PRODUCT MONOGRAPH

PrROSIVER™

Ivermectin

Cream, 1% w/w

Topical Rosacea Therapy

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Date of Preparation:
February 15, 2017

Submission Control No: 172733

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PrROSIVER™

Ivermectin Cream

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	Cream / 1%	Cetyl alcohol, stearyl alcohol, methyl parahydroxybenzoate (methyl paraben), propyl parahydroxybenzoate (propyl paraben), propylene glycol. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ROSIVER (ivermectin) Cream, 1% is indicated for the topical treatment of inflammatory lesions (papules and pustules) of rosacea in adults 18 years of age or older.

Geriatrics (≥ *65 years of age*):

Approximately 300 subjects aged 65 years and older were treated over all clinical trials with ROSIVER. In pivotal trials, efficacy and safety in subjects ≥ 65 years of age were found to be comparable to that in adults less than 65 years of age.

Pediatrics (< *18 years of age*):

Safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

ROSIVER (ivermectin) Cream, 1% is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

General

The medicinal product contains:

•Cetyl alcohol and stearyl alcohol, which may cause local skin reactions (eg. contact dermatitis),
•Methyl parahydroxybenzoate (methyl paraben) and propyl parahydroxybenzoate (propyl paraben), which may cause allergic reactions (possibly delayed),
•Propylene glycol, which may cause skin irritation.

Interactions with known irritants or photo-enhancers have not been studied. Concomitant use of potentially irritating topical products or procedures should be avoided.

Immune

Photosafety and sensitization potential were not specifically evaluated in humans. Dermal studies in guinea pigs produced evidence of probable delayed sensitization and possible photoallergenicity. See TOXICOLOGY.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies from the topical use of ivermectin in pregnant women. ROSIVER (ivermectin) Cream, 1% should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

Reproductive toxicity studies have shown that ivermectin administered orally is teratogenic in rats and rabbits. See TOXICOLOGY

Nursing Women: Following oral ivermectin administration, ivermectin is excreted in human milk, (milk concentrations were 0.37-fold of those measured in plasma (37.9 ± 0.54 ng/mL) following an oral dose of 150 µg/kg).

Excretion in human milk following topical administration has not been evaluated. In oral studies in rats, ivermectin was excreted in the milk of dams at about 4-fold the maternal plasma concentrations; ivermectin related toxic central nervous system, physical and behavioral development effects and mortality were observed in the litters, which were attributed to the low p-glycoprotein activity of the blood-brain barrier of the rat pups.

Due to the potential for serious adverse reactions from ROSIVER in nursing infants, 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

During clinical trials, 2047 subjects with inflammatory lesions of rosacea received ROSIVER once daily. A total of 1555 subjects were treated once daily for at least 12 weeks, and 519 subjects were treated for approximately one year.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Adverse drug reactions, reported in ≥ 0.1% and ≤ 1% of subjects treated with ROSIVER for at least 3 months in vehicle-controlled clinical trials, are shown in Table 1 below:

Table 1: Adverse Drug Reactions Reported in Controlled Clinical Trials

System Organ Class / Preferred Term	ROSIVER n= 910 (%)	Vehicle n= 461 (%)
Skin and subcutaneous tissue disorders	**62 (6.8%)**	**49 (10.6%)**
Skin burning sensation	9 (1.0)	10 (2.2)
Skin irritation	8 (0.9)	11 (2.4)
Pruritis	7 (0.8)	5 (1.1)
Dry skin	5 (0.5)	3 (0.7)

The safety profile remained stable under conditions of long-term use as observed in long-term treatment for up to one year.

DRUG INTERACTIONS

Overview

No clinical drug interaction studies have been conducted with ROSIVER (ivermectin) Cream, 1%.

Ivermectin is a known substrate of p-glycoprotein.

In vitro studies have shown that ivermectin, at ROSIVER therapeutic systemic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes. Based on these results, there

is no potential for clinically relevant systemic drug-drug interactions between ivermectin and other drugs under the conditions of topical use of Ivermectin 1% Cream.

Interactions with known irritants or photo-enhancers have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Hands should be washed after applying ROSIVER.

Cosmetics may be applied after ROSIVER has dried.

ROSIVER is not for oral, ophthalmic, or intravaginal use.

Recommended Dose and Dosage Adjustment

Once daily application of five pea-sized amounts (one to each of the five areas of the face: forehead, chin, nose, each cheek) per day.

Administration

Apply ROSIVER once daily at bedtime. Use a pea-size amount for each area of the face: forehead, chin, nose, each cheek.

Spread as a thin layer across the entire face, avoiding the eyes and lips.

OVERDOSAGE

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

There are no reports of overdosage with ROSIVER (ivermectin) Cream, 1%.

In cases of accidental or significant exposure to unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other adverse effects that have been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.

In case of accidental ingestion, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present. Ivermectin is largely excreted via the feces, and therefore prompt gastrointestinal decontamination (induced emesis and gastric lavage with airway secured) followed by the administration of activated charcoal may be helpful.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of ROSIVER in treating rosacea is unknown.

Pharmacodynamics

Anti-inflammatory properties of topical ivermectin have been observed in animal models of skin inflammation.

Ivermectin is known to have endectocidal properties via selective high affinity binding to glutamate-gated anion channels and γ-aminobutyric acid-gated chloride channels. These channels occur in peripheral motor synapses of parasites, but occur only in the central nervous system in mammals. Ivermectin is normally excluded from the mammalian central nervous system by mature levels of p-glycoprotein activity

See DETAILED PHARMACOLOGY.

Pharmacokinetics

Absorption: The absorption of ivermectin from ROSIVER was evaluated in a clinical trial in adult subjects with severe papulopustular rosacea, under maximal use conditions. At steady state (after 2 weeks of treatment), the highest mean (± standard deviation) plasma concentrations of ivermectin peaked within 10 ± 8 hours post-dose (C_{max}: 2.10 ± 1.04 ng/mL range: 0.69 - 4.02 ng/mL) and the highest mean (± standard deviation) $AUC_{0\text{-}24hr}$ was 36.14 ± 15.56 ng.hr/mL (range: 13.69-75.16 ng.hr/mL). In addition, systemic exposure assessment in longer treatment duration (Phase 3 studies) evidenced that there was no plasma accumulation of ivermectin over the 52-week treatment period. These levels obtained under steady-state conditions are lower than those observed following oral administration of ivermectin

Distribution: An in vitro penetration study in excised human skin demonstrated that after topical application of ivermectin 1% cream, the penetrated dose represented approximately 2% of the applied dose (1.59% in stratum corneum, 0.55% in epidermis plus dermis and 0.03% in receptor fluid).

Ivermectin is greater than 99% bound to human plasma proteins (99.5% to human serum albumin) without significant binding to erythrocytes, based on in vitro studies.

Human fetal transfer of ivermectin has not been studied, however following oral administration to pregnant rats, the fetuses are exposed to ivermectin and/or its metabolites.

Ivermectin is a known substrate of P-glycoprotein.

Following oral administration, ivermectin is excreted in human milk. Milk concentrations were 0.37-fold of those measured in maternal plasma following an oral dose of 150 µg/kg (14.13 ± 0.43 ng/mL in milk; 37.9 ± 0.54 ng/mL in plasma).

Metabolism: Ivermectin is metabolized in the liver. In vitro studies using human hepatic microsomes and recombinant CYP450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4 into three metabolites.

In vitro studies show that ivermectin, at ROSIVER therapeutic systemic concentrations, does not inhibit the CYP450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, 4A11 or 2E1, and does not induce CYP450 enzyme expression (1A2, 2B6, 2C9 or 3A4).

Two major metabolites of ivermectin were identified in a maximal use topical, clinical pharmacokinetic study (3''-O-demethyl ivermectin and 4a-hydroxy ivermectin). Similar to the parent compound, metabolites reached steady state conditions by 2 weeks of treatment, with no evidence of accumulation up to 12 weeks.

Excretion: In humans, ivermectin and its metabolites were excreted almost exclusively in feces, with less than 1% of the administered dose excreted in urine. Terminal plasma ivermectin half-life averaged 6 days (mean: 145 hours, range 92-238 hours) in patients receiving a once daily cutaneous application of ROSIVER for 28 days, in the maximal use, clinical pharmacokinetic study.

Special Populations and Conditions

Studies to assess the effect of ROSIVER in special populations were not conducted. The very low systemic exposures observed in clinical studies indicate that no new safety issues would be anticipated for ROSIVER in special patient populations.

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C).

SPECIAL HANDLING INSTRUCTIONS

Hands should be washed immediately after applying ROSIVER (ivermectin) Cream, 1%. Access to ROSIVER by children or pets should be prevented during usage, disposal and storage of the product.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ROSIVER (ivermectin) Cream, 1% w/w (10 mg/g) is a white to pale yellow hydrophilic cream (oil-in-water emulsion) and is supplied in a 15g, 30g, 45g and 60g laminated tubes with a child-resistant cap. Physician samples are supplied in 2 g laminate tubes with a non-child-resistant cap.

Medicinal ingredient: Ivermectin

Non medicinal ingredients:

Carbomer copolymer (type B), Cetyl alcohol, Citric acid monohydrate, Dimeticone (20 Cst), Disodium edetate, Glycerol, Isopropyl palmitate, Macrogol cetostearyl ether, Methyl parahydroxybenzoate, Oleyl alcohol, Phenoxyethanol, Propylene glycol, Propyl parahydroxybenzoate, Purified water, Sodium hydroxide 10% w/w aqueous solution, Sorbitan stearate(Type 1), Stearyl alcohol

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ivermectin

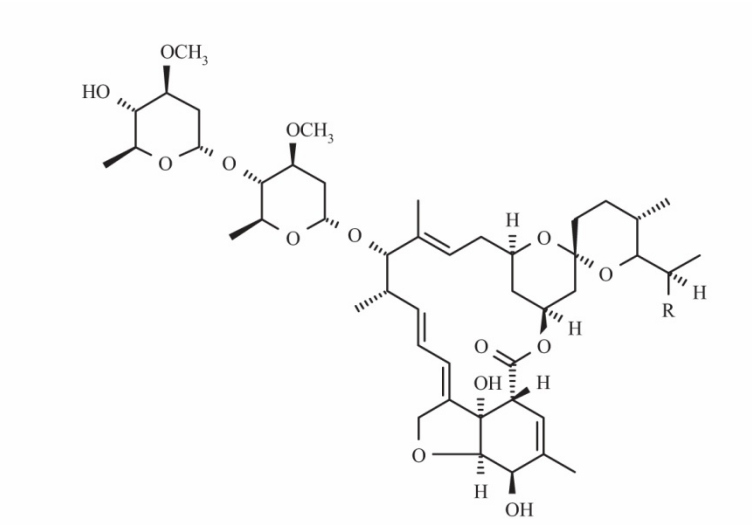
Chemical name: Ivermectin is a mixture of component H_2B_{1a} and H_2B_{1b}

Component H_2B_{1a}:
5-*O*-demethyl-22,23-dihydroavermectin A_{1a}

Component H_2B_{1b}:
5-*O*-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroavermectin A_{1a}

Molecular formula and (molecular mass): Component H_2B_{1a}: $C_{48}H_{74}O_{14}$ (875)
Component H_2B_{1b}: $C_{47}H_{72}O_{14}$ (861)

Structural formula:



Component H_2B_{1a}: R = C_2H_5, Component H_2B_{1b}: R = CH_3.

Physicochemical properties: Ivermectin is a white or yellowish-white, crystalline powder, slightly hygroscopic. Practically insoluble in water, freely soluble in methylene chloride and soluble in ethanol (96%).

CLINICAL TRIALS

ROSIVER (ivermectin) Cream, 1% applied once daily at bedtime was evaluated in the treatment of inflammatory lesions of rosacea in two pivotal randomized, double-blind, vehicle-controlled clinical trials, which were identical in design.

Study demographics and trial design

Table 2 - Summary of patient demographics

Study	Trial design	Dosage, route of administration and duration	Study subjects, N	Mean age (Range)	Gender, N
Study 1	Multicenter, randomized, double-blind, parallel-group, vehicle-controlled	Ivermectin 1% Cream once daily Ivermectin Cream Vehicle once daily Once daily Topical (facial application) 12 weeks	683	50.4 (19-88)	Male, 217 Female, 466
Study 2	Multicenter, randomized, double-blind, parallel-group, vehicle-controlled	Ivermectin 1% Cream once daily CD5024 Cream Vehicle once daily Topical (facial application) 12 weeks	688	50.2 (18-89)	Male, 229 Female, 459

Results

The co-primary efficacy endpoints in both pivotal trials were the success rate based on the IGA outcome (percentage of subjects "clear" and "almost clear" at Week 12 of the study) and absolute change from baseline in inflammatory lesion counts. The IGA scale is based on the following definitions:

Grade	Score	Clinical Description
Clear	0	No inflammatory lesions present, no erythema
Almost Clear	1	Very few small papules/pustules, very mild erythema
Mild	2	Few small papules/pustules, mild erythema
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

Using the 5-point Investigator Global Assessment (IGA) scale, 79% of subjects were scored as moderate (IGA=3) and 21% scored as severe (IGA= 4) at baseline.

The following table presents efficacy outcomes from both pivotal studies.

Table 3 - Results of Phase III pivotal studies

	Study 1		Study 2	
	ROSIVER (N=451)	**Vehicle (N=232)**	**ROSIVER (N=459)**	**Vehicle (N=229)**
Investigator Global Assessment				
Number (%) of Subjects Clear or Almost Clear in the IGA at Week 12	173 (38.4)	27 (11.6)	184 (40.1)	43 (18.8)
Inflammatory Lesions				
Mean Inflammatory Lesion Count at Baseline	31.0	30.5	33.3	32.2
Mean Inflammatory Lesion Count at Week 12	10.6	18.5	11.0	18.8
Mean Absolute Change (% Change) in Inflammatory Lesion Count from Baseline at Week 12	-20.5 (-64.9)	-12.0 (-41.6)	-22.2 (-65.7)	-13.4 (-43.4)
p-value	<0.001	-	<0.001	-

The results from both pivotal clinical studies demonstrated that ROSIVER applied once daily for 12 weeks was statistically more effective than vehicle cream in terms of IGA success rate and absolute change in inflammatory lesion counts ($p<0.001$).

Starting from 4 weeks of treatment, ROSIVER was significantly more effective than vehicle cream for both the co-primary efficacy endpoints ($p<0.05$).

IGA was assessed during the 40-week investigator-blinded extension of the two pivotal studies and the percentages of subjects treated with ROSIVER achieving an IGA score of 0 (“clear”) or 1 (“almost clear”) continued to increase up to Week 52. The Success Rate (IGA = 0 or 1) at Week 52 was 71% and 76% in Studies 1 and 2, respectively.

The efficacy and safety of ROSIVER in the treatment of inflammatory lesions of rosacea were also evaluated in another supportive randomized, investigator-blinded, active-controlled clinical study. The study was conducted in 962 subjects aged 18 years and older who were treated for 16 weeks with either ROSIVER once daily or Metronidazole 0.75% w/w cream twice daily. In this study, 99.7% of subjects were Caucasian and 65.2% were female; on the IGA scale, 83.3% of subjects were scored as moderate (IGA=3) and 16.7% scored as severe (IGA=4) at baseline.

The results of the study demonstrated that ROSIVER was statistically more effective than Metronidazole 7.5 mg/g cream on the primary efficacy endpoint (Mean Percent Change in Inflammatory Lesion Counts) with a reduction of 83.0% and 73.7% from baseline after 16 weeks of treatment for the ivermectin and metronidazole groups respectively ($p<0.001$). The superiority of ROSIVER at Week 16 was confirmed by the Success Rate based on IGA and Absolute Change in Inflammatory Lesion Counts (secondary endpoints ($p<0.001$)).

DETAILED PHARMACOLOGY

Primary pharmacodynamics

The mechanism of action of ivermectin in ROSIVER in treating rosacea is unknown.

Secondary pharmacodynamics

Animal Models of inflammation:
In mouse ear edema models, topical ivermectin treatment showed anti-inflammatory activities (dose-dependent reduction of ear edema, reduction of tumor necrosis factor alpha).
In a mouse model of allergen-induced atopic dermatitis, topical application of ivermectin reduced all inflammation symptoms including ear edema, epidermal thickness, skin eosinophil peroxidase, skin mastocyte count, and serum IgE content.
The pharmacological activity of the 2 major human ivermectin metabolites has not been studied.

MICROBIOLOGY

Microbiological activity was not specifically studied in the development of ROSIVER.
Ivermectin is known to bind selectively to specific neurotransmitter receptors that function in the peripheral motor synapses of parasites, producing an endectocidal effect in nematodes, arthropods and insects.

TOXICOLOGY

General Toxicology:

Repeat-dose dermal application studies of ivermectin 1% cream in minipigs did not show systemic toxic effects or local toxicity. The exposure in minipigs via dermal application at the highest dose given in the study was comparable to the systemic exposure in humans at the therapeutic dose of ROSIVER.

Genotoxicity:

Ivermectin was not mutagenic *in vitro* in bacterial and photo-bacterial reverse mutation assays, in the mouse lymphoma assay, and *in vivo* in the oral micronucleus test in rats.

Carcinogeniticy:

Chronic (1 year) repeated topical application of ROSIVER enhanced simulated solar ultraviolet radiation-induced non-melanoma skin carcinogenesis in albino Skh HR-1 hairless mouse (tumour potency factor in both sexes combined was 1.69; 1.74 in male mice and 1.51 in female

mice - compared with an expected no adverse effect tumour potency factor of 1.00). Increased incidence of skin irritation induced by both the vehicle cream and by ROSIVER cream in this study is very likely to be the cause for increased incidence of UV radiation-induced skin tumors in these groups, when compared to mice only exposed to UV radiation.

In a 2-year topical carcinogenicity study in mice (without simulated solar light exposure), ROSIVER was not tumorigenic when applied daily at doses corresponding to up to 10 mg/kg/day of ivermectin. At this dose, the plasma AUC in mice was 645.54 (m)/352 (f) times the human plasma AUC associated with the maximum recommended topical use of ROSIVER.

In a 2-year oral carcinogenicity study in rats, ivermectin was considered not tumorigenic when administered daily at doses up to 3 mg/kg/day. At this dose, the plasma exposure of animals represented at least 282 times the human plasma AUC associated with the maximum recommended topical use of ROSIVER. An increase in the incidence of benign hepatocellular adenomas and related hepatic pre-neoplastic changes was reported in males only (at a 9mg/kg/day ivermectin oral dose [832 times the human plasma AUC associated with the maximum recommended topical use of ROSIVER]). There was also a higher incidence of pancreatic benign islet cell adenomas in males, and islet cell carcinoma with no evidence of distant metastasis in females. These neoplastic changes in rodents are not currently considered to be relevant to humans.

Reproductive and Developmental Toxicology:

Ivermectin was found to have no effect on the fertility of male and female rats at oral doses up to 9 mg/kg/day (animal:human AUC ratio ≈ 484).

Teratology studies in the rabbit demonstrated maternal toxicity and carpal flexures in the fetus at an oral ivermectin dose of 4.5mg/kg/day. The NOAEL was established at 3.5 mg/kg/day, a dose corresponding to plasma levels 68 times higher than those obtained at the maximum recommended human dose by topical route (1g application of ROSIVER once daily).

In the rat, cleft palates were observed at the oral ivermectin dose of 12 mg/kg/day. The dose of 4 mg/kg/day was the NOAEL for maternal toxicity and embryofetal development, a dose corresponding to plasma levels 334 times higher than those obtained at the maximum recommended human dose by topical route (1g application of ROSIVER once daily).

The neonatal toxicity in oral rat studies was not related to in-utero exposure, but to postnatal exposure through maternal milk which resulted in high levels of ivermectin in the brain and in plasma of offspring.

Special Toxicology Studies:

Local tolerance studies in rabbits showed that ivermectin 1% cream is irritant on the skin and non-irritant in the eye. Guinea pig studies showed that ivermectin 1% cream is a potential sensitizer and photosensitizer (as is the vehicle cream). Ivermectin 1% cream is not phototoxic following a single topical application followed by ultraviolet radiation.

REFERENCES

1. Stein Gold L, Kircik L, Fowler J, Tan J, Draelos Z, Fleischer A, Appell M, Steinhoff M, Lynde C, Liu H, Jacovella J. Efficacy and Safety of Ivermectin 1% Cream in Treatment of Papulopustular Rosacea: Results of Two Randomized, Double-Blind, Vehicle-Controlled Pivotal Studies *J Drugs Dermatol.* 2014; 13(3): 316-323.

2. Stein Gold L, Kircik L, Fowler J, Mark Jackson J, Tan J, Draelos Z, Fleischer A, Appell M, Steinhoff M, Lynde C, Sugarman J, Liu H, and Jacovella J Long-Term Safety of Ivermectin 1% Cream vs Azelaic Acid 15% Gel in Treating Inflammatory Lesions of Rosacea: Results of Two 40-Week Controlled, Investigator-Blinded Trials. *J Drugs Dermatol.* 2014; 13(11): 1380-1386.

PART III: CONSUMER INFORMATION

PrROSIVER™
Ivermectin Cream, 1% w/w

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

ABOUT THIS MEDICATION

What the medication is used for:
ROSIVER is used for the topical treatment of bumps and pimples found with rosacea.

Rosacea is a chronic, inflammatory skin condition that occurs in adults. It can produce small, red, pus-filled bumps or pimples on your nose, cheeks, forehead and chin (but not the same as whiteheads or blackheads found with acne). Rosacea symptoms can vary from person to person and severity is hard to predict.

What it does:
ROSIVER reduces the bumps and pimples of rosacea but the exact way it works in rosacea is unknown.

When it should not be used:
If you are allergic to ivermectin or any of the ingredients in ROSIVER (see **What the nonmedicinal ingredients are:)** or the components of the container.

What the medicinal ingredient is:
ROSIVER contains the medicinal ingredient ivermectin that belongs to a group of medicines called avermectins.

What the nonmedicinal ingredients are:
Carbomer copolymer type B, cetyl alcohol, citric acid monohydrate, dimeticone 20 Cst, disodium edetate, glycerol, isopropyl palmitate, macrogol cetostearyl ether, methyl parahydroxybenzoate, oleyl alcohol, phenoxyethanol, propyl parahydroxybenzoate, propylene glycol, purified water, sodium hydroxide, sorbitan stearate, stearyl alcohol.

What dosage forms it comes in:
ROSIVER is a white to pale yellow topical cream supplied in 15g, 30g, 45g and 60g tubes. Physician samples are supplied in 2 g tubes.

WARNINGS AND PRECAUTIONS

ROSIVER is not recommended in children under the age of 18 years.

Not for oral, ophthalmic, or intravaginal use.

The use of ROSIVER is not recommended during pregnancy, because its effect on your unborn baby is unknown. If you are breast-feeding, you should not use this medicine or stop breastfeeding before you use it.

If irritation occurs during treatment discuss with your doctor. Your doctor may tell you to take the medicine less frequently, discontinue Rosiver temporarily or stop treatment with ROSIVER.

Do not cover the treated areas with dressings.

Avoid alcoholic cleansers, astringents, abrasives, peeling agents and any other irritants which can further irritate the skin of those with rosacea.

Avoid excessive exposure to sunlight, which could aggravate rosacea.

BEFORE you use ROSIVER talk to your doctor or pharmacist if:

- you are pregnant or planning to become pregnant
- you are breastfeeding or planning to breastfeed
- you have any allergies to this drug or its ingredients or components of the container.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

No drug interactions studies were done for ROSIVER.

PROPER USE OF THIS MEDICATION

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

ROSIVER is only intended for adults and only for use on the skin of the face. Do not use this medicine on other parts of your body, especially moist surfaces such as your eyes or mouth. Do not swallow.

Usual adult dose:

Before application, wash your hands, and wash the affected area with a mild cleanser and dry.

Apply a pea-size amount to each of the five areas of the face (i.e., forehead, chin, nose and each cheek) at bedtime. ROSIVER should be applied smoothly and evenly across the entire face. Do not spot treat. Wash hands after treatment.

Avoid contact with the eyes and lips. Should this occur, wash these areas immediately with water. If your eyes continue to hurt,

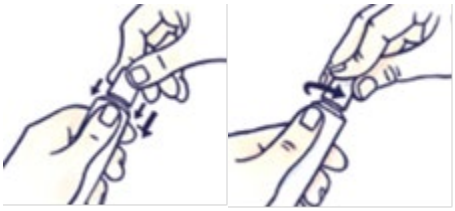
see your doctor,

Do not apply cosmetics immediately before the daily application of ROSIVER. You should use these products only after the applied ROSIVER has dried.

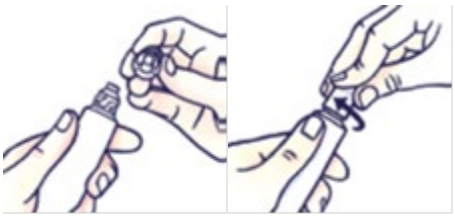
You may notice a distinct improvement after 4 weeks of treatment. In the case of no improvement after 3 months, you should discontinue ROSIVER and consult your doctor.

How to open the tube with a child-resistant cap:
To avoid spilling, do not squeeze the tube while opening or closing.

Push down on the cap and turn counterclockwise (turn to the left). Then pull the cap off.



How to close the tube with a child-resistant cap:
Push down and turn clockwise (turn to the right).



Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to apply Rosiver at bedtime, simply resume your daily application at the next bedtime. Do not take a double dose of ROSIVER to make up for a forgotten dose .

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects are:
- Burning feeling of the skin

Uncommon side effects are:
- Irritation of the skin
- Itching of the skin
- dry skin

In case of an allergic reaction or severe skin irritation, stop use and contact your doctor immediately.

This is not a complete list of side effects. For any unexpected effects while taking ROSIVER contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°C to 30°C).
Keep out of reach and sight of children and pets.

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:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **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 0701D
    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.galderma.ca
or by contacting the sponsor, Galderma Canada Inc., at:
1-800-467-2081

This leaflet was prepared by Galderma Canada Inc., Thornhill, ON L3T 7V9

Last revised: February 15, 2017