CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 20273/004

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 20273/S004

Trade Name: Dovonex Ointment, 0.005%

Generic Name: (calcipotriene ointment)

Sponsor:Westwood Squibb Pharmaceutical, Inc.

Approval Date: July 7, 1999

Indication: Provides for the use of Dovonex (calcipotriene ointment) Ointment, 0.005%, for treatment of plaque psoriasis in adults.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20273/S004

APPROVAL LETTER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20273/S004

MEDICAL REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20273/S004

STATISTICAL REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20273/S004

ADMINISTRATIVE DOCUMENTS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20273/S004

CORRESPONDENCE

N20273

N20273

NT OF HEALTH & HUMAN SERVICES

K1.1

K1.1

Food and Drug Administration
Rockville MD 20857

NDA 20-273/SE8-004

Westwood Squibb Pharmaceutical Inc.
Attention: David L. Silberstein
Manager, Regulatory Affairs
100 Forest Avenue
Buffalo, New York 14213-1091

JUL 7 1999

Dear Mr. Silberstein:

Please refer to your supplemental new drug application dated July 8, 1998, received July 8, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dovonex (calcipotriene ointment) Ointment, 0.005%.

We also acknowledge receipt of your submission dated January 8 and 14, 1999.

This supplemental new drug application provides for the use of Dovonex (calcipotriene ointment) Ointment, 0.005%, for treatment of plaque psoriasis in adults.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-273/SE8-004." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Kevin Darryl White, Project Manager, at (301) 827-2020.

Sincerely,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

JUL 7 1999

Medical Officer's Review of Labeling Supplement to NDA 20-273

Supplement Number: 04

Submission Date: July 8, 1998
CDER Stamp Date: July 8, 1998
First Draft: February 5, 1998 1999 SW 6/3/99

Sponsor: Westwood Squibb
100 Forest Avenue
Buffalo, New York 14213-1091
Telephone (716) 887-3400 Fax (716) 887-3638

Drug: Dovonex (calcipotriene ointment) 0.005%

Pharmacologic Category: Vitamin D analog

Dosage Form: Topical

Approved Indication: 'Moderate' Plaque Psoriasis

Desired Indication: Plaque Psoriasis

Background: Twice daily application of Dovonex Ointment 0.005% was approved by the US Food and Drug Administration for the treatment of "moderately" severe plaque type psoriasis in December of 1993. A subsequent submission (supplement 03) containing data supporting once daily application of Dovonex Ointment, was approved in March, 1997.

Resume: The sponsor requests deletion of the adjective from the current label. Submitted in support of this proposed labeling change is a re-analysis of data previously submitted to the original NDA and its subsequent supplements. The re-analysis entailed dividing the study patients into 2 groups determined by the absolute value of their baseline psoriasis score. On a scale of 0 to 8, the sponsor designated patients with baseline severity scores greater than or equal to 6 as "high" severity and those with scores less than 6 as "low" severity. With adequate numbers of patients in both groups, efficacy and safety would have presumably been demonstrated for all qualities of disease. However on further inspection, it was noted that no patients with a disease severity less than 4 was admitted to the study. Clinically the grading scale would be interpreted as mild (0,1,2), moderate (3,4,5), or severe (6,7,8). As there were no patients with clinically mild disease admitted to the trial; support for the label change requires other data.

Other Data: Dovonex Cream and Dovonex Solution were FDA approved for the treatment of psoriasis in 1995 and 1997, respectively. No quantification of the severity of disease was included in the label for those products. The sponsor was asked to provide demographic data for the study patients in the trials used to support those approvals. The assumption is that if the patient demographics including disease severity were quantitatively and qualitatively similar for all formulations, then the restrictive could be removed from the label for the ointment. Therefore this review compares the three formulations.

Tables 1 – 4 provide the demographics for patients with a severity score greater than or equal to 6. There were no within study significant p values.

Table 1) Patient Demographics Dovonex **Ointment** "High" Severity (BID)

Treatment	Number	Gender	Age (mean)	% BSA (Mean)
Dovonex	69	96%M	48 years	15.7%
Vehicle	59	93%M	48 years	15.7%

Note: S #000 - label modification for once (QD) or twice daily (BID) dosing

Table 2) Patient Demographics Dovonex **Ointment** "High" Severity (QD)

Treatment	Number	Gender	Age (mean)	% BSA (Mean)
Dovonex	66	71%M	49 years	15.6%
Vehicle	62	89%M	46 years	13.8%

Table 3) Baseline Patient Demographics Dovonex **Cream** "High" Severity

Treatment	Number	Gender	Age (mean)	% BSA (Mean)
Dovonex	52	69%M	46 years	13.9%
Vehicle	54	76%M	47 years	15.4%

Table 4) Baseline Patient Demographics Dovonex **Solution** "High" Severity

Treatment	Number	Gender	Age (mean)
Dovonex	38	63%M	41.7 years
Vehicle	40	62%M	50.0 years

Note: BSA not assessed in scalp psoriasis

Reviewer comment: All patients were approximately equal in the percent of body surface involved and there were no differences in their demographics otherwise to suggest that one formulation should be labeled differently than another.

Tables 5 thru 8 include those patients with a disease severity score less than 6 (0 – 5).

Table 5) Patient Demographics Dovonex **Ointment** "Low" Severity (BID)

Treatment	Number	Gender	Age (mean)	% BSA (Mean)
Dovonex	237	61%M	48 years	7.6%
Vehicle	247	61%M	48 years	8.0%

Table 6) Baseline Patient Demographics Dovonex **Ointment** "Low" Severity (QD)

Treatment	Number	Gender	Age (mean)	% BSA (Mean)
Dovonex	150	51%M	46 years	8.2%
Vehicle	153	65%M	46 years	7.7%

Table 7) Baseline Patient Demographics Dovonex **Cream** " Low Severity

Treatment	Number	Gender	Age (mean)	% BSA (Mean)
Dovonex	127	65%M	48 years	8.1%
Vehicle	129	60%M	48 years	8.1%

Table 8) Baseline Patient Demographics Dovonex **Solution** "Low" Severity

Treatment	Number	Gender	Age (mean)
Dovonex	119	50%M	48.2 years
Vehicle	113	50%M	46.9 years

Reviewer comments: As was true in the "high" severity groups, the patient demographics including the percent of body surface involvement were similar.

Summary: There is no rationale for maintaining the limiting adjective in the Dovonex Ointment 0.005% label. More recently approved formulations do not have that restriction for clinically similar patient groups.

Recommendation: to be deleted from the label for Dovonex Ointment 0.005%.

/S/

Ella L. Toombs, MD

(In the in-box on 7/7/99)

Cc:
HFD-540
HFD-540/TL/Walker
HFD-540/DivDir/Wilkin
HFD-540/CSO/White
HFD-540/Biostat/Ping

SW 6/3/99

/S/

7/7/99

As above. Also, the Physicians Global Assessment by Response Category and Treatment (ITT Population) for twice daily dosing is compelling for both "Low" Severity and "High" Severity Groups (Tables A-9.1 and A-9.2, pp. 11469-11472). Once

HFD-540 White

APR - 6 1999

STATISTICAL REVIEW AND EVALUATION

NDA: 20-273 (Efficacy Supplement-revised labeling)
Applicant: Westwood-Squibb Pharmaceuticals Inc.
Name of Drug: Dovonex (calcipotriene ointment)
Route of Administration: Topical
Documents Reviewed: NDA 20-273: Supplement S-04: Revised labeling (dated July 08, 1998)
Indication: Psoriasis
Related NDAs: NDA 20-273 (Original, and Supplements)
Medical Officer: Ella Toombs, M. D. (HFD-540)

Introduction :

Dovonex (calcipotriene ointment), 0.005% is currently labeled (NDA 20-273, Supplement S-03) "for the treatment of moderate plaque psoriasis in adults", and maybe used once or twice daily. In this supplement, the sponsor requests further modification of labeling to delete the adjective from this indication.

In support of this change, the sponsor submitted a reanalysis of clinical data previously submitted to support approval of the original NDA and the labeling supplement S-03.

Data from clinical studies DE127-001 and DE127-003 was submitted as part of the original NDA submission. In these two studies, study medication was applied twice-daily. Data from clinical studies DE127-007 and DE127-009 was submitted as part of the supplement S-03 for revised labeling. In these two studies, study medication was applied once-daily.

The four protocols required subjects to apply the assigned randomized treatment to the affected lesions (except those on the face and scalp) twice-daily (in trials DE127-001 and DE127-003) or once-daily (in trials DE127-007 and DE127-009) for eight weeks. Investigators evaluated subjects prior to treatment (week 0) and after 1,2,4,6 and 8 weeks of treatment assessing erythema, scaling, plaque evaluation, and overall disease severity using 9-point (0-8) ordinal severity scales. A Physician's Global assessment, comparing disease condition to baseline, was performed after 1,2,4,6 and 8 weeks of treatment using a 7-point (0=completely clear to 6=worse) ordinal scale. Subjects were observed for the occurrences of adverse clinical events throughout the study.

A reanalysis of these studies was undertaken to determine efficacy of treatment with regard to each categorization of severity. The subjects were separated into two groups according to baseline severity of their psoriasis conditions. One group consisted of subjects whose condition was classified as moderate in severity (baseline overall severity score < 6), and another group consisted of subjects whose condition was classified as severe (baseline overall severity score ≥ 6).

Table 1 Mean grade for characteristics of plaque psoriasis and overall disease severity (Evaluable subjects) (baseline severity <6-"low" group) -Twice-daily dosing

	Overall severity		Plaque elevation		Scaling		Erythema	
Treatment-twice-daily	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8
Calcipotrience ointment	(n=237) 3.57	(n=219) 1.57	(n=237) 4.73	(n=219) 1.44	(n=237) 4.74	(n=219) 1.36	(n=237) 4.31	(n=219) 1.97
Vehicle	(n=247) 3.53	(n=210) 2.95	(n=247) 4.63	(n=210) 3.26	(n=247) 4.61	(n=210) 2.74	(n=247) 4.31	(n=210) 3.54
Clinical differences	0.04	1.38	0.1	1.82	0.13	1.38	0.0	1.57
P-value	0.789	<0.001	0.296	<0.001	0.035	<0.001	0.654	<0.001

Table 2 Mean grade for characteristics of plaque psoriasis and overall disease severity (Evaluable subjects) (baseline severity ≥ 6 -"high" group) -Twice-daily dosing

	Overall severity		Plaque elevation		Scaling		Erythema	
Treatment-twice-daily	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8
Calcipotrience ointment	(n=69) 6.45	(n=64) 2.33	(n=69) 5.91	(n=64) 2.03	(n=69) 6.23	(n=64) 1.87	(n=69) 5.94	(n=64) 2.53
Vehicle	(n=59) 6.58	(n=55) 4.78	(n=59) 6.15	(n=55) 4.38	(n=59) 6.36	(n=55) 3.62	(n=59) 6.27	(n=55) 4.67
Clinical differences	0.13	2.45	0.24	2.35	0.13	1.75	0.33	2.14
P-value	0.643	<0.001	0.488	<0.001	0.411	<0.001	0.413	<0.001

Table 3 Mean grade for characteristics of plaque psoriasis and overall disease severity (Evaluable subjects) (baseline severity <6-"low" group) - Once-daily dosing

	Overall severity		Plaque elevation		Scaling		Erythema	
Treatment-twice-daily	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8
Calcipotrience ointment	(n=150) 3.84	(n=139) 1.87	(n=150) 4.67	(n=139) 1.88	(n=150) 4.66	(n=139) 1.55	(n=150) 4.29	(n=139) 2.25
Vehicle	(n=153) 3.77	(n=128) 2.91	(n=153) 4.53	(n=128) 3.16	(n=153) 4.46	(n=128) 2.56	(n=153) 4.25	(n=128) 3.36
Clinical differences	0.07	1.04	0.14	1.28	0.20	1.01	0.04	1.11
P-value	0.345	<0.001	0.046	<0.001	0.227	<0.001	0.573	<0.001

Table 4 Mean grade for characteristics of plaque psoriasis and overall disease severity (Evaluable subjects) (baseline severity ≥ 6 -"high" group) - -Once-daily dosing

	Overall severity		Plaque elevation		Scaling		Erythema	
Treatment-twice-daily	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8	Week 0	Week 8
Calcipotrience ointment	(n=66) 6.67	(n=60) 2.73	(n=66) 6.21	(n=60) 2.30	(n=66) 6.61	(n=60) 1.95	(n=66) 6.00	(n=60) 2.80
Vehicle	(n=62) 6.37	(n=48) 4.98	(n=62) 6.02	(n=48) 4.58	(n=62) 6.19	(n=48) 3.42	(n=62) 5.87	(n=48) 4.79
Clinical differences	0.30	2.25	0.19	2.28	0.42	1.47	0.13	1.99
P-value	0.016	<0.001	0.117	<0.001	0.037	<0.001	0.173	<0.001

Table 5 Physician's global assessment
(Baseline severity <6-"low" group) -Twice-daily dosing
(Evaluable subjects)

	Marked improvement or better				
	Calcipotrience Ointment		Vehicle		
week	N	%	N	%	p-value
1	31	14	3	1	<0.001
2	76	34	9	3	<0.001
4	119	53	20	9	<0.001
6	143	66	29	13	<0.001
8	155	71	41	19	<0.001

Table 6 Physician's global assessment
(Baseline severity ≥ 6-"high" group) -Twice-daily dosing
(Evaluable subjects)

	Marked improvement or better				
	Calcipotrience Ointment		Vehicle		
week	N	%	N	%	p-value
1	3	4	0	0	0.064
2	15	22	6	5	0.001
4	28	43	12	9	<0.001
6	36	60	8	15	<0.001
8	43	67	13	24	<0.001

Table 7 Physician's global assessment
(Baseline severity <6-"low" group) - Once-daily dosing
(Evaluable subjects)

	Marked improvement or better				
	Calcipotrience Ointment		Vehicle		
week	N	%	N	%	p-value
1	6	4	1	1	<0.001
2	26	18	3	2	<0.001
4	49	35	10	7	<0.001
6	70	51	16	12	<0.001
8	79	56	22	18	<0.001

Table 8 Physician's global assessment
(Baseline severity ≥ 6-"high" group) - Once-daily dosing
(Evaluable subjects)

	Marked improvement or better				
	Calcipotrience Ointment		Vehicle		
week	N	%	N	%	p-value
1	2	3	1	2	<0.001
2	7	11	2	3	<0.001
4	17	27	3	6	<0.001
6	27	44	4	8	<0.001
8	36	61	4	8	<0.001

Table 9 Investigator-adjusted Cochran-Mantel-Haenzel Test for differences between treatments for adverse events classified as skin related or skin peresthesia

(Baseline severity < 6-"low" group)-twice-daily	Calcipotrience Ointment (N=239)		Vehicle (N=249)		
Skin related adverse events[1]	N	%	N	%	p-value[2]
	42	18	39	16	0.684
(Baseline severity ≥ 6-"high" group)-twice-daily	Calcipotrience Ointment (N=69)		Vehicle (N=59)		
Skin related adverse events[1]	N	%	N	%	p-value[2]
	12	17	11	19	0.719
(Baseline severity < 6-"low" group)-once-daily	Calcipotrience Ointment (N=150)		Vehicle (N=154)		
Skin related adverse events[1]	N	%	N	%	p-value[2]
	30	20	48	31	0.032
(Baseline severity ≥ 6-"high" group)-once-daily	Calcipotrience Ointment (N=67)		Vehicle (N=62)		
Skin related adverse events[1]	N	%	N	%	p-value[2]
	24	36	21	34	0.675

[1] This category includes those subjects with no adverse event or no skin-related or skin-paresthesia adverse events.
[2] Investigator-adjusted

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

The Dovenex treatment group was statistically significantly superior to the vehicle group for both the "low" severity group and the "high" severity group, either once daily or twice daily.

/S/ Apr. 6, '99

Ping Gao, Ph.D. /S/ Apr. 6 /1999
Mathematical Statistician, DOB III

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, DOB III

HFD 540
NDA 20-273
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Toombs
HFD-540/Mr. White
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Dr. Gao
HFD-344/Dr. Carreras

Chron.

This review contains 5 pages.
MS word/d: \nda\20-273\20-273.doc\April 6, 1999; Ping Gao /(301)-827-2083

EXCLUSIVITY SUMMARY for NDA # 20-273 SUPPL # SE8-004

Trade Name DOVONEX OINTMENT Generic Name CALCIPOTRIENE

Applicant Name WESTWOOD SQUIBB PHARMACEUTICAL HFD- 540

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-554 _____

NDA # 20-611 _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /✓/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/

Signature

Title: PROJECT MANAGEMENT

6/29/99

Date

/S/

Signature of Division Director

7/7/99

Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-273 Supplement # 004 Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE8

HFD 540 Trade and generic names/dosage form: DOVONEX (CALCIPOTRIENE) OINTMENT Action: AP AE NA

Applicant WESTWOOD SQUIBB Therapeutic Class ANTI-PSORIASIS

Indication(s) previously approved TREATMENT OF MODERATE PLAQUE PSORIASIS

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application TREATMENT OF ~~MODERATE~~ PLAQUE PSORIASIS

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ___ Children (2-12yrs) ✓ Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

✓ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

✓ (4) If no protocol has been submitted, attach memo describing status of discussions. (PPSR) Proposed pediatric study request relevant comments CF & letter sent to sponsor.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from PROJECT MANAGEMENT (e.g., medical review, medical officer, team leader)

/S/ PROJ. MGR 6/29/99

Signature of Preparer and Title Date

/S/ 7/7/99

Orig NDA/~~BLA~~ # 20-273

HFD 540/Div File

NDA/BLA Action Package

HFD-006/ KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

ORIGINAL 11586

SE8-004 BM

Bristol-Myers Squibb
Pharmaceutical Research Institute

100 Forest Avenue Buffalo, NY 14213-1091 716 887-3400 Fax: 716 887-3638

January 8, 1999

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
9201 Corporate Dr.
Rockville, MD 20850

Re: NDA 20,273
DOVONEX (calcipotriene ointment) 0.005%
Amendment to Supplement S#-04

Dear Dr. Wilkin:

Reference is made to the original submission of Supplement S#-04 to NDA 20,273 for DOVONEX (calcipotriene ointment) 0.005%, received at the Agency on July 8, 1998. Reference is also made to a telephone contact between Dr. Ella Toombs and Kevin Darryl White of FDA and David Silberstein of Westwood-Squibb on January 8, 1999.

During the teleconference, Dr. Toombs requested that tables of the demographics of subjects in the Cream NDA studies (NDA 20,554) be provided to aid in her review. She asked that the data be dichotomized for severity similarly to the data for the Ointment originally provided in this supplement. The requested information is attached. It is also provided as a Word97 file as an attachment to an electronic mail note to Kevin Darryl White. As can be seen from examination of the data, the populations studied are comparable in the cream and ointment clinical studies.

If there are any questions regarding this submission, or additional information is required, please contact me at (716) 887-3641, or via fax at (716) 887-3638. I can also be reached via electronic mail at "silbersd@bms.com".

Sincerely,

David L. Silberstein, Manager
Worldwide Regulatory Affairs

Attachment
Submitted in duplicate
Desk Copies via electronic mail and facsimile [(301) 827-2075] to K. D. White

Bristol-Myers Squibb
Pharmaceutical Research Institute

100 Forest Avenue Buffalo, NY 14213-1091 716 887-3400 Fax: 716 887-3638

January 14, 1999

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Document Control Room
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9201 Corporate Dr.
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During the teleconference, Dr. Toombs requested that tables of the demographics of subjects in the Cream (NDA 20,554) and Scalp Solution (NDA 20,611) studies be provided to aid in her review. She asked that the data be dichotomized for severity similarly to the data for the Ointment originally provided in this supplement. The requested information for the Cream was provided in an amendment dated January 8, 1999. This amendment provides similar information for the Scalp Solution. The text of this amendment is also provided as a Word97 file as an attachment to an electronic mail note to Kevin Darryl White. As can be seen from examination of the data, the populations studied are comparable in the ointment, cream and solution clinical studies.

If there are any questions regarding this submission, or additional information is required, please contact me at (716) 887-3641, or via fax at (716) 887-3638. I can also be reached via electronic mail at "silbersd@bms.com".

Sincerely,

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