

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pratio-TOPISALIC
Betamethasone Dipropionate (0.5 mg / g as base)
and Salicylic Acid (20 mg / g)

Lotion

Topical Corticosteroid and Keratolytic

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ratio-TOPISALIC Lotion (Betamethasone Dipropionate and Salicylic Acid) are indicated for:

- anti-inflammatory, antipruritic and keratolytic activity in the topical management of subacute and chronic hyperkeratotic and dry dermatoses responsive to corticosteroid therapy.

1.1 Pediatrics

Pediatrics: Based on the available data, the safety and efficacy of Betamethasone Dipropionate and Salicylic Acid in pediatric patients have not been established.

1.2 Geriatrics

Geriatrics: There is no known evidence to suggest that use in the geriatric population is associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

ratio-TOPISALIC Lotion is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- viral diseases including vaccinia, varicella, herpes simplex.
- fungal infections.
- tuberculosis of the skin.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- ratio-TOPISALIC Lotion should not be used under occlusive dressing.

3.2 Recommended Dose and Dosage Adjustment

ratio-TOPISALIC Lotion: A thin film of ratio-TOPISALIC Lotion should be applied to cover completely the affected areas of the scalp. The usual frequency of application is twice daily.

For some patients, adequate maintenance may be achieved with less frequent application.

If symptomatic response is not noted within a few days to a week, the local application of corticosteroids should be discontinued, and the patient re-evaluated.

4 MISSED DOSE

If a dose is missed, the patient can resume treatment with the next scheduled application.

5 OVERDOSAGE

Symptoms: Excessive or prolonged use of topical corticosteroids can suppress pituitary-adrenal function, resulting in secondary adrenal insufficiency, and produce manifestations of hypercorticism, including Cushing's disease.

Excessive or prolonged use of topical preparations containing salicylic acid may cause symptoms of salicylism. Overdosage of salicylates may cause temporary hearing or visual disturbances, drowsiness and nausea. If this occurs, discontinue use until symptoms disappear.

Treatment: Appropriate symptomatic treatment is indicated. Acute hypercorticoid symptoms are usually reversible. Treat electrolyte imbalance, if necessary. In case of chronic toxicity, slow withdrawal of corticosteroids is advised.

Treatment of salicylism is symptomatic. Measures should be taken to rid the body rapidly of salicylate. Administer oral sodium bicarbonate to alkalinize the urine and force diuresis.

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	Lotion / Betamethasone Dipropionate 0.05% and Salicylic acid 2%.	hydroxyethyl cellulose, isopropanol, purified water and triethanolamine

- ratio-TOPISALIC Lotion: Each g of ratio-TOPISALIC Lotion contains 0.64 mg of betamethasone dipropionate, equivalent to 0.5 mg of betamethasone, and 20 mg of salicylic acid. Plastic squeeze bottles of 30 mL and 60 mL.

7 WARNINGS AND PRECAUTIONS

General

Systemic absorption of topical corticosteroids or salicylic acid will be increased if extensive body surface areas are treated. Suitable precautions should be taken under these conditions or when long-term use is anticipated, particularly in infants and children.

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

Occlusive dressings should not be used, as this may result in an increase in the systemic absorption of topical corticosteroids or salicylic acid.

Driving and Operating Machinery

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Application over extensive lesions may result in significant systemic absorption producing hypercorticism manifesting itself by adrenal suppression, moon facies, striae and suppression of growth.

Genitourinary

Avoid contact with mucous membranes. Keep ratio-TOPISALIC Lotion away from the genital area and other orifices.

Immune

If an overt infection is present, appropriate antimicrobial treatment is indicated.

Ophthalmologic

These drugs should not be used in or near the eyes since ratio-TOPISALIC Lotion is not formulated for ophthalmic use.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Skin

Avoid contact with mucous membranes.

Suitable precautions should be taken in using topical corticosteroids in patients with stasis dermatitis and other skin diseases with impaired circulation.

Prolonged use of corticosteroid preparations may produce striae or atrophy of the skin or subcutaneous tissue. If this occurs, treatment should be discontinued.

If irritation, sensitization, excessive dryness, or unwanted scaling develops with the use of ratio-TOPISALIC, treatment should be discontinued.

7.1 Special Populations

7.1.1 Pregnant Women

Since safety of topical corticosteroid use in pregnant women has not been established, drugs of this class should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively in large amounts or for prolonged periods of time in pregnant patients.

7.1.2 Breast-feeding

Since it is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in breast milk, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Based on the available data, the safety and efficacy of Betamethasone Dipropionate and Salicylic Acid in pediatric patients have not been established.

Any of the side effects that have been reported following systemic use of corticosteroids, including adrenal suppression, may also occur with topical corticosteroids, especially in infants and children.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and to exogenous corticosteroid effects than mature patients because of a greater absorption due to a larger skin surface area to body weight ratio. Use of topical corticosteroids in children should be limited to the least amount compatible with an effective

therapeutic regimen. Chronic corticosteroid therapy may interfere with growth and development of children.

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following local adverse skin reactions have been reported with the use of topical steroids; burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis.

The following may occur more frequently with the use of occlusive dressings: maceration of the skin, secondary infection, skin atrophy, striae, miliaria. In addition, the salicylic acid component may cause local reddening of the skin, desquamation, pruritus and smarting. Continuous application of salicylic acid preparations to the skin may cause dermatitis. Hypersensitivity to salicylic acid may occur.

Systemic adverse reactions, such as vision blurred, have also been reported with the use of topical corticosteroids.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Betamethasone dipropionate with salicylic acid combines the anti-inflammatory, antipruritic and vasoconstrictive activity of betamethasone dipropionate with the keratolytic effects of salicylic acid.

9.2 Clinical Pharmacology

Betamethasone dipropionate was compared with other fluorinated topical corticosteroids in the McKenzie/Stoughton vasoconstrictor test. In this test, betamethasone dipropionate was significantly more active ($p < 0.05$) than fluocinolone acetonide, fluocortolone caproate plus fluocortolone, flumethasone pivalate and betamethasone valerate¹. While the direct applicability

¹ As evaluated via a probit relative potency assay, outlined in D.J. Finney's Probit Analysis, Hafner Publishing 1971.

of this vasoconstrictor test to clinical situations has not been conclusively demonstrated, the results showed betamethasone dipropionate to be active in a concentration of 0.000016%, the lowest concentration tested which showed activity.

The keratolytic property of salicylic acid has been recognized for a long time.

The percutaneous absorption of betamethasone-17, 21-dipropionate and salicylic acid was studied after one and two weeks of treatment of psoriasis and eczema. The treated areas varied between 8 and 41 dm². No change in the plasma cortisol levels was detectable by the routinely used laboratory method. The treatment gave no detectable salicylate concentrations in plasma.

9.3 Bioequivalence

A one-period, randomized, vasoconstrictor study was performed in asymptomatic, healthy, non-tobacco using, female subjects. The bioequivalence of **ratio-TOPISALIC lotion** (betamethasone dipropionate with salicylic acid) to **Diprosalic[®] lotion** was determined following application of a single dose (5 µL) of each product to the flexor surface of each subject's forearms. The degree of vasoconstriction was determined by the use of a ChromaMeter, and area under the response curve was determined for each site using the ChromaMeter data. Mean results are presented in the following table:

	N	Means		Ratio%	90% Confidence Interval	
		Test	Reference		Lower (%)	Upper (%)
ChromaMeter	45	16.4	15.2	107.7	94.6	122.6

Conclusion: The 90% confidence interval for the ChromaMeter data was within the 80-125% TPD acceptance range. Based on the results, **ratio-TOPISALIC** and Diprosalic[®] lotion are considered bioequivalent.

10 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

Drug Substance

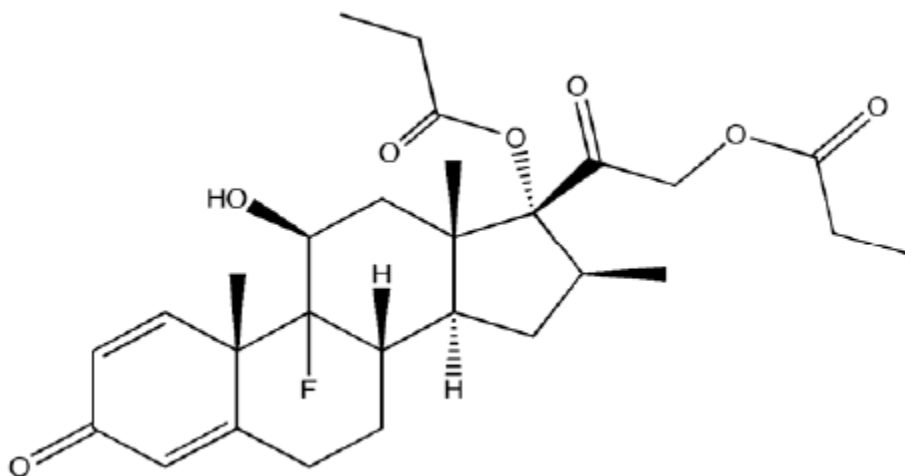
Proper name: **Betamethasone-17, 21-dipropionate**

Chemical name: 9 α -Fluoro-16 β -methyl-11 β , 17 α 21-trihydroxy-1, 4-pregnadiene-3,20-dione 17,21dipropionate.

Molecular formula and: C₂₈H₃₇FO₇

Molecular mass: 504.61 g/mol

Structural formula:



Physicochemical properties: Betamethasone dipropionate is a white to cream coloured powder, free from foreign matter with melting point between 170° and 179° with decomposition.

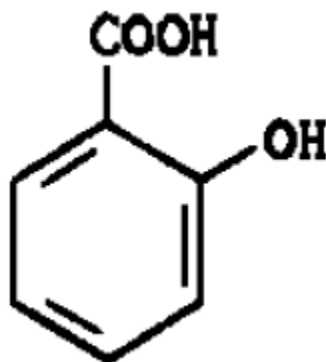
Proper name: **Salicylic Acid**

Chemical name: 2-hydroxy benzoic acid.

Molecular formula: $C_7H_6O_3$

Molecular weight: 138.12 g/mol

Structural formula:



Description: Salicylic acid is a fluffy white crystalline powder, free from foreign matter with melting range between 158° and 161°C.

12 NON-CLINICAL TOXICOLOGY

Acute Toxicity

When applied to the intact skin of rats and rabbits, doses of Betamethasone Dipropionate and Salicylic Acid ointment up to 3.3 g/kg caused no deaths or other observable disturbances. Betamethasone Dipropionate and Salicylic Acid ointment was also administered by gastric tube to fasted rats in doses of 5-20 g/kg. This dosage caused no deaths or symptoms of toxicity either in the immediate post-treatment period or in the 14-day observation period.

Chronic Toxicity

In rats, daily epicutaneous administration of Betamethasone Dipropionate and Salicylic Acid ointment, dosed at 333 mg/kg/day for 60 consecutive days, did not result in mortality, changes in the general physical condition or in the weight of vital organs. Some evidence of steroid absorption, namely a retardation of growth, was seen.

Subacute Dermal Toxicity

Betamethasone Dipropionate and Salicylic Acid Ointment:

18 New Zealand White rabbits, weighing between 2.2 and 3.0 kg were treated with Betamethasone Dipropionate and Salicylic Acid ointment or vehicle for 3 consecutive weeks. The ointment or the vehicle was applied once daily to the intact or abraded skin of three males and three females in the following groups:

1. Vehicle control (1.0 g/kg body weight).
2. Low dose (0.5 g/kg body weight)
3. High dose (1.0 g/kg body weight)

No drug-related skin reactions were seen in any of the rabbits. Systemically, the usual pharmacological effects following corticosteroid absorption were evidenced. Two of the low dose rabbits (abraded skin) died of respiratory infection.

Betamethasone Dipropionate and Salicylic Acid Lotion:

Betamethasone Dipropionate and Salicylic Acid lotion, salicylic lotion or the lotion vehicle was applied twice daily for 21 consecutive days to the intact or the abraded skin of 48 New Zealand White rabbits (2.5 - 3.9 kg), with 3 males and 3 females per group. The treatment groups were as follows:

1. Vehicle control (1.0 g/kg/day)
2. Low dose (0.5 g/kg/day)
3. High dose (1.0 g/kg/day)
4. Positive control (salicylic acid - 1.0 g/kg/day).

The rabbits were observed daily and the skin reactions were numerically graded (Draize score) before the first application on the last treatment day of each week. Body weights were recorded

weekly. On day 22, the rabbits were autopsied and skin specimens were taken for histological examination.

In both the intact and abraded experiments, losses in body weight, skeletal muscle atrophy and abdominal distension were seen in many of the rabbits treated with the low and high dose of Betamethasone Dipropionate and Salicylic Acid lotion but not in the control or positive control groups.

Nine of the rabbits died in the Betamethasone Dipropionate and Salicylic Acid lotion groups (intact and abraded skin). Prior to death, the rabbits had one or more of the following symptoms; decreased food consumption, body weight loss, mucous in stools and abdomen distension.

Necropsy Findings

All rabbits had white foci on the liver and/or renal cortices, or pitted renal cortices. Three had pericarditis; two had impaction of the cecum. In addition, there was one case of the following accompanying diseases; pulmonary congestion; abscesses and infarcts of the kidney; hemorrhage and ulcerations of the stomach, mucous in the cecum, distension of urinary bladder, uterus and swelling near the urethra; hemorrhage in the medulla, enlarged kidney, flatulence in the small intestine, and blood in between the capsule and cortex; clear fluid in the peritoneal cavity.

The compound was well tolerated locally. At autopsy, the treated skin appeared normal. The livers of all Betamethasone Dipropionate and Salicylic Acid lotion treated rabbits were either friable or pale. Both Betamethasone Dipropionate and Salicylic Acid lotion and salicylic acid inhibited healing of skin lesions in the abraded skin groups. The changes seen in the blood picture were representative of a typical systemic response to corticosteroids: decreases in hematocrit and hemoglobin values, and lymphocytes count; slight increases in neutrophils and SGPT.

In summary, under the conditions of study, Betamethasone Dipropionate and Salicylic Acid lotion was well tolerated locally in rabbits. Common pharmacological effects of corticosteroids were detected, but there were no unexpected signs of toxicity.

Reproduction and Teratology

Betamethasone Dipropionate

Rabbits

Forty-nine virgin female New Zealand White rabbits were bred and divided into four groups as follows:

	Dose (mg/kg)
Control	-
Depo-Medrol (positive control)	0.050
Betamethasone dipropionate (low dose)	0.015
Betamethasone dipropionate (high dose)	0.050

After mating, and every other day from Day 6 through Day 18, the dams were given the preparation mentioned above intra-muscularly. On day 30 after mating, all does were sacrificed and their offspring removed.

Clinical observations

The appearance and behaviour of all dams were normal during the study. In addition, the body weight of all dams increased at normal rates during the study.

Pregnancy data

In both groups treated with betamethasone dipropionate, the incidence of resorptions increased with the dosage level. Because those dams that had resorptions usually lost an entire litter, the average litter sizes were not appreciably different among the various groups. The incidence of late fetal deaths was similar in all groups.

Offspring data

The average body weights of offspring were similar to controls in both the positive control and the low dose groups. Body weights of offspring from the high dose group were probably below normal (statistical analyses were not done). The 24 hours survival rates of offspring from both groups treated with betamethasone dipropionate were reduced.

Abnormalities

In the low dose group, six offsprings from one litter had umbilical hernias with protrusion of the intestine. In the high dose group, three pups from one litter had umbilical hernias; one of these also had a cephalocele and another had an abnormally flexed front paw. Three pups from a different litter all had cephalocele and cleft palate; two of these also had umbilical hernia. There were no abnormalities in the control and positive control groups. Betamethasone dipropionate caused the teratogenic effects typical of many other corticosteroids.

Mice:

Fifteen mice were given intramuscular doses of betamethasone dipropionate daily from day 6 through day 15 after mating, at the following dosage levels:

- 0.325 mg/kg/day
- 1.63 mg/kg/day
- 3.25 mg/kg/day
- 32.5 mg/kg/day

One mouse from each group was found not to be pregnant. At 0.325 mg/kg/day, the remaining mice (3) had normal litters with 37 total offspring. At 1.63 mg/kg/day, 1 mouse had a normal litter, 1 mouse delivered 1 live offspring with stunted growth with the remaining conceptuses resorbed; the third mouse had all conceptuses resorbed.

At 3.25 and 32.5 mg/kg, all mice (5) had conceptuses resorbed.

Rats:

Ten rats that had mated were given betamethasone dipropionate intramuscularly in daily doses of either 1 mg/kg or 3 mg/kg from day 6 through day 15 after mating. There were no indications of adverse effects of either the dams or their offspring. 112 pups were produced; all were normal.

13 REFERENCES:

Product Monograph, ^{Pr}DIPROSALIC[®] lotion and ointment, Merck Canada Inc., Control No. 229611; Date of revision: November 4, 2019.

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

Pratio-TOPISALIC Lotion
Betamethasone Dipropionate and Salicylic Acid

Read this carefully before you start taking **ratio-TOPISALIC** 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 **ratio-TOPISALIC**.

What is ratio-TOPISALIC used for?

- **ratio-TOPISALIC** is used to treat persistent skin problems where the top of the skin is covered by a layer of scales. **ratio-TOPISALIC** will remove the layer of scales and reduce the swelling, redness and itchiness caused by your skin problem.

How does ratio-TOPISALIC work?

ratio-TOPISALIC is a combination of 2 drugs, betamethasone dipropionate and salicylic acid.

- salicylic acid will work on the surface of your skin by softening the top layer of the scales. This allows the second drug to reach underneath the infected skin to help heal it.
- betamethasone dipropionate will reduce the swelling, redness and itchiness off your skin.

What are the ingredients in ratio-TOPISALIC?

Medicinal ingredients: betamethasone dipropionate, salicylic acid.

Non-medicinal ingredients:

hydroxyethyl cellulose, isopropanol, purified water and triethanolamine.

ratio-TOPISALIC comes in the following dosage forms:

Lotion: 30 mL and 60 mL Plastic squeeze bottles

Do not use ratio-TOPISALIC if you:

- are allergic to betamethasone dipropionate, salicylic acid, or any of the other ingredients of ratio-TOPISALIC.
- have any infections like small pox (vaccinia), chicken pox (varicella), cold sores or genital herpes (herpes simplex virus), fungal infections or a skin infection (tuberculosis of the skin).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you apply ratio-TOPISALIC. Talk about any health conditions or problems you may have, including if you:

- are pregnant or planning on becoming pregnant. It is not known if ratio-TOPISALIC can harm your unborn baby. Your healthcare professional will decide whether giving you

ratio-TOPISALIC outweighs the potential risk to the unborn baby.

- are breastfeeding or planning to breastfeed. It is not known whether ratio-TOPISALIC can pass into your breastmilk. Your healthcare professional will decide whether to stop breastfeeding or stop the use of ratio-TOPISALIC.
- have any infections.
- If you have diseases of your skin that are caused by poor blood flow. An example is stasis dermatitis.

Other warnings you should know about:

- Avoid getting ratio-TOPISALIC in your genital area.
- Avoid getting the ratio-TOPISALIC inside your eyes, mouth, ears and nose.
- In children, limit the use of ratio-TOPISALIC to the minimum required amount needed. Long-term use of this medicine may affect your child's hormones. This may affect your child's growth and development.

Eyes:

- Avoid using ratio-TOPISALIC in or near your eyes.
- Talk to your healthcare professional if you develop:
 - Blurred vision
 - Other eyesight problems

Skin:

- Do not put any bandages or plasters over the medicine.
- Do not use excessive amounts of ratio-TOPISALIC on the large areas of the body.
- Talk to your healthcare professional if you develop:
 - Irritation
 - Sensitive skin
 - Extremely dry skin
 - Unwanted scaling of your skin
 - Flaking of your skin
 - Stretch marks (striae)

These symptoms may happen when you are using a corticosteroid for a long time. Your may need to stop your treatment.

Use of ratio-TOPISALIC on large infected areas of the skin may:

- Reduce the creation of hormones
- Cause swelling of face (moon facies)
- Reduce growth.

Driving and using machines: Give yourself time after taking ratio-TOPISALIC to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to apply ratio-TOPISALIC:

Lotion: A thin film should be applied twice a day to the affected areas of your scalp. Apply the lotion to cover the entire affected area.

If you do not notice an improvement within a few days to a week, stop the use of ratio-TOPISALIC and you should consult your healthcare professional.

Overdose:

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

Missed dose

If you miss an application of this medication, resume treatment with the next scheduled dose. Do not apply more than once at the same time.

What are possible side effects from using ratio-TOPISALIC?

These are not all the possible side effects you may feel when taking ratio-TOPISALIC. If you experience any side effects not listed here, contact your healthcare professional.

Local skin problems have been reported when applying topical steroids. The following have been reported:

- Burning
- Itching
- Irritation
- Dryness
- Swelling of the hair follicles

- Excessive hair growth
- Acne outbreaks that result in redness and blushing
- Patches of lighter skin tone
- Skin rash around the mouth
- Red, itchy rash caused by
 - direct contact with a substance or
 - an allergy reaction to the substance

Plasters and Bandages should not be used over ratio-TOPISALIC. The following may occur more often if plasters or bandages are used:

- Softening and breaking down of skin
- A new infection after treatment (secondary infection)
- Thinning of the skin (skin atrophy)
- Stretch marks
- Heat Rash

Salicylic acid, an ingredient found in ratio-TOPISALIC, may cause the following:

- local reddening of the skin
- skin peeling
- itching
- feeling a sharp stinging pain

The continual use of products containing salicylic acid to the skin may cause eczema. An allergy to salicylic acid may occur.

Blurry vision has also been reported with the use of topical corticosteroids.

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/medeffectcanada.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:

Store between 15°C and 30°C.

Keep out of reach and sight of children.

If you want more information about ratio-TOPISALIC:

- 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 Teva Canada Limited website www.tevacanada.com, or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

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