

Acne Treatments Reviewed, Starting With Touch

BY SHERRY BOSCHERT
San Francisco Bureau

STANFORD, CALIF. — The art and science of treating acne in adolescents start with touching the patient.

"Many adolescents have a feeling that their acne is very dirty, and they take it personally," Dr. Alfred T. Lane said at a pediatric update sponsored by Stanford (Calif.) University.

They think of themselves as bad people,

he suggested, but "I think that by touching them, we develop a relationship with them that says we're very accepting of their condition."

He first asks permission by saying, "May I touch your skin?" and makes sure that the patient saw him clean his hands with an antiseptic gel when he entered the exam room.

Making sure patients are motivated to adhere to a treatment regimen and helping them to set reasonable expectations for

results are important next steps, said Dr. Lane, professor of dermatology and pediatrics at the university.

As a pediatrician, before training in dermatology, he often would offer to treat adolescent acne detected during visits for other reasons, such as for a sports physical exam. The teenager usually would agree, then not return for the 6-week follow-up visit. If he saw the patient months later for some other reason, the acne typically would be unchanged and the teen would

say he or she didn't use the medication.

"Then, when I started my dermatology residency, I used the same medications and 6 weeks later everybody was better. It was because they were motivated" to adhere to topical or oral therapy, he said. "Now, if I see patients for another condition and I notice their acne, I don't even ask about it, unless they ask me."

Even motivated adolescents will have unreasonable expectations, however, and must be educated that improvements from acne therapy won't be seen for 4-8 weeks or sometimes more. "An adolescent wants instant results, just like with their text messaging," said Dr. Lane, who is also chair of dermatology at the university.

When choosing the therapy, match your choice to the type of problem, he added, as in the following examples:

► "Cocktail party" acne. When some-

RENOVA® (tretinoin cream) 0.02%

© 2005 OrthoNeutrogena 05DD0022 2/05 Printed in USA

FOR TOPICAL USE ON THE FACE. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Brief Summary

RENOVA (tretinoin cream) 0.02% contains the active ingredient tretinoin in a cream base.

IMPORTANT NOTE — This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

INDICATIONS AND USAGE:

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

RENOVA (tretinoin cream) 0.02% is indicated as an adjunctive agent (see second bullet point below) for use in the mitigation (palliation) of fine facial wrinkles in patients who use comprehensive skin care and sunlight avoidance programs. **RENOVA DOES NOT ELIMINATE WRINKLES, REPAIR SUN-DAMAGED SKIN, REVERSE PHOTOAGING, OR RESTORE MORE YOUTHFUL OR YOUNGER SKIN.** In double-blinded, vehicle-controlled clinical studies, many patients in the vehicle group achieved desired palliative effects on fine wrinkling of facial skin with the use of comprehensive skin care and sunlight avoidance programs including sunscreens, protective clothing, and non-prescription emollient creams.

• RENOVA 0.02% has NOT DEMONSTRATED A MITIGATING EFFECT on significant signs of chronic sunlight exposure such as coarse or deep wrinkling, tactile roughness, mottled hyperpigmentation, lentiginosities, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.

• RENOVA should be used under medical supervision as an adjunct to a comprehensive skin care and sunlight avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing.

• Patients with visible actinic keratoses and patients with a history of skin cancer were excluded from clinical trials of RENOVA 0.02%. Thus the effectiveness and safety of RENOVA 0.02% in these populations are not known at this time.

• Neither the safety nor the effectiveness of RENOVA for the prevention or treatment of actinic keratoses or skin neoplasms has been established.

• Neither the safety nor the efficacy of using RENOVA 0.02% daily for greater than 52 weeks has been established, and daily use beyond 52 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See WARNINGS section.)

CONTRAINDICATIONS:

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS:

• RENOVA 0.02% is a dermal irritant, and the results of continued irritation of the skin for greater than 52 weeks in chronic use with RENOVA are not known. There is evidence of atypical changes in melanocytes and keratinocytes and of increased dermal elastosis in some patients treated with RENOVA 0.05% for longer than 48 weeks. The significance of these findings and their relevance for RENOVA 0.02% are unknown.

• RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of RENOVA because of heightened sunburn susceptibility. Patients should be warned to use sunscreens (minimum SPF of 15) and protective clothing when using RENOVA. Patients with sunburn should be advised not to use RENOVA until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using RENOVA and follow the precautions outlined in the Patient Package Insert.

RENOVA should be kept out of the eyes, mouth, angles of the nose, and mucous membranes. Topical use may cause severe local erythema, pruritus, burning, stinging, and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether and consider additional appropriate therapy.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with caution in patients with this condition.

Application of larger amounts of medication than recommended has not been shown to lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.

PRECAUTIONS:

General: RENOVA should be used only as an adjunct to a comprehensive skin care and sunlight avoidance program. (See INDICATIONS AND USAGE section.)

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of RENOVA should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using tretinoin-containing products.

Information for Patients: See Patient Package Insert

Drug Interactions: Concomitant topical medications, medicated or abrasive soaps, shampoos, cleansers, cosmetics with a strong drying effect, products with high concentrations of alcohol, astringents, spices or lime, permanent wave solutions, electrolysis, hair depilatories or waxes, and products that may irritate the skin should be used with caution in patients being treated with RENOVA because they may increase irritation with RENOVA.

RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of this clinical formulation (0.02%). A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day. These doses are 10 and 20 times the maximum human systemic dose, when adjusted for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.5 times the maximum human systemic dose, adjusted for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose is defined as 1 gram of 0.02% RENOVA applied daily to a 50 kg person (0.004 mg tretinoin/kg body weight). Studies in hairless albino mice suggest that con-

current exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

In dermal Segment I fertility studies in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (20 times the maximum human systemic dose adjusted for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (10 times the maximum human systemic dose adjusted for total body surface area) and above were observed. A dermal Segment III study with RENOVA has not been performed in any species. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (83 times the human topical dose adjusted for total body surface area).

Pregnancy:

Teratogenic effects: Pregnancy Category C.

ORAL tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. It was teratogenic and fetotoxic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (42 times the maximum human systemic dose normalized for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which, metabolically, is closer to humans for tretinoin than the other species examined, fetal malformations were reported at doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (417 times the maximum human systemic dose adjusted for total body surface area), although increased skeletal variations were observed at all doses. A dose-related increase in embryolethality and abortion was reported. Similar results have also been reported in pigtail macaques.

TOPICAL tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (42 times the maximum human systemic dose adjusted for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was dermally applied.

There are other reports in New Zealand White rabbits administered doses of greater than 0.2 mg/kg/day (17 times the maximum human systemic dose adjusted for total body surface area) of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

In contrast, several well-controlled animal studies have shown that dermally applied tretinoin may be fetotoxic, but not overtly teratogenic, in rats and rabbits at doses of 1.0 and 0.5 mg/kg/day, respectively (42 times the maximum human systemic dose adjusted for total body surface area in both species).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin (Retin-A). Although no definite pattern of teratogenicity and no causal association has been established from these cases, 5 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of

these spontaneous reports in terms of risk to the fetus is not known.

Non-teratogenic effects:

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (42 times the maximum human systemic dose normalized for total body surface area). Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death, in rats when administered 2.5 mg/kg/day (104 times the maximum human systemic dose adjusted for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women. RENOVA should not be used during pregnancy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, mitigation of fine facial wrinkles with RENOVA 0.02% may be postponed in nursing mothers until after completion of the nursing period.

Pediatric Use: Safety and effectiveness in patients less than 18 years of age have not been established.

Geriatric Use: In clinical studies with RENOVA 0.02%, patients aged 65 to 71 did not demonstrate a significant difference for improvement in fine wrinkling when compared to patients under the age of 65. Patients aged 65 and over may demonstrate slightly more irritation, although the differences were not statistically significant in the clinical studies for RENOVA 0.02%. Safety and effectiveness of RENOVA 0.02% in individuals older than 71 years of age have not been established.

ADVERSE REACTIONS:

(See WARNINGS and PRECAUTIONS sections.)

In double-blind, vehicle-controlled studies involving 339 patients who applied RENOVA 0.02% to their faces, adverse reactions associated with the use of RENOVA were limited primarily to the skin. Almost all patients reported one or more local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus. In 32% of all study patients, skin irritation was reported that was severe, led to temporary discontinuation of RENOVA 0.02%, or led to use of a mild topical corticosteroid. About 7% of patients using RENOVA 0.02%, compared to less than 1% of the control patients, had sufficiently severe local irritation to warrant short-term use of mild topical corticosteroids to alleviate local irritation. About 4% of patients had to discontinue use of RENOVA because of adverse reactions.

Approximately 2% of spontaneous post-marketing adverse event reporting for RENOVA 0.05% were for skin hypo- or hyperpigmentation. Other spontaneously reported adverse events for RENOVA 0.05% predominantly appear to be local reactions similar to those seen in clinical trials.

OVERDOSAGE:

Application of larger amounts of medication than recommended has not been shown to lead to more rapid or better results, and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

Rx only.



Ortho Dermatological
Division of Ortho-McNeil Pharmaceutical, Inc.
Skillman, New Jersey 08558

© OMP 2000
Issued September 2000
653-10-856-1B

U.S. Patents 4,603,146 and 4,877,805



©SCOTT LEIGH/STOCKPHOTO.COM

Many adolescents feel that their acne is dirty, and they take it personally.

one approaches Dr. Lane at a party and asks what to use for their child's acne, over-the-counter benzoyl peroxide lotion is the simplest and safest answer, he said.

► **Papules.** The benzoyl peroxide lotion or a prescription gel version and topical retinoids are the treatments of choice for acne papules, often in a combination regimen of benzoyl peroxide applications in the morning and a retinoid at night.

Benzoyl peroxide can be used once or twice daily but can cause dry skin and irritant dermatitis, especially if used more frequently. Chronic use can cause allergic contact dermatitis in about 1% of patients, so start by applying it to an arm for several days before moving to the face.

The retinoids—tretinoin or adapalene cream or gel—may cause photosensitivity, which can be minimized by applying it in the evening. In the first few weeks these agents may cause irritant dermatitis or even some acne pustules, so tell the patient "there's a chance that you may get worse before you're better," said Dr. Lane, who reported having no conflicts of interest.

Ask patients to wait 20-30 minutes after washing their face before using a retinoid, which should be applied to dry skin. For some adolescent boys, this is a deal-breaker, "so I tell them 'If you can't wait 30 minutes, just put the retinoid on and don't wash your face,'" he said.

Continued on following page

Continued from previous page

Using benzoyl peroxide in the morning and a retinoid at night provides synergistic effects, but applying anything at the same time as a retinoid is likely to cause skin irritation, he added.

► **Pustules.** If pustules are present, add a twice-daily topical antibiotic (erythromycin or clindamycin), which is safe to combine with benzoyl peroxide but shouldn't be applied at the same time as a tretinoin.

Some vehicles may dry the skin, while others may feel greasy, either of which can work to the advantage of individual

patients. Rarely, clindamycin may cause diarrhea.

Acne on the back or chest often does not respond well to retinoids or benzoyl peroxide, and teenage boys often won't adhere to any topical therapy (including topical antibiotics), so systemic antibiotics may be needed before you can get them to transition to topical therapies, Dr. Lane noted. Tetracyclines are his first choice for systemic therapy, followed by erythromycin.

Systemic side effects can cause GI irritation or yeast vaginitis and may decrease the effectiveness of oral contraceptives.

Some adolescent girls with acne may

benefit from hormonal therapy, but Dr. Lane leaves this approach to the patient's primary care physician.

► **Cysts and scars.** More aggressive treatment is appropriate for acne with cysts and scars, and many of these patients will end up receiving isotretinoin from a dermatologist who can follow them carefully for numerous potential side effects.

For patients aged 18-25 years, isotretinoin therapy will get rid of acne for 10 years or longer in 30%, and 40% will have recurrent acne that responds to topical therapies or antibiotics. The odds are even better for patients aged 12-15 years, Dr. Lane said. ■

Incontinentia Pigmenti Not All That Rare

BY SHERRY BOSCHERT
San Francisco Bureau

STANFORD, CALIF. — A rare genetic disorder that usually is lethal to male babies and can leave abnormalities of the skin, eyes, and other body parts in females, may be more common than originally thought.

Incontinentia pigmenti is caused by a mutation in the IKBKG gene (also known as NEMO), which resides on the X chromosome. A genetic diagnosis can be helpful in females with suspected incontinentia pigmenti because they carry a 50:50 risk of passing the mutation on to their offspring, Dr. Louanne Hudgins said at a pediatric update sponsored by Stanford University.

Typically, blistering on the skin of a neonate or infant progresses to a wart-like rash, swirling macular hyperpigmentation, and linear hypopigmentation.

Patients with incontinentia pigmenti often have patchy alopecia of the scalp, dystrophic nails, and tooth abnormalities (few or abnormal shaped).

Other ectodermal-derived tissues are affected, too. Patients with incontinentia pigmenti often have patchy alopecia of the scalp, dystrophic nails, and tooth abnormalities (fewer teeth than normal or abnormal tooth formation, such as a cone-shaped tooth).

Associated eye problems are the most significant finding in survivors with incontinentia pigmenti. They often have retinal vascular proliferation, which can lead to retinal detachment.

"The mother may look completely normal or may have linear patches without as much hair" as a typical scalp, but genetic testing can identify incontinentia pigmenti in 80% of cases, said Dr. Hudgins, professor of pediatrics and chief of medical genetics at Stanford.

She and her associates used to test for incontinentia pigmenti only in girls who had all of the associated findings, and rarely made the diagnosis. More recently, however, "we've been doing the testing in kids with a few findings, and are finding the mutation. I think it's more common than we thought it was," she said. "In our genetic disorders of the skin clinic, we see as many as four or five cases per year" of incontinentia pigmenti.

Even with a presumptive diagnosis, it's important to order an ophthalmologic exam. "If this child is at risk for retinal detachment, you need to have that child followed by ophthalmology on a regular basis so you can maintain the best vision possible," she said. Dental and dermatologic evaluations also are warranted. "If they have ongoing skin problems, it's certainly a good idea to have a dermatologist follow them," said Dr. Hudgins, who reported having no conflicts of interest. ■

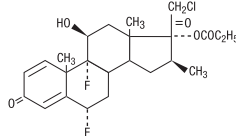
Ultravate® (halobetasol propionate ointment) Ointment, 0.05%

DESCRIPTION

Ultravate® (halobetasol propionate ointment) Ointment, 0.05% contains halobetasol propionate, a synthetic corticosteroid for topical dermatological use. The corticosteroids constitute a class of primarily synthetic steroids used topically as an anti-inflammatory and antipruritic agent.

Ultravate® (halobetasol propionate cream) Cream, 0.05% contains halobetasol propionate, a synthetic corticosteroid for topical dermatological use. The corticosteroids constitute a class of primarily synthetic steroids used topically as an anti-inflammatory and antipruritic agent.

Chemically halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1, 4-diene-3-20-dione, 17-propionate, C₂₈H₃₇ClF₂O₅. It has the following structural formula:



Halobetasol propionate has the molecular weight of 485. It is a white crystalline powder insoluble in water.

Each gram of Ultravate Ointment contains 0.5 mg/g of halobetasol propionate in a base of aluminum stearate, beeswax, pentarythritol cocoate, petrolatum, propylene glycol, sorbitan sesquioleate, and stearyl citrate.

Halobetasol propionate has the molecular weight of 485. It is a white crystalline powder insoluble in water.

Each gram of Ultravate Cream contains 0.5 mg/g of halobetasol propionate in a cream base of cetyl alcohol, glycerin, isopropyl isostearate, isopropyl palmitate, steareth-21, diazolidinyl urea, methylchlorisothiazolinone, (and) methylisothiazolinone and water.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, halobetasol propionate has anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of the anti-inflammatory activity of the topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Human and animal studies indicate that less than 6% of the applied dose of halobetasol propionate enters the circulation within 96 hours following topical administration of the ointment or cream.

Studies performed with Ultravate indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

Ultravate Ointment 0.05% is a super-high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond two consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

Ultravate Cream 0.05% is a super-high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond two consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

CONTRAINDICATIONS

Ultravate Ointment and Cream are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General

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

Patients applying a topical steroid to a large surface area or to areas under occlusion 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.

Ultravate Ointment produced HPA axis suppression when used in divided doses at 7 grams per day for one week in patients with psoriasis. These effects were reversible upon discontinuation of treatment.

Ultravate Cream produced HPA axis suppression when used in divided doses at 7 grams per day for one week in patients with psoriasis. These effects were reversible upon discontinuation of treatment.

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 requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see **PRECAUTIONS: Pediatric Use**).

If irritation develops, Ultravate Ointment or Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or anti-bacterial agent should be used. If a favorable response does not occur promptly, use of Ultravate Ointment or Cream should be discontinued until the infection has been adequately controlled.

Ultravate Ointment should not be used in the treatment of rosacea or perioral dermatitis, and it should not be used on the face, groin, or in the axillae.

Ultravate Cream should not be used in the treatment of rosacea or perioral dermatitis, and it should not be used on the face, groin, or in the axillae.

Information for Patients

Patients using topical corticosteroids should receive the following information and instructions:

- 1) The medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- 2) The medication should not be used for any disorder other than that for which it was prescribed.
- 3) The treated skin area should not be bandaged, otherwise covered or wrapped, so as to be occlusive unless directed by the physician.
- 4) Patients should report to their physician any signs of local adverse reactions.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression: ACTH-stimulation test; A.M. plasma cortisol test; Urinary free-cortisol test.

Ultravate® (halobetasol propionate cream) Cream, 0.05%

For Dermatological Use Only. Not for Ophthalmic Use.

Rx only

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

Positive mutagenicity effects were observed in two genotoxicity assays. Halobetasol propionate was positive in a Chinese hamster micronucleus test, and in a mouse lymphoma gene mutation assay *in vitro*.

Studies in the rat following oral administration at dose levels up to 50 µg/kg/day indicated no impairment of fertility or general reproductive performance.

In other genotoxicity testing, halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the sister chromatid exchange test in somatic cells of the Chinese hamster, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test to determine point mutations.

Pregnancy

Teratogenic effects: Pregnancy Category C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Halobetasol propionate has been shown to be teratogenic in SPF rats and chinchilla-type rabbits when given systemically during gestation at doses of 0.04 to 0.1 mg/kg in rats and 0.01 mg/kg in rabbits. These doses are approximately 13, 33 and 3 times, respectively, the human topical dose of Ultravate Ointment and Cream. Halobetasol propionate was embryotoxic in rabbits but not in rats.

Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats, but not in rabbits.

There are no adequate and well-controlled studies of the teratogenic potential of halobetasol propionate in pregnant women. Ultravate Ointment or Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ultravate Ointment or Cream is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Ultravate Ointment or Cream in pediatric patients have not been established and use in pediatric patients under 12 is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment.

Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and 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 an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilloedema.

Geriatric Use

Of approximately 850 patients treated with Ultravate® Ointment in clinical studies, 21% were 61 years and over and 6% were 71 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients; and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Of approximately 400 patients treated with Ultravate Cream in clinical studies, 25% were 61 years and over and 6% were 71 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients; and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In controlled clinical trials, the most frequent adverse events reported for Ultravate Ointment included stinging or burning in 1.6% of the patients. Less frequently reported adverse reactions were pustulation, erythema, skin atrophy, leukoderma, acne, itching, secondary infection, telangiectasia, urticaria, dry skin, miliaria, paresthesia, and rash.

The following additional local adverse reactions are reported infrequently with topical corticosteroids, and they may occur more frequently with high potency corticosteroids, such as Ultravate Ointment. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

In controlled clinical trials, the most frequent adverse events reported for Ultravate Cream included stinging, burning or itching in 4.4% of the patients. Less frequently reported adverse reactions were dry skin, erythema, skin atrophy, leukoderma, vesicles and rash.

The following additional local adverse reactions are reported infrequently with topical corticosteroids, and they may occur more frequently with high potency corticosteroids, such as Ultravate Cream. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

OVERDOSAGE

Topically applied Ultravate Ointment can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

Topically applied Ultravate Cream can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSEAGE AND ADMINISTRATION

Apply a thin layer of Ultravate Ointment to the affected skin once or twice daily, as directed by your physician, and rub in gently and completely.

Ultravate (halobetasol propionate ointment) Ointment is a super-high potency topical corticosteroid; therefore, treatment should be limited to two weeks, and amounts greater than 50 g/wk should not be used. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Ultravate Ointment should not be used with occlusive dressings.

Apply a thin layer of Ultravate Cream to the affected skin once or twice daily, as directed by your physician, and rub in gently and completely.

Ultravate (halobetasol propionate cream) Cream is a super-high potency topical corticosteroid; therefore, treatment should be limited to two weeks, and amounts greater than 50 g/wk should not be used. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Ultravate Cream should not be used with occlusive dressings.

HOW SUPPLIED

Ultravate® (halobetasol propionate ointment) Ointment, 0.05% is supplied in the following tube sizes:

15 g (NDC 10631-102-15)

50 g (NDC 10631-102-50)

Ultravate® (halobetasol propionate cream) Cream, 0.05% is supplied in the following tube sizes:

15 g (NDC 10631-103-15)

50 g (NDC 10631-103-50)

STORAGE

Store between 15°C and 30°C (59°F and 86°F).

U.S. Patent No. 4,619,921

Manufactured by Ranbaxy Laboratories Inc.

Jacksonville, FL 32257 USA

Revised June 2008