PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

DIPROSALIC®

Betamethasone Dipropionate and Salicylic Acid Lotion
Betamethasone Dipropionate and Salicylic Acid Ointment

Betamethasone 0.5 mg/g (as Betamethasone Dipropionate) and Salicylic Acid 20 mg/g
Betamethasone 0.5 mg/g (as Betamethasone Dipropionate) and Salicylic Acid 30 mg/g

60 mL topical lotion
50 g topical ointment

Topical Corticosteroid and Keratolytic

Organon Canada Inc.
16766 route Transcanadienne
Kirkland, Quebec
H9H 4M7

www.organon.ca

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DIPROSALIC® Lotion and Ointment (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 Diprosalic 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

DIPROSALIC® 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

- DIPROSALIC® Lotion and/or Ointment should not be used under occlusive dressing.

3.2 Recommended Dose and Dosage Adjustment

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

DIPROSALIC® Ointment: A thin film of DIPROSALIC® Ointment should be applied to cover completely the affected area. The ointment should be massaged gently and thoroughly into the

skin. The usual frequency of application is twice daily, in the morning and at night.

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%.	edetate disodium, hydroxypropylmethylcellulose, isopropyl alcohol, water and sodium hydroxide to adjust pH to approximately 5.0.
Topical	Ointment / Betamethasone Dipropionate 0.05% and Salicylic Acid 3%	white petrolatum and mineral oil

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

- DIPROSALIC® Ointment: Each g of DIPROSALIC® Ointment contains 0.64 mg of betamethasone dipropionate, equivalent to 0.5 mg of betamethasone, and 30 mg of salicylic acid, in a paraben-free ointment base of white petrolatum and mineral oil. Tubes of 50 g.

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 DIPROSALIC® Lotion and Ointment 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 DIPROSALIC® 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 DIPROSALIC®, 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 Diprosalic 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 valerate[1]. While the direct applicability 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.

10 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C. Protect from light.

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

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

Drug Substance

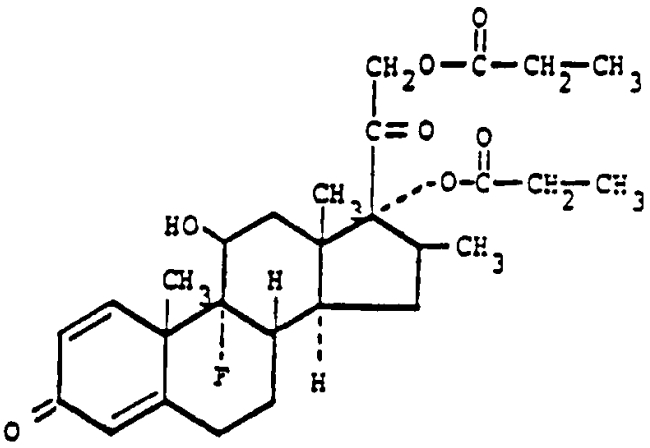
Proper name: Betamethasone-17, 21-dipropionate

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

Molecular formula and: $C_{28}H_{37}FO_7$

molecular mass: 504.61

Structural formula:



Physicochemical properties: Betamethasone dipropionate is a white to cream coloured powder, free from foreign matter with melting point ±3°, between 170° and 179° with decomposition.

Proper name: Salicylic Acid

Chemical name: 2-hydroxy benzoic acid.

12 NON-CLINICAL TOXICOLOGY

Acute Toxicity

When applied to the intact skin of rats and rabbits, doses of DIPROSALIC® Ointment up to 3.3 g/kg caused no deaths or other observable disturbances. DIPROSALIC® 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 DIPROSALIC® 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
DIPROSALIC® Ointment:
18 New Zealand White rabbits, weighing between 2.2 and 3.0 kg were treated with DIPROSALIC® 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.

DIPROSALIC® Lotion:
DIPROSALIC® 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 DIPROSALIC® Lotion but not in the control or positive control groups.

Nine of the rabbits died in the DIPROSALIC® 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 DIPROSALIC® Lotion treated rabbits were either friable or pale. Both

DIPROSALIC® 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, DIPROSALIC® 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 appreciable 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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

DIPROSALIC®
Betamethasone Dipropionate and Salicylic Acid Lotion
Betamethasone Dipropionate and Salicylic Acid Ointment

Read this carefully before you start taking **DIPROSALIC®** 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 **DIPROSALIC®**.

What is DIPROSALIC® used for?

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

How does DIPROSALIC® work?

DIPROSALIC is a combination of 2 drugs, betamesthasone dipropionate and salicyclic acid.

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

What are the ingredients in DIPROSALIC®?

Medicinal ingredients: betamethasone dipropionate, salicylic acid.
Non-medicinal ingredients:

Lotion: edetate disodium, hydroxypropylmethylcellulose, isopropyl alcohol, water and sodium hydroxide.

Ointment: mineral oil and white petrolatum.

DIPROSALIC® comes in the following dosage forms:

Lotion: 60 mL Plastic squeeze bottles
Ointment: 50 g Tubes

Do not use DIPROSALIC® if you:

- are allergic to betamethasone dipropionate, salicylic acid, or any of the other ingredients of DIPROSALIC®.
- 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 take DIPROSALIC®. 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 DIPROSALIC® can harm your unborn baby. Your healthcare professional will decide whether giving you DIPROSALIC® outweighs the potential risk to the unborn baby.
- are breastfeeding or planning to breastfeed. It is not known whether DIPROSALIC® can pass into your breastmilk. Your healthcare professional will decide whether to stop breastfeeding or stop the use of DIPROSALIC®.
- have any infections.
- 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 DIPROSALIC® in your genital area.
- Avoid getting the ointment inside your eyes, mouth, ears and nose.
- In children, limit the use of DIPROSALIC® 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 DIPROSALIC® 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 DIPROSALIC® on 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. You may need to stop your treatment.

Use of DIPROSALIC® 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 DIPROSALIC® 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 take DIPROSALIC®:
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.

Ointment: A thin film should be applied twice a day, in the morning and night, to the affected area. The ointment should be massaged gently and thoroughly into the skin. The ointment should cover the entire affected area.

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

Overdose:

If you think you have taken too much DIPROSALIC®, 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 DIPROSALIC®?

These are not all the possible side effects you may feel when taking DIPROSALIC®. 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 DIPROSALIC®. 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 DIPROSALIC®, 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/medeffect-canada.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. Protect from light.

Keep out of reach and sight of children.

If you want more information about DIPROSALIC®:
- 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 Organon Canada website www.organon.ca, or by calling Organon Canada at 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

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