethanol or acetone, which themselves can contribute to irritation. It is a member of the retinoid family of compounds and an endogenous metabolite of Vitamin A. Other components of this formulation are Purified Water, Carbomer 934P in the 0.1% w/w strength and Carbomer 974P in the 0.04% w/w strength, Glycerin, Disodium EDTA, Propylene Glycol, Propylene Glycol Dicaprylate/Dicaprate, Sorbic Acid, PPG-20 Methyl Glucose Ether Distearate, Cyclomethicone and Dimethicone Copolyol, Benzyl Alcohol, Trolamine, and Butylated Hydroxytoluene.

STABILITY AND STORAGE RECOMMENDATIONS

Keep container closed when not in use. Store between 15^{o} C - 25^{o} C. Protect pump containers from heat.

AVAILABILITY OF DOSAGE FORMS

RETIN-A MICRO tretinoin gel (microsphere) 0.04% w/w and 0.1% w/w are supplied as 50 g pumps and 2 g tubes (samples).

INFORMATION FOR THE CONSUMER

PrRETIN-A MICRO®
Tretinoin Gel (microsphere)
0.1% w/w and 0.04% w/w

This leaflet is part III of a three-part "Product Monograph" published when RETIN-A-MICRO was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RETIN-A MICRO. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RETIN-A MICRO contains tretinoin which is related to Vitamin A. RETIN-A MICRO is effective against:

- blackheads,
- whiteheads, and
- inflammatory lesions of acne such as papules and pustules.

It is applied to the skin.

What it does:
This medicine works by causing the outer layer of the skin to grow more rapidly, which decreases the amount of the protein "keratin" in the skin. As a result, the surface layer of the skin becomes thinner and pores are less likely to become blocked, reducing the occurrence of whiteheads, blackheads and pimples.

When it should not be used:
Do not use if you have an allergy to RETIN-A or any of the ingredients.

What the medicinal ingredient is:
Tretinoin

What the important nonmedicinal ingredients are:
Other components of this formulation are Purified Water, Carbomer, Glycerin, Disodium EDTA, Propylene Glycol, Propylene Glycol Dicaprylate/Dicaprate, Sorbic Acid, PPG-20 Methyl Glucose Ether Distearate, Cyclomethicone and Dimethicone Copolyol, Benzyl Alcohol, Trolamine, and Butylated Hydroxytoluene.

What dosage forms it comes in:
RETIN-A MICRO is a microsphere gel in 0.04% w/w and 0.1% w/w strengths. It is supplied as a topical gel in a 50 g pump.

WARNINGS AND PRECAUTIONS

BEFORE you use RETIN-A MICRO talk to your doctor or pharmacist if:

- You are pregnant or might become pregnant. **If you are female of child-bearing age, you should only use Retin-A Micro after consulting your doctor and seeking advice for contraceptive counselling. If you become pregnant, discontinue use of RETIN-A MICRO and consult your doctor.**
- You are breastfeeding. It is not known if RETIN-A MICRO can pass through your milk to the baby.
- You are planning to be in the sun.
- You are using or plan to use any other medicine for your acne at the same time as RETIN-A MICRO.
- You are taking medicines for other health conditions. Some medicines may make your skin more sensitive to sunlight.

Avoid exposure to sunlight as much as possible while using RETIN-A MICRO. Do not use ultraviolet (UVB) or long-wavelength ultraviolet (UVA) sunlamps. If you have sunburn, you should not use RETIN-A MICRO until you are completely recovered. Do not apply RETIN-A MICRO to areas of the skin where you have other problems such as sunburn, eczema, severely inflamed skin or open lesions.

Safety and effectiveness in children below the age of 12 have not been established.

INTERACTIONS WITH THIS MEDICATION

Use other acne medicine only on your doctor's advice and follow the doctor's instructions carefully. The medications you used in the past might cause redness or peeling.

See also below **"WHAT SHOULD I AVOID WHILE USING RETIN-A MICRO?"**.

PROPER USE OF THIS MEDICATION

Usual dose: Use once per day.

1. Wash with a mild, non-medicated soap and dry skin gently.
2. Apply RETIN-A MICRO once daily before bedtime (or as directed by your doctor).
3. You should not use more than the amount of RETIN-A MICRO, suggested by your physician or to apply RETIN-A MICRO more frequently than instructed. Too much medication may irritate the skin, waste medication and will not give faster or better results.
4. Keep the medication away from the corners of the nose, mouth, eyes and open wounds or other areas where treatment is not intended. Spread it away from these areas when applying.
5. **Pump:** fully depress the pump twice to dispense 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 lightly. Smooth gently into the skin. Some patients may experience a slight visible residue of medication after application.
6. Keep container closed when not in use.
7. If your doctor has prescribed another topical acne treatment

(i.e. benzoyl peroxide or topical antibiotic), do not apply RETIN-A MICRO at the same time of day as the other products.

8. Early in therapy, some patients may notice an appearance of new blemishes (papules and pustules). At this stage it is important to continue using RETIN-A MICRO.
9. Don't be discouraged if you see no immediate improvement. Don't stop treatment at the first signs of improvement. Therapeutic results may be noticed after two weeks, and more than four weeks of therapy are required before consistent beneficial effects are observed. It is likely that your doctor will have you use RETIN-A MICRO for 6 to 8 weeks before checking your progress. Patients in clinical trials were treated for 12 weeks.

What should I avoid while using RETIN-A MICRO?

- Spend as little time as possible in the sun. Use a daily sunscreen with a SPF 15 rating or higher, sun protective clothing, and a wide brimmed hat to protect you from sunlight. When outside, even on hazy days, areas treated with RETIN-A MICRO should be protected. Do not use sunlamps. RETIN-A MICRO may make you get sunburned more easily. If you do get sunburned, stop using RETIN-A MICRO until your skin is completely back to normal. Talk to your doctor about how to protect you skin if you must be in sunlight a lot.

- Avoid cold weather and wind as much as possible and use clothing to protect you from the weather. Skin treated with RETIN-A MICRO may dry out or get wind burned more easily.

- Avoid skin products that may dry or irritate your skin. Such products are those that contain astringents, alcohol, or spices and include certain medicated soaps, shampoos and hair permanent solutions. Avoid contact with the peel of limes. Your skin may become very dry, red swollen, blistered, or crusted with these products. If you get severe skin irritation or skin irritation that will not go away, stop using RETIN-A MICRO and call your doctor. You should talk to your doctor about the use of all skin care products while using RETIN-A MICRO .

- Avoid washing your face too often and do not scrub your face hard when washing it. Use a mild, non-medicated soap and wash gently and pat dry.

Overdose:
If you have applied too much RETIN-A MICRO, remove any excess applied. You may get severe skin irritation with redness, peeling, blistering and itchiness. If this happens, stop the treatment and contact your doctor. It is recommended that you apply a moisturizer or a moisturizer with sunscreen that will not aggravate your acne (non-comedogenic) every morning after you wash.

Overdose:
If you have applied too much RETIN-A MICRO, remove any excess applied. You may get severe skin irritation with redness, peeling, blistering and itchiness. If this happens, stop the treatment and contact your doctor. It is recommended that you apply a moisturizer or a moisturizer with sunscreen that will not aggravate your acne (non-comedogenic) every morning after you wash.

Missed Dose:
If you forget to use RETIN-A MICRO, apply it when you remember, and then go back to using it as you would normally. If it is almost time for your next application, skip the one you missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Peeling, burning, itching, dryness, stinging and redness may occur with some people during the first one or two weeks of therapy. These reactions can easily be minimized by following the instructions carefully. Should the effects become excessively troublesome, discontinue use and consult your doctor.

This is not a complete list of side effects. For any unexpected effects while taking RETIN-A MICRO, contact your doctor or pharmacist.

HOW TO STORE IT

Keep RETIN-A MICRO in a cool, dry place where the temperature is below 25°C. Protect pump containers from heat. Keep your medicines where children cannot reach them. Do not store RETIN-A MICRO or any other medicine, in the bathroom or near a sink. Do not leave medicines in the car or on windowsills. Heat and dampness can destroy some medicines.

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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Bausch Health, Canada Inc., at: 1-800-361-4261

This leaflet was prepared by Bausch Health, Canada Inc.

Last revised: August 27, 2020

PHARMACOLOGY

Animal Studies

The pharmacokinetics and biotransformation of dermal tRA (tretinoin) have been studied extensively in animals. After application of ^{3}H-tRA in tretinoin Microsponge Gel, the systemic exposure to total radioactivity was low, and decreased in the order: mice>> rats> rabbits> dogs. These levels paralleled both the agility of the animals for grooming and the known relationship of the permeability of the skin of the animals used in these studies. The high levels in mice (up to 0.2 mcg/mL) were probably due to ingestion of tRA. A comparable study in humans showed that the plasma levels achieved in these laboratory animals were orders of magnitude higher than those following the application of a potential therapeutic dose to man (see below).

Human Studies

Irritation Potential

Although tretinoin is intrinsically irritating to the skin, RETIN-A MICRO (microsphere) has been found to be significantly less irritating than Retin-A Cream, 0.1% w/w. In a trial in women with sensitive skin, but without acne or other skin diseases, when the products were applied to opposite facial cheeks for up to 14 days, RETIN-A MICRO (microsphere) was significantly better tolerated and less irritating than Retin-A Cream. In an irritancy study in both men and women with healthy skin, the cumulative 21-day irritation score for RETIN-A MICRO (microsphere) was consistent with a mild local irritant, whereas Retin-A Cream was substantially more irritating (see Figure 1). The lower irritancy of RETIN-A MICRO (microsphere) may be attributable to the design of its vehicle, which contains the patented MICROSPONGE System (acrylates copolymer microspheres).

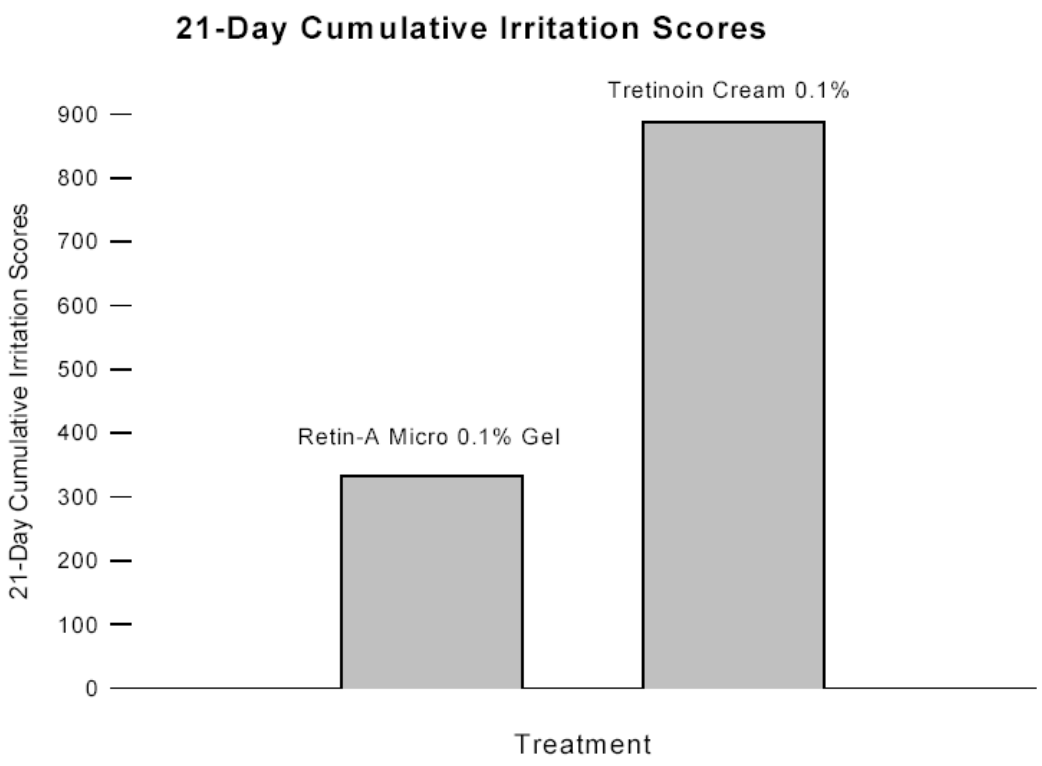


Figure 1: The maximum possible 21-day cumulative irritation score was 3,000; the vehicles associated with RETIN-A MICRO (microsphere) 0.1% w/w and tretinoin cream 0.1% w/w had 21-day scores of 2 and 7, respectively. Statistical analysis indicated that RETIN-A MICRO (microsphere) 0.1% w/w (score=332) was significantly less irritating then tretinoin cream 0.1% w/w (score=887), and that each tretinoin-containing product was significantly different from its vehicle.

Pharmacokinetics

A pharmacokinetics study (B0281S) was conducted in 44 healthy male and female subjects who received single or repeated daily topical applications of TMG 0.1% w/w or RETIN-A Cream 0.1% w/w. Percutaneous absorption was determined by cumulative excretion of radioactivity into the urine and feces. Mean (SD) total absorption was 0.82 (0.11) % and 1.41 (0.54) %, respectively, for subjects administered single or multiple dose(s) of TMG 0.1% w/w. Mean (SD) total absorption with RETIN-A Cream 0.1% w/w was 1.13 (0.31) % and 2.26 (0.55) % of the dose, respectively, for subjects who received single or multiple dose(s). Mean (SD) peak total plasma radioactivity concentrations were 0.062 (0.03) and 0.163 (0.078) ng·equivalents/mL after a single dose and after multiple doses of TMG 0.1% w/w, respectively. Mean (SD) peak total plasma radioactivity concentrations with RETIN-A Cream 0.1% w/w were 0.105 (0.046) and 0.242 (0.096) ng·equivalents/mL after a single dose and after multiple doses, respectively. Although absorption in all treatment groups was minimal, there was a statistically significant difference in overall absorption between subjects administered multiple doses of TMG 0.1% w/w and subjects administered multiple doses of RETIN-A Cream 0.1% w/w (p=0.0001). Endogenous concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid (*CIS*-RA), all-*trans*-4-oxo-retinoic acid (OXO-RA), and 13-*cis*-4-oxo-retinoic acid (*CIS*-OXO), generally ranged from 1-3 ng/mL and were essentially unaltered after either single or multiple applications of either TMG 0.1% w/w or RETIN-A Cream 0.1% w/w. The results of Study B0281S were

consistent with those previously observed with various 0.05% tretinoin cream formulations.

TOXICOLOGY

Animal Studies

The preclinical toxicity of topically administered tretinoin has been extensively evaluated. The primary adverse effect is on the skin at the site of application. Secondarily there is evidence of systemic compensatory mechanisms in response to the dermal insult. Although oral administration of tretinoin can produce plasma levels adequate to produce systemic toxicity, the systemic exposure to tretinoin in animals treated dermally usually remains below the threshold required to produce these effects.

The APS MICROSPONGE formulation itself (no drug) demonstrated low potential for irritancy with no incremental risk due to the percutaneous absorption when compared to other topical tretinoin formulations. The polymer is highly cross-linked and is considered inert. The amount of possible residual monomers and solvents in the finished formulation have been shown to have safety factors greater than $3X10^6$, based on acute non-clinical toxicity studies.

Acute Toxicity

The acute oral toxicity of TMG 0.1% w/w was evaluated in rats. In each study, all animals survived the 14-day observation period, and there were no gross abnormalities noted at necropsy. In each acute toxicity study, it was concluded that the test articles were not toxic orally to rats under the test conditions.

Long-Term Toxicity

Multidose toxicity studies with TMG 0.1% w/w were performed in mice and dogs. The primary toxic effect of topically applied TMG 0.1% w/w in laboratory animals is dermal irritation in various degrees. Secondary effects are evident in the lymph systems that service the application sites, i.e., increased numbers of circulating leucocytes and lymphoid hyperplasia. These lesions are generally reversible on withdrawal of dosing. In the 3-month dermal toxicity study in mice, retinoid-like effects (increased food consumption, slight decreases in erythrocyte parameters in the males, decreased cholesterol and triglycerides in the males, decreased T_4 concentrations, and decreased absolute and relative testes weights and absolute ovarian weights), were seen at the high dose of 5 mg/kg/day, probably due to ingestion of tretinoin. The analysis of plasma samples collected during the study supported this conclusion. Pre-dose concentrations of the retinoids were consistently below the limit of quantification (<5 ng/mL). By contrast, certain of the samples collected at 4 hours post-dose from the mid and high dose groups contained measurable concentrations of tRA, together with quantifiable levels of 13-*cis*-RA.

Carcinogenicity

Although there have been no direct studies on the carcinogenic potential of TMG 0.1% w/w, it has been previously demonstrated that topical application of tretinoin to mice for 20 months at

dose levels up to 1.0 mg/kg (100 X the clinical dose of TMG 0.1% w/w) was not carcinogenic.

There is considerable conflicting information on the possible role of tretinoin in photocarcinogenicity studies in laboratory animals with simulated ultraviolet radiation. In addition, the human relevance of dermal carcinogenicity studies in albino mice has been questioned because these mice lack melanin and have no facility for developing a protective tan. In studies using pigmented mice, no evidence of photocarcinogenic activity has been seen. More importantly, with the experience of a quarter century of use, there is no clinical evidence that topically applied tretinoin enhances photocarcinogenicity.

Mutagenicity

There is no evidence that tretinoin possesses mutagenic potential as evaluated by the Ames assay or the Micronucleus Assay.

Reproduction and Teratology

Percutaneous administration of TMG 0.1% w/w does not affect the development of rat or rabbit conceptuses when administered at doses up to 500 X or 100 X the clinical dose, respectively. In rats, the maternal no-observable-effect-level (NOEL) for TMG 0.1% w/w was less than 0.2 mg tretinoin/kg/day, as 0.2 mg/kg/day was the lowest dose tested and caused cutaneous responses (erythema, edema, desquamation) and reduced body weight gain and feed consumption. The developmental NOEL for TMG 0.1% w/w was greater than or equal to 1.0 mg tretinoin/kg/day (>100 X the recommended clinical dose); no adverse effects on embryo-fetal viability, fetal body weight, or fetal morphology occurred at this, the highest dose tested. Thus, TMG 0.1% w/w was not considered to be a developmental toxicant in rats.

Two developmental toxicity studies were performed in New Zealand white rabbits. The maternal NOEL for TMG 0.1% w/w in the first study was less than 0.2 mg tretinoin/kg/day; all doses of the test article formulation significantly increased the severity of skin irritation, as compared with the level of skin irritation caused by the vehicle formulation. However, the vehicle formulation alone also caused skin irritation. No other adverse effects were caused by doses of the test article as high as 1.0 mg tretinoin/kg/day. The developmental NOEL for TMG 0.1% w/w was 0.2 mg tretinoin/kg/day (20 X the recommended clinical dose). Treatment with the 0.5 and 1.0 mg tretinoin/kg/day doses appeared possibly associated with increased incidences of varying degrees of dilation of the lateral and/or third ventricles in the brain and other alterations in some of the fetuses. Because all doses caused a maternal response, and alterations that occurred in the fetuses did not always present clear dose-dependent patterns, a clear causal relationship of the test article formulation and these fetal abnormalities could not be established. In addition, there were several animals with measurable parent and/or metabolite concentrations at sporadic intervals in the study, suggesting possible exposure by the oral route. Plasma analyses for determination of tretinoin and its metabolites, 13-*cis*-retinoic acid (13-*cis*-RA), all-*trans*-4-oxo-retinoic acid (4-oxo-tRA), and 4-oxo-13-*cis*-retinoic acid (4-oxo-13-*cis*-RA), indicated that, in general, the concentrations of these retinoids after treatment with TMG 0.1% w/w were all below the lower limit of quantification of 5 ng/mL, with the exception that tretinoin and/or 13-*cis*-RA were observed in a few samples collected from the mid-dose group and the high-dose group 24 hours after the first and final high dose, indicating minimal dermal

absorption. However, the measurable concentrations of tretinoin and/or 13-*cis*-RA observed in the mid dose group and the high dose group 24 hours after the first and final dose suggested the possibility of sporadic ingestion.

An additional rabbit study was performed that took precautions to prevent ingestion of topically administered TMG 0.1% w/w (i.e. through grooming behaviour). There were no anomalies in any of the pups in this repeat rabbit teratology study at doses as high as 1.0 mL/kg of TMG 0.1% w/w (1.0 mg/kg tretinoin). This dose represents a multiple of 100 times the clinical dose (500 mg TMG 0.1% w/w) for a 50 kg individual.

Human Studies

Clinical studies performed with TMG 0.1% w/w demonstrate that TMG 0.1% w/w is less irritating than tretinoin cream 0.1% w/w. Additional, studies have shown that TMG 0.1% w/w does not cause contact sensitization, phototoxicity, or photoallergenic reactions in humans.

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