CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-967/S004

Trade Name: Ultravate Cream, 0.05%

Generic Name: (halobetasol propionate cream)

Sponsor: Westwood Squibb Pharmaceuticals, Inc

Approval Date: April 2, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-967/S004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-967/S-004

Westwood-Squibb Pharmaceuticals, Inc.
Attention: David L. Silberstein
Associate Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Silberstein:

Please refer to your supplemental new drug application dated May 4, 1992, received May 11, 1992, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultravate®(halobetasol propionate cream) Cream, 0.05%.

Your submission of February 19, 1996 constituted a complete response to our September 7, 1995 action letter.

This supplemental new drug application provides for revised labeling in accordance with the Division of Topical Drug Products' labeling recommendations for topical corticosteroid drug products and includes the results of the hypothalamic-pituitary-adrenal (HPA) axis suppression study as requested by the Agency at the time of the NDA approval.

We completed our review of this supplemental new drug application as amended, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on February 19, 1996. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

We request the following revisions to be made to the labeling as soon as possible and no later than 6 months after the date of this letter:

- In the INDICATIONS AND USAGE section, add "Use in children under 12 years of age is not recommended." as the last sentence to the first paragraph.
- In the INDICATIONS AND USAGE section, add the second paragraph to read "As with other highly active corticosteroid, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary."
- In the PRECAUTIONS, Information for Patients section, delete "5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressing."
- In the DOSAGE AND ADMINISTRATION section, the first sentence of the second paragraph should read "Ultravate (halobetasol propionate cream) Cream is a super-high potency topical corticosteroid;..."

These revisions are consistent with the conditions of the September 7, 1995 Approvable Letter. Report the changes in the Annual Report.

If a letter communicating important information about this drug product (i.e. a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be necessary.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}
Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Kelsey
4/2/03 03:50:06 PM
for Dr. Wilkin

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-967/S004

APPROVABLE LETTER

NDA 19-967/S-004

Westwood-Squibb Pharmaceuticals Inc.
Attention: Charles Ireland
100 Forest Avenue
Buffalo, New York 14213-1091

SEP 7 1995

Dear Mr. Ireland:

Please refer to your supplemental new drug application dated May 4, 1992, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultravate® (halobetasol propionate cream) Cream, 0.05%.

We acknowledge receipt of your amendment dated March 21, 1995.

The supplement provides for revised labeling in accordance with the Division of Topical Drug Products' labeling recommendations for topical corticosteroid drug products and includes the results of the hypothalamic-pituitary-adrenal (HPA) axis suppression study as requested by the Agency at the time of NDA approval.

We have completed the review of this supplemental new drug application as amended, and it is approvable. Before this application may be approved, however, we request that you submit fifteen copies of the final printed labeling (FPL) for the drug product that are identical to the enclosed revised version of the draft based on your March 21, 1995 submission. Ten of the copies should be individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug product becomes available, further revision of the FPL may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental new drug application, notify us of you intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the supplemental new drug application.

This change may not be implemented until you have been notified in writing that these supplemental new drug application is approved.

Should you have any questions, please contact Regina Joyce at 301-594-4109.

Sincerely yours,

Jonathan Wilkin, M.D.
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

cc: NDA 19-967
HFD-540 DivFile
District Office
HFD-2/Lumpkin (with labeling)
HFD-82 (with labeling)
HFD-240 (with labeling)
HFD-638 (with labeling)
HFD-730 (with labeling)
HFD-500
HFD-540 Derm File
HFD-540/SMO/Chambers mac 8/4/95
HFD-540/Pharm/Alam gma 8/30/95
HFD-540/CSO/Holmes
HFD-540/Clin/Joyce (with labeling) GJ 7/25/95

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-967/S004

LABELING

Bristol-Myers Squibb Company

Ultravate® Title Page
(halobetasol propionate cream) Cream, 0.05%

For Dermatological Use Only. Not for Ophthalmic Use.

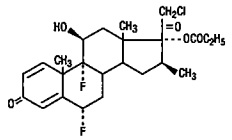
Rx only

F.P.O.

DESCRIPTION

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-6α, 9-difluoro-11β, 17-dihydroxy-16β-methylpregna-1, 4-diene-3-20-dione, 17-propionate, $C_{25}H_{31}ClF_2O_5$. 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 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, methylchloroisothiazolinone, (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 A_2 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 A_2.

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 cream.

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

INDICATIONS AND USAGE

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 Cream is 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 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 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 antibacterial agent should be used. If a favorable response does not occur promptly, use of Ultravate Cream should be discontinued until the infection has been adequately controlled.

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.

0.2500
0.3750
1.1250
0.3125
0.3125
1/2
1/2
0.3125
1.1250

Front

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.

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 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 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 Cream is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Ultravate 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 papilledema.

Geriatric Use

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

DOSAGE AND ADMINISTRATION

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 cream) Cream, 0.05% is supplied in the following tube sizes:

15 g (NDC 0072-1400-15)
50 g (NDC 0072-1400-50)

STORAGE

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

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

Bristol-Myers Squibb Company

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
51-022863-00
Revised April 2003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-967/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Dermatologic and Dental Drug Products
HFD-540

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 19-967/S-004 with Final Printed Labeling (FPL)

Name of Drug: Ultravate®(halobetasol propionate cream) Cream, 0.05%

Applicant: Westwood-Squibb Pharmaceuticals, Inc.
Attention: David L. Silberstein
Associate Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Material Reviewed

Submission Date:	**Receipt Date:**
19 February 1996	28 February 1996

Background and Summary

The submission dated February 19, 1996 provides a complete response to the September 7, 1995 Approvable Letter for NDA 19-967/S-004. This submission contains fifteen sets of the final printed labeling as requested in the approvable letter. Included in the approvable letter was the statement: "This change may not be implemented until you have been notified in writing that this supplemental new drug application is approved."

The original SLR-004 submission dated May 4, 1992 provided for revised labeling in accordance with the Division of Topical Drug Products' labeling recommendations for topical corticosteroid drug products and includes the results of the hypothalamic-pituitary-adrenal (HPA) axis suppression study as requested by the Agency at the time of the NDA approval (December 27, 1990).

Review

1. The FPL submitted in the complete response dated February 19, 1996 was compared with the labeling that issued with the September 7, 1995 Approvable Letter for NDA 19-967/S-004. The differences are as follows:

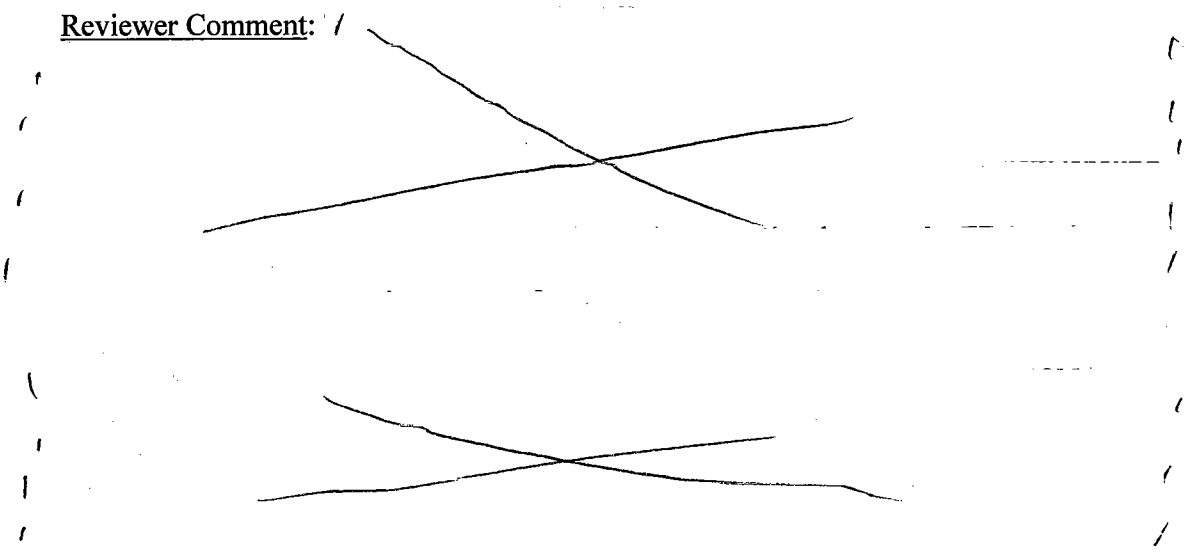
   - INDICATIONS and USAGE section:
     The last sentence of the first paragraph "Use in children under 12 years of age is not recommended." [redacted]

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

Reviewer Comment: This should be corrected and added to the labeling.

- PRECAUTIONS, Information for Patients section:
  Item #5 has been added: "5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressing."

  Reviewer Comment:



  The elderly are particularly at risk when using multiple steroid products that may be poorly monitored. This will be referred for clinical review and follow-up.

- DOSAGE AND ADMINISTRATION section:
  In the first sentence of the second paragraph The sentence should read as follows: "Ultravate (halobetasol propionate cream) Cream is a super-high potency topical corticosteroid;..."

  Reviewer Comment: This should be added to the labeling.

2. The FPL for S-004 was also compared to the package insert submitted in the most recent Annual Report dated December 17, 2002. The label in the annual report is identical to the FPL submitted February 19, 1996 in the complete response to the September 7, 1995 Approvable Letter for NDA 19-967/S-004. The approvable letter clearly stated: "This change may not be implemented until you have been notified in writing that this supplement new drug application is approved." labeling has been in use since 1996.

Conclusions

Recommendation: Approval of SLR-004 (with FPL) with FDA proposed revisions to labeling to be implemented as soon as possible. This labeling has been in use since 1996 [redacted] Since the product labeling has been in use during this period, it is appropriate to approve S-004 at this time and request the revisions to be made as soon as possible and no later than 6 months.

The following are the revisions, including the approved revisions of September 7, 1995, to be requested in the approval letter for SLR-004:

- In the INDICATIONS AND USAGE section, add "Use in children under 12 years of age is not recommended." as the last sentence to the first paragraph.
- In the INDICATIONS AND USAGE section, add the second paragraph to read "As with other highly active corticosteroid, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary."
- In the PRECAUTIONS, Information for Patients section delete "5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressing."
- In the DOSAGE AND ADMINISTRATION section, the first sentence of the second paragraph should read "Ultravate (halobetasol propionate cream) Cream is a super-high potency topical corticosteroid;..."

Leslie Vaccari, BSN, RAC
Regulatory Project Manager
Office of Drug Evaluation V

Supervisory Comment/Concurrence:

Mary Jean Kozma-Fornaro
Chief, Project Management Staff

Drafted: LAV/3/12/03
Revised/Initialed:3/31/03
Finalized: 3/31/03

CSO LABELING REVIEW

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leslie Vaccari
8/4/03 08:21:50 AM
CSO

SLR-004 CSO Review CBE with FPL

Mary Jean Kozma Fornaro
8/4/03 09:13:26 AM
CSO