PRODUCT MONOGRAPH

ratio-TOPISALIC

Betamethasone dipropionate (0.50 mg/g as base)

and salicylic acid (20 mg/g)

Lotion

Topical corticosteroid and keratolytic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario M1B 2K9

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ACTION AND CLINICAL PHARMACOLOGY

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

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.

INDICATIONS AND CLINICAL USE

ratio-TOPISALIC lotion (betamethasone dipropionate with salicylic acid) provides anti-inflammatory, anti-pruritic and keratolytic activity in the topical management in conditions of the scalp that involve subacute and chronic hyperkeratotic and dry dermatoses responsive to corticosteroid therapy.

CONTRAINDICATIONS

ratio-TOPISALIC lotion (betamethasone dipropionate with salicylic acid) is contraindicated in bacterial/fungal skin infections, tuberculosis of the skin, syphilitic infections, chicken pox, eruptions following vaccinations and viral diseases of the skin in general. Hypersensitivity to any one component of Alti-Topisalic lotion is a contraindication to its use.

WARNINGS

These drugs should not be used in or near the eyes since **ratio-TOPISALIC** lotion (betamethasone dipropionate with salicylic acid) is not formulated for ophthalmic use **and systemic absorption may cause increased intra ocular pressure, glaucoma or**

cataracts. As well, keep **ratio-TOPISALIC** lotion away from the genital area and other orifices.

Pediatrics:

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.

Systemic absorption of topical corticosteroids will be increased if extensive body surface areas are treated or if the occlusive technique is used. Suitable precautions should be taken under these conditions or when long-term use is anticipated, particularly in infants and children. Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of 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, and intracranial hypertension have been reported in children receiving corticosteroids. Manifestations of adrenal suppression in children include: linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Pregnancy and lactation:

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.

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.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low doses. Systemically administered corticosteroids are secreted into human milk and could suppress growth, interfere with endogenous corticosteroid production or cause untoward effects.

PRECAUTIONS

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycaemia and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids.

Conditions which augment systemic absorption include application of the more potent steroids, use over a large surface area, prolonged use, occlusive dressings. Patients applying a large dose to a large surface area should be evaluated periodically for evidence of HPA axis suppression.

This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA suppression.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur that require supplemental systemic corticosteroids.

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.

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

If irritation, sensitization, excessive dryness, or unwanted scaling develop with the use of **ratio-TOPISALIC** lotion (betamethasone dipropionate with salicylic acid), treatment should be discontinued.

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

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

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.

Occlusive dressings should not be used.

ADVERSE REACTIONS

The following local adverse skin reactions have been reported rarely with the use of topical steroids: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation. The following may occur more frequently with occlusive dressing: maceration of the skin, secondary infection, skin atrophy, striae, miliaria, perioral dermatitis and allergic contact dermatitis. In addition, the salicylic acid component may cause local reddening of the skin, desquamation, pruritus and smarting. Hypersensitivity to salicylic acid may occur.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Topically applied Alti-Topisalic can be absorbed in sufficient amounts to produce systemic effects. Acute overdosage is very unlikely to occur. However, in the case of chronic overdosage or misuse, the features of hypercorticism may appear. Treatment should be discontinued in this case.

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. 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.

DOSAGE AND ADMINISTRATION

A thin film of **ratio-TOPISALIC** lotion (betamethasone dipropionate with salicylic acid) 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 a symptomatic response is not noted within a few days to a week, the local applications of corticosteroid should be discontinued and the patient re-evaluated. Therapy should be discontinued as soon as lesions heal.

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

PHARMACEUTICAL INFORMATION

Drugs substance: **Betamethasone-17, 21-dipropionate**

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

Structural formula:

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

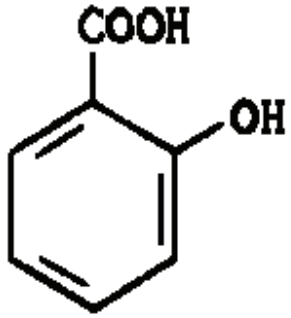
Molecular weight: 504.61

Description: Betamethasone dipropionate is a white to cream colored powder, free from foreign matter with melting point between 170 and 179^{o} with decomposition.

Drugs substance: **Salicylic acid, USP**

Chemical name: 2-hydroxy benzoic acid.

Structural formula:



Molecular formula: $C_7H_6O_3$

Molecular weight: 138.12

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

Composition:

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. **Nonmedicinal ingredients in alphabetical order:** hydroxyethyl cellulose, isopropanol, purified water and triethanolamine.

Stability and storage recommendations: Store between 15°C and 30°C.

AVAILABILITY OF DOSAGE FORMS

Available in plastic squeeze bottles of 30 mL and 60 mL.

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]. 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 dm^2. No change in the plasma cortisol levels was detectable by the routinely used laboratory method. The treatment gave no detectable salicylate concentrations in plasma.

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:

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

The 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:
Vehicle control (1.0 g/kg body weight)
Low dose (0.5 g/kg body weight)
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 or the lotion vehicle was applied twice daily for 21 consecutive days to the intact or the abraded skin of 28 New Zealand White rabbits (2.5 - 3.9 kg), with 3 males and 3 females per group. The treatment groups were as follows:
10 Vehicle control (1.0 g/kg/day)
20 Low dose (0.5 g/kg/day)
30 High dose (1.0 g/kg/day)
40 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 distention 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 distention.

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, distention 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 lymphocyte counts; 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)	0.05

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.

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